Review Article

Pediatric Education and Research
Volume 5 Number 3, September - December 2017
DOI: https://dx.doi.org/10.21088/per.2321.1644.5317.11

Recent Advances and Consensus Based Management Options for Lupus Nephritis in Children

Varun Anand*, Radha Ghildiyal, Santosh Kondekar***, Alpana Kondekar*****

*Assistant Profess, **Professor ***Associate Professor, Department of Pediatrics, Topiwala National Medical College and B.Y.L. Ch. Nair Hospital, Mumbai, Maharashtra 400008, India.

Abstract

Pediatric lupus nephritis, though rare; has significant morbidity and mortality. Often it may get undiagnosed or get diagnosed late due to lack of awareness about its intricacies of management. Hereby an effort is made to compile the recent definitions and advances in management of pediatric lupus nephritis.

Keywords: Nephritis; Lupus; Renal Hypertension.

Introduction

Systemic lupus erythematosus (SLE) is autoimmune disorder with formation of autoantibodies and immune complexes, causing inflammation and potential damage to a various target organs like skin, kidney, musculoskeletal system, lungs, heart and central nervous system. Paediatric SLE is more severe than SLE in adults, requiring aggressive treatment. SLE is more common in girls (4:3 pre-puberty; 4:1 post-puberty) [1]. American College of Rheumatology (ACR) has given 11 criteria for the diagnosis of SLE and if ≥ 4 criteria are present, disease is said to be positive with 95% of sensitivity and 96% of specificity (Table 1) [2]. Systemic lupus international collaborating clinics (SLICC) revised and validated the ACR, SLE classification criteria in order to improve clinical relevance and gave new classification to diagnose SLE in 2012 (Table 2) [3] . Luis et al conducted a comparison study between the two classification with 2055 SLE patients and found the sensitivity of SLICC 2012 was higher than ACR 1997 (93.2% versus 85.6%; P < 0.0001) [4]. Of all the patients with SLE, 15-20% is diagnosed during childhood [5]. Median age of onset

Table 1: ACR Criteria for Classification of SLE* [2]

Malar rash
Discoid rash
Photosensitivity
Oral ulcers
Arthritis: non-erosive, affecting ≥2 joints
Serositis: Pleuritis, Pericarditis, peritonitis
Renal disorder: Proteinuria (≥ 0.5 g/day or persistently > +++), RBC casts
Neurological disorder: Seizures, Psychosis (exclude other causes)
Hematological disorder: Hemolytic anemia, Leukopenia (<4000/ mm^3 on two occasions), Lymphopenia (<1500/ mm^3 on two occasions), Thrombocytopenia (<100000/mm^3)
Immunological disorder: Elevated antinuclear antibodies (after exclusion of drug-induced lupus), anti–double stranded (ds) DNA and anti-Smith antibodies, Positive antiphospholipid antibodies
Antinuclear antibody positive

*Presence of 4/11 criteria establishes the diagnosis of SLE.

Corresponding Author: Santosh Kondekar, Associate Professor, Department of Pediatrics, Topiwala National Medical College and B.Y.L. Ch. Nair Hospital, Mumbai, Maharashtra 400008, India.
E-mail: askme@aol.in

Received on 01.09.2017, **Accepted on** 14.09.2017

of childhood SLE is between 11 and 12 years (rare below 5 years), and 80% of patients are female [6,7]. Renal disease in childhood SLE is present in up to 80% of Asians which is much higher than other part of world and is called Lupus Nephritis (LN) [8]. Glomerulonephritis is the most important cause of morbidity and mortality. LN usually arises within 5 year of diagnosis of SLE; however, renal failure rarely occurs. According to a study done in Madhya Pradesh from 2011 to 2015, LN was the commonest feature at disease onset, at the time of diagnosis and throughout the disease course among children with SLE [9].

Table 2: Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus [3]

Clinical Criteria	Immunological Criteria
Acute cutaneous lupus Malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash or subacute cutaneous lupus	**Positive antinuclear antibody**
Chronic cutaneous lupus Classic discoid rash, lupus panniculitis, mucosal lupus, lupus erythematous tumidus, chilblains lupus, discoid lupus/lichen planus overlap	**Positive double-stranded DNA antibody**
Oral or nasal ulcers	**Positive anti-Smith antibody**
Nonscarring alopecia	**Antiphospholipid antibody positivity** Positive lupus anticoagulant, high titer anticardiolipin antibody (IgA, IgG, IgM), or positive anti–B2-glycoprotein I antibody (IgA, IgG, IgM)
Synovitis (≥2 joints)	**Low complement** Low C3, C4, or Ch50 level
Serositis Pleurisy or pericardial pain ≥1 day, pleural effusion or rub, pericardial effusion or rub, ECG evidence of pericarditis	**Positive direct Coombs test** (in the absence of hemolytic anemia)
Renal RBC casts + or urine protein/creatinine ratio >500 mg protein/d	
Neurologic Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy or acute confusional state	
Hemolytic anemia	
Leukopenia (<4,000/mm3) or **lymphopenia** (<1,000/mm3)	
Thrombocytopenia (<100,000/mm3)	

* Presence of 4 criteria (including at least 1 clinical and 1 immunologic criterion) establishes the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.

Prevalence and Incidence

The manifestation of SLE varies with racial, ethnic, environmental and genetic factors. Prevalence study data is sparse in India. According to one study of North India with population survey of 91,888, a point prevalence of SLE was 3.2 per 100,000 (95% CI = 0-6.86 per 100,000) [10]. This is a much lower figure than reported from the west. In a prospective epidemiologic study of 5.78 million Taiwan children of age less than 16 years, the prevalence of pediatric SLE was 6.3 per 100,000 (95% CI: 5.7-7.0) which was 6.2 more times more common in girls than boys. (11.2 per 100,000, 95% CI: 10.0-12.5 VS 1.8 per 100,000, 95% CI: 1.4-2.4) [6]. In Asia overall incidence rates for SLE ranges from 0.9 –3.1 per one lac population, while prevalence rates ranges from 4.3– 45.3 per one lac population [11]. Higher rates of renal involvement, one of the main systems involved at death, were observed for Asians (21– 65% at diagnosis and 40 – 82% over time) than for whites [11].

According to a metaanalysis published in 2010, Asians SLE patients are more prone to develop LN because of Fcã receptor IIIA-V/F158 polymorphism [12]. According to many studies the incidence of Lupus nephritis is higher in African, Asian and Latin American Mestizo populations compared to Caucasians [13,14,15,16]. Genes variation in different ethnics may be responsible for this variability.

Classification

The histological classification of lupus nephritis (LN) was initially proposed in 1975 by the World Health Organization (WHO) and modified in 1982 and 1995 (Table 3) [17].

Table 3: WHO Classification of lupus nephritis (1995) [17]

WHO class I : minimal mesangial LN	Light microscopy- no histological anormality Immunoflorescence/ electron microscopy – mesangial immune deposits.
WHO class II: Pure mesangial alterations	a. Mesangial widening and/or mild hypercellularity b. Moderate hypercellularity
WHO Class III nephritis Focal segmental glomerulonephritis	a. With active necrotizing lesions b. With active and sclerosing lesions c. With sclerosing lesions
WHO class IV Diffuse glomerulonephritis	a. Without segmental lesions b. With active necrotizing lesions c. With active and sclerosing lesions d. With sclerosing lesions
WHO class V nephritis: 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
WHO class VI nephritis:	Advanced sclerosing glomerulonephritis

Table 4: Classification of lupus nephritis (ISN/RPS) 2002 [18]

ISN/RPS Working Group - Revised Histopathological Classification of LN (Revised after a consensus conference in 2002)

1. Minimal mesangial LN – LM : Normal glomeruli
IF : Mesangial immune deposits

2. Mesangial proliferative LN –
LM : Purely mesangial hypercellularity of any degree or mesangial matrix expansion with mesangial immune deposits
IF or EM : none / few isolated subepithelial or subendothelial deposits

3. Focal LN - Active or inactive focal (<50% involved glomeruli), segmental, or global endo- or extra-capillary GN, typically with focal, subendothelial immune deposits, with or without focal or diffuse mesangial alterations.
III (A) Active focal proliferative LN
III (A/C) Active and sclerotic focal proliferative LN
III (C) Inactive sclerotic focal LN

4. Diffuse segmental (IV-S) or global (IV-G) LN - Active or inactive diffuse (>50% involved glomeruli), segmental, or global endo- or extra-capillary GN with diffuse subendothelial immune deposits, with or without mesangial alterations.
This class is divided into: **diffuse segmental (IV-S)** when >50% of the involved glomeruli have segmental lesions, **diffuse global (IV-G)** when >50% of the involved glomeruli have global lesions.
IV (A) : Active diffuse segmental or global proliferative LN
IV (A/C) : Diffuse segmental or global proliferative and sclerotic LN
IV (C) : Diffuse segmental or global sclerotic LN

5. Membranous LN - LM and IF or EM: Numerous global or segmental subepithelial immune deposits ± mesangial alterations. May occur in combination with III or IV in which case both will be diagnosed.

6. Advanced sclerotic LN: ≥90% glomeruli globally sclerosed without residual activity.

Transformation of the histologic lesion from one class to another is common especially in inadequately treated patients and usually results in progression to a more severe histologic lesion. WHO classification was modified in 2002 (Table 4), by International Society of Nephrology and Renal Pathology Society Working Group (ISN/RPS) [18]. The most striking advantage of ISN/RPS classification is the high interobserver and intraobserver reproducibility with clinical relevance and association resulting from a uniform reporting system used around the world [19,20].

According to a South Indian study, done from jan 1999 to dec 2004, diffuse proliferative glomerulonephritis (WHO Class- IV) was the commonest class, seen in 63% of cases whereas in Asia it was found in 39.4–54% of case of LN [21,22] .

In India, it was reported that the most common secondary glomerulonephritis was LN (80.1%) [23, 24]. Renal histopathology guides for the introduction of appropriate treatment.

Pathophysiology

Generation of autoantibodies directed against self-antigens causes damage to target organs like kidney, skin, musculoskeletal system, heart, lungs and CNS. Antibodies to ds-DNA form immune complexes, which deposit in glomeruli, and initiate inflammation leading to glomerulonephritis. In more severe forms

of LN, proliferation of endothelial, mesangial and epithelial cells occurs and the production of matrix proteins lead to fibrosis [25] Pathogenesis of LN which involves autoimmunity is a complex process which involves role of the complement cascade which opsonises the immune complex, autoantibodies, breaking of tolerance, immunity and innate immune system in driving renal damage. Interferon gamma, IL-17 and compensatory FOXP3 levels are elevated, which indicates role of Th1 and Th17 for determining severity of LN [26]. The innate immune system may induce the adaptive immune system through toll like receptors by activating auto-reactive B cells and instigating a T cell response [27].

Clinical Presentation

According to a Taiwan study done between January 1999 and December 2011, in pediatric SLE patients the mean age at diagnosis was 12.4±2.5 years (range, 4.0–17.2 years) and the female-to-male ratio was 5.94:1 [28]. Hormonal influence is the cause of female predominance. Increased estrogen, prolactin and decreased androgen at pubertal age were considered the cause of this predisposition, which was proved in mouse models. But in human, little evidence was found with estrogen and prolactin related exposure. In a study done at south west Asia, Oman most common clinical features were articular (76%), followed by mucocutaneous (70%), haematological manifestations (68%) and renal involvement (64%) (Table 5) [22].

Agrawal et al, from CMC Vellore reported, fever (94.2%) as most common manifestation followed by renal manifestations (77.1%) [29]. In another study, done in 1994 with 201 children of SLE, (Table-6) LN was found in 84% of cases [30]. In another study renal disease was found to be the most common presenting feature of pediatric SLE [31].

Table 5: Clinical features of children with SLE in Asia [22]

Clinical features	Taiwan	Oman	China	Taiwan	Kuwait
Age at diagnosis (years)	13	8.6	-	13.5	10.7
Fever (%)	18.2	62	88.3	-	-
Weigh loss (%)	30	52	-	4.6	-
Alopecia (%)	20	36	-	13	-
Cutaneous rashes (%)	72	70	84.4	77	51
Mucosal (%)	40	10	-	26	29
Arthritis/arthralgia (%)	53	76	-	57	43
Hematological (%)	72	68	67.5	79.7	34
Leukopenia	38	14	-	34.6	-
Lymphopenia	32	16	-	58.8	-
Hemolytic anemia	56.2	60	-	44.4	20
Thrombocytopenia	19.7	20	-	19.6	23
Renal involvement (%)	81	64	76.6	58.8	29
Pulmonary (%)	9	26	-	-	9
Pleural effusion	9	14	-	15	-
Pneumonitis	-	16	-	-	-
Cardiac (%)	8	10	-	5.2	6
Neuropsychiatric (%)	34.5	18	37.3	34.6	14
Headache	-	-	31.8	-	-
Seizure	28	-	29.1	24.4	-
Psychosis	5	-	-	21.9	-
Stroke	-	-	-	-	-
Chorea	1.5	-	-	28.1	-

Table 6: Presenting symptoms of SLE in children [30]

Malaise, weight loss, growth retardation	96%
Cutaneous abnormalities	96%
Hematological abnormalities	91%
Fever	84%
Lupus nephritis	84%
Musculoskeletal complaints	82%
Pleural/pulmonary disease	67%
Hepatosplenomegaly and/or lymphadenopathy	58%
Neurological disease	49%
Other manifestations (cardiac, ocular, gastrointestinal, Raynaud's phenomenon)	13%-38%

Diagnosis

- Urine microscopy (hematuria, proteinuria, albuminuria)
- Leukopenia, anaemia, thrombocytopenia found during active disease should be monitored.
- Coagulation screen & DCT (to look for evidence of hemolysis)
- ANA is very sensitive for SLE (95-99%), but not very specific (~50%). ANA-negative lupus is extremely rare. Antibodies against ds-DNA and anti-Smith are specific for SLE (~98%) but not as sensitive (40-65%).
- Anti phospholipid antibody was found to be positive in 78% of cases in an observational study of Saudi Arabia, done between January 2002 and June 2014 [32].
- Anti-C1q antibody has high sensitivity (80%-100%) and specificity and both antibodies reflect the disease activity. The other antibodies (Anti-Sjögren's syndrome, Anti-Smith and anti-Sjögren's syndrome B) have variable sensitivity and specificity.
- Most LN children have antichromatin/ nucleosome antibodies (specificity - 98%; sensitivity 69%), and they may be positive when the anti-dsDNA antibodies are negative [33].
- Urinary biomarkers as fractional excretion of Endothelial-1 (ET-1), MCP-1, vascular cell adhesion molecule-1 (VCAM-1), may also be useful but require validations [34].
- Serum C3 and C4 levels are decreased.
- Percutaneous renal biopsy enables direct visualization, grading and classification which helps to guides selection of immunosuppressive therapies. It also provides disease activity index and chronicity index which further guides the need for increase in immunosuppressive therapy.

Indications of doing renal biopsy are renal involvement with reproducible proteinuria ≥ 0.5 g/ 24 h with haematuria, persisting isolated glomerular haematuria and/or cellular casts, persisting isolated glomerular haematuria, isolated leucocyturia (with exclusion of causes like infection or drugs) and unexplained renal insufficiency with normal urinary findings [35] . Different type of microscopy and their role are shown in Table 7.

Table 7: Microscopy with specific findings

Type of Microscopy	Function
Light microscopy	≥8 glomeruli should be examined with haematoxylin and eosin, periodic acid-Schiff, Masson's trichrome and silver stain [18]
Immunofluorescence or immunohistochemistry	Done for immunoglobulin and complement deposits (IgG, IgA, IgM, C3, C1q, κ and λ light chains) [36, 37]
Electron microscopy	Helps in recognition of proliferative and membranous lesions [38, 39, 40]

According to Consensus of the Brazilian Society of Rheumatology published in 2015, a renal biopsy should be done when serum creatinine is elevated with no apparent cause and associated with SLE, isolated proteinurea ≥ 1.0 g/24 h or proteinurea ≥ 0.5 g/24 h associated with glomerular dysmorphic hematuria and/or the presence of cellular casts [41].

Treatment [42]

There are six international guidelines along with KDIGO (Kidney Disease: Improving Global Outcomes) Glomerulonephritis Work Group from different geographical area (American, European, Spain, Netherland) published in 2012 with level of evidence for the management of LN in both adults and pediatric age group on the basis of trials conducted in the past 40 years [43]. Because of the lack of good prospective randomised control trials the treatment protocol used at various centres is same as that of adults [44]. Therefore, there is wide variation in treatment protocols at various centres. In 2008, first European League Against Rheumatism (EULAR) recommendations on the management of SLE were published [45]. In 2012, Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) gave recommendations for the management of adult and paediatric LN [44]. Treatment of LN is implemented in 2 stages, first is induction phase in which immunosuppressive therapy is given to produce clinical and serological remission (normalization of anti-DNA antibody and C3 C4 levels) and second is maintenance phase which is usually given after remission for 2-3 years.

Class I lesions - require no specific therapy.

Class II lesions – there is no specific therapy as there is very little evidence of the progression of the disease in further stages [46]. According to ACR

guidelines no immunosuppressive therapy is required. As per EULAR/ERA-EDTA oral glucocorticoids (0.25–0.5 mg/kg/day) can be given. Azathioprine (1–2 mg/kg/day), can be added with glucocorticoids as a steroid sparing agent, if proteinuria > 1 g/24 h with glomerular haematuria is present.

Class III, IV - KADIGO recommends initial therapy with corticosteroids, combined with either cyclophosphamide (CYC) or Mycophenolate mofetil (MMF). Addition of cyclophosphamide to corticosteroids for initial treatment decreases the frequency of kidney relapse, CKD and ESRD if compared to corticosteroids alone [47].

Oral prednisone with tapering according to clinical response over 6–12 months is the initial therapy. For severe cases, intravenous pulses of methylprednisolone should be given during 3 consecutive days @ 15–30 mg/kg/day or 600-1000 mg/m^2/day (maximum 1 g/day) and can be repeated depending on the severity of the disease. Methylprednisolone pulses should be followed by oral prednisolone (1–2 mg/ kg/day to a maximum dose of 60 mg /day) and tapered after 4-6 weeks on achieving remission to a dose of 0.5 mg/kg/day. Oral Cyclophosphamide (500-1000 mg/m^2 intravenous, monthly pulses for 6 months) should be added to this regimen to induce remission. Oral cyclophosphamide 1.0–1.5 mg/kg/d (maximum dose 150mg/d) for 2–4 months has been used as an alternative to i.v. cyclophosphamide with equivalent efficacy [48, 49]. After completion of induction phase, maintenance therapy with azathioprine or MMF, and low-dose oral corticosteroids should be given. KADIGO guidelines suggest continuation of maintenance theray for at least 1 year before consideration is given to taper the immunosuppressive therapy once the remission is achieved. If complete remission has not been achieved after 12 months of maintenance therapy, consider performing a repeat kidney biopsy before determining if a change in therapy is indicated. While maintenance therapy is being tapered, if kidney function deteriorates and/or proteinuria worsens, treatment should be increased to the previous level of immunosuppression that controlled the LN. The average duration of immunosuppression was 3.5 years in seven RCTs. [50,51, 52]. Therapy is monitored with serial measurements of proteinuria and SCr.

Class V lesions - Pure class V LN and persistent nephrotic proteinuria should be treated with corticosteroids plus an additional immunosuppressive agent like cyclophosphamide, calcineurin inhibitor, MMF or azathioprine. There have been no studies of the effect of treatment of class V LN on long-term kidney outcomes. Antiproteinuric and antihypertensive medications may reduce proteinuria by as much as 30–50% in class V LN [53, 54].

Class VI – Despite the absence of active LN, patients may still have extrarenal manifestations of systemic lupus requiring immunosuppression. Therefore child should be treated with corticosteroids and immunosuppressive therapy.

Members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) after considering the existing medical evidence and current treatment approaches, formulated consensus treatment plans for induction therapy of newly-diagnosed proliferative LN. These guidelines were developed in three phases, first phase of the project consisted of an online Delphi survey that was sent to the 103 members of the CARRA SLE Disease Specific Committee and second phase consisted of a formal face-to-face consensus meeting with 32 elected by voting ,experienced pediatric rheumatologists, held over 2 days in April, 2010. Third phase done for finalization through the third Delphi survey with 216 (response rate 137/216=63%) members to achieve CARRA-wide consensus. Final consensus guidelines are shown in table no 8 [55].

Azathioprine is an immunosuppressive drug used in recurrent flare SLE patients when daily requirement of prednesolone is >15 mg [56]. Some international centres are using azathioprine as induction therapy, but outcomes are similar [57, 58]. Some meta-analyses showed superiority of MMF than to IV cyclophosphamide in term of response [59, 60]. But in a larger international randomized, controlled trial with 370 patients with classes III through V LN with both induction phase of 24 weeks and maintenance phase with tapering oral prednesolone

Table 8: CARRA consensus guidelines for treatment of LN [55]

Induction Phase	Immunosuppressive therapy	MMF 600 mg/m2/dose (max dose 1.5 gm, taken two times per day) **OR** i.v. Cyclophosphamide 500 mg/m2/month for 6 months (max dose 1.5 gm)
Maintenance Phase	Glucocorticoids	Oral Oral + i.v. i.v.

did not detect a significantly different response rate between the two groups: 56.2% patients responded to MMF compared with 53.0% in IV cyclophosphamide group [61].

Mycophenolate mofetil suppresses T and B cells which do not attack target organs but weakens the immunity. The ACR guidelines recommend MMF as the preferred agent for African Americans and Hispanics. In certain situations (black and Hispanic patients or to avoid premature ovarian failure), MMF is considered of first choice as induction therapy in LN [33, 34].

Rituximab (RTX) a chimeric monoclonal antibody specific for human CD20, may be effective in patients with WHO type IV LN resistant to conventional immunosuppressive therapies. ACR [62] as well as the EULAR guidelines [44] for the management of LN recommend the use of Rituximab as add on or as monotherapy with resistant disease. Few retrospective case series in children of Greece , Berlin , Germany too revealed the effective use of Rituximab in pediatric LN [63, 64].

Tacrolimus is a more effective Calcineurin inhibitor than cyclosporine and has a much better safety profile. Tacrolimus has been used in both induction as well as maintenance phase [65, 66]. Its role in pediatric lupus nephritis also been studied with good efficacy and safety profile [67].

As per all guidelines review use of hydroxychloroquine should be considered for all lupus patients. It is useful in children with marked skin disease, lethargy and arthritis. Annual eye screening, even in the absence of visual symptoms, is recommended as hydroxychloroquine causes macular toxicity and corneal changes [68]. Antimalarials, not only prevent lupus flares and increase long-term survival but also protect against irreversible organ damage [69, 70].

In very severe and refractory cases not responding to above medication, 5 -10 cycles of plasma exchanges can be considered with few positive outcome reports [71,72].

General Management

Dietary counselling should be done and supplementation with Vit D3, calcium rich diet should be given. Avoid nephrotoxic drugs and NSAIDS [73]. Monitoring of growth using growth charts and pubertal development assessment is important. ACE inhibitors and angiotensin II receptor blockers have been routinely used to treat proteinurea and associated hypertension in LN which helps in delay of kidney deterioration and cardiovascular disease [74,75]. Restrict fat intake or use lipid-lowering therapy such as statins for hyperlipidemia secondary to nephrotic syndrome. Restrict protein intake if renal function is significantly impaired.

Vaccination

Vaccination should be performed, before starting immunosuppressive therapy or if disease in inactive period. Vaccines that can be used are Pneumococcal (23-valent polysaccharide), Influenza, Diphtheria and tetanus (dT) and other inactive vaccines. Live virus vaccines like MMR and herpes zoster should be avoided. Immunisation should be done carefully as it may induce a disease flare [76,77,78,79,80].

Prognosis

With the evaluation of new therapies in the treatment of LN, survival and outcome has improved.

- Complete Response is demonstrated by an inactive urinary sediment, $\geq$ 50 % reduction in proteinuria to subnephrotic levels , decrease in proteinuria to $\leq$ 0.2 g/24 h and normal or near-normal GFR with stable renal function [74].
- Partial Response is a level of improvement, usually defined as an inactive sediment, proteinuria $\leq$ 0.5 g/24 h, with normal or near-normal GFR within 10% of normal GFR if previously abnormal (GFR > 90 mL/min/1.73m^2) or stable renal function with urine protein: creatinine ratio < 50 mg/mmol.
- Sustained Response of at least 3 to 6 months can be regarded as a remission but cannot be judged to be a complete remission in the absence of a biopsy [81].

Poor Prognostic Indicators

1. Delay in treatment of more than 5 months from onset of nephritis
2. Young age at onset of nephritis
3. Male gender
4. Black race
5. Hypertension
6. Nephrotic syndrome
7. Elevated creatinine level (> 3 mg/dL) at presentation
8. Persistently elevated anti-dsDNA and low C3 and C4 levels

9. Renal biopsy findings showing diffuse proliferative GN or high chronicity index.

Few disease activity indices have been developed to measure and validate reversible inflammation which include the British Isles Lupus Assessment Group (BILAG), European Consensus Lupus Activity Measurement (ECLAM), Systemic Lupus Activity Measure (SLAM), SLE Disease Activity Index (SLEDAI), revised versions as SLEDAI-2K and Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) SLEDAI. These indices are used for longitudinal observational studies as well as clinical trials [82].

At diagnosis and after one year patients with both renal and CNS disease had the highest SLE Disease Activity Index (SLEDAI) scores ($P < .0001$) [83].

Repeat renal biopsy at the end of induction is suggested in some studies for prognostic value [84, 85]. Complete remission rates at 6–12 months in various western studies with mixed races were between 8% and 30% [48, 61, 85]. But in Chinese clinical trials complete remission rate was between 60–80% [87, 88]. In a retrospective study of north India, over 20 years renal survival rate was 91%, 81% and 76% at 5, 10, and 15 years, respectively . And in the worst-case scenario, survival was 79%, 70%, and 66%, respectively at 5, 10, 15 years [89].

References

1. Petty RE, Laxer RM. Systemic lupus erythematosus. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB. Textbook of Pediatric Rheumatology. Philadelphia, PA: Elsiever Saunders; 2005.p.342-91.
2. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
3. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.
4. luis Ines, Candida Silva, Maria Galindo et al. Classification of Systemic Lupus Erythematosus: Systemic Lupus International Collaborating Clinics Versus American College of Rheumatology Criteria. A Comparative Study of 2,055 Patients From a Real-Life, International Systemic Lupus Erythematosus Cohort. Arthritis Care & Research 2015 Aug;67(8):1180–1185 DOI 10.1002/acr.22539.
5. Klein-gitelman M, Reiff A, Silverman ED. Systemic lupus erythematosus in childhood. Rheum Dis Clin N Am 2002;28:561-577.
6. Huang JL, Yao TC, See LC. Prevalence of pediatric systemic lupus erythematosus and juvenile chronic arthritis in a Chinese population: a nation-wide prospective populationbased study in Taiwan. Clin Exp Rheumatol 2004;22:776-780 [PMID: 15638056].
7. Malaviya AN, Chandrasekaran AN, Kumar A, Sharma PN. Occasional series-Lupus round the world: systemic lupus Erythematosus in India. Lupus 1997; 6:690-700.
8. Osio-Salido E, Manapat-Reyes H: Epidemiology of systemic lupus erythematosus in Asia. Lupus 2010; 19:1365–1373.
9. Sudhir Mehta. Study of clinical features and outcome of childhood systemic lupus erythematosus. European Journal of Pharmaceutical and Medical Research. 2016;3(2):378-380.
10. Malaviya AN, Singh RR, Singh YN, Kapoor SK, Kumar A. Prevalence of systemic lupus erythematosus in India. Lupus. 1993;2:115-8.
11. W. Jakes, Sang-cheol bae, Worawit Iouthrenoo. Systematic Review of the Epidemiology of Systemic Lupus Erythematosus in the Asia-Pacific Region: Prevalence, Incidence, Clinical Features, and Mortality Rupert. American College of Rheumatology, 2012 Feb;64(2):159–168 DOI 10.1002/acr.20683 © 2012.
12. Li LH, Yuan H, Pan HF, Li WX, Li XP, Ye DQ: Role of the Fcã receptor IIIA-V/F158 polymorphism in susceptibility to systemic lupus erythematosus and lupus nephritis: a metaanalysis. Scand J Rheumatol 2010;39:148–154.
13. L. M. Ortega, D. R. Schultz, O. Lenz, V. Pardo, and G. N. Contreras, "Lupus nephritis: pathologic features, epidemiology and a guide to therapeutic decisions," Lupus, 2010;19(5):557–574.
14. Seligman VA, Lum RF, Olson JL, Li H, Criswell LA. Demographic differences in the development of lupus nephritis: a retrospective analysis. Am J Med 2002;112(9):726-9.
15. Pons-Estel BA, Catoggio LJ, Cardiel MH, Soriano ER, Gentiletti S, Villa AR, et al. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". Medicine Baltimore 2004;83:1–17.
16. Alarcon GS, Bastian HM, Beasley TM, Roseman JM, Tan FK, Fessler BJ, et al. Systemic lupus erythematosus in a multi-ethnic cohort (LUMINA) XXXII: [corrected] contributions of admixture and socioeconomic status to renal involvement. Lupus 2006;15:26–31.
17. Tak-Kuan, Lai-Meng, Phaik-Leng. A comparison of 1995 WHO classification with 2003 ISN/RPS classification of lupus nephritis: a single centre observation. Malaysian J Pathol 2015;37(3):239–246.
18. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB et al. The classification of

glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004;15:241–50.

19. Markowitz GS, D'Agati VD. Classification of lupus nephritis. Curr Opin Nephrol Hypertens. 2009 May;18(3):220-5.
20. Saba Kiremitci and Arzu Ensari. Classifying Lupus Nephritis: An Ongoing Story The Scientific World Journal.Volume 2014 (2014), Article ID 580620, 10 page.
21. Seema H.S. A clinicopathological study of pediatric lupus nephritis in teritary hospital of bangalore. Int J Cur Res Rev 2015 Jun;7(12).
22. Huang JL, Yeh K W, Yao TC , Huang YL, CHUNG HT, Ou L S et al. Pediatric Lupus in Asia. Lupus 2010; 19:1414-18.
23. Das U, Dakshinamurty KV, Prayaga A. Pattern of biopsy proven renal disease in a single center of south India: 19 years experience. Ind J Nephrol 2011;21: 250–7.
24. Gupta K, Muthukumar T, Dotial A, Prasad R, Joshi K, Joshi K et al. A study of tubular Dysfunction in Indian patients with Lupus Nephritis : Hong Kong J Nephrol 2003;5(2):90–7.
25. Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med. 2008;358:929-39.
26. Yazici MU, Orhan D, Kale G, Besbas N, Ozen S. Studying IFN-gamma, IL-17 and FOXP3 in pediatric lupus nephritis. Pediatr Nephrol. 2014;29:853–862.
27. Rosalie M. Sterner, Stella P. Hartono and Joseph P. Grande. The Pathogenesis of Lupus Nephritis. J Clin Cell Immunol. 2014;5(2). doi:10.4172/2155-9899.1000205.
28. Jhong-Yong Wu , Kuo-Wei Yeh, Jing-Long Huang. Early predictors of outcomes in pediatric lupus nephritis: Focus on proliferative lesions. Seminars in Arthritis and Rheumatism 2014;42:513–520. www.elsevier.com/locate/semarthrit.
29. Agarwal I, T Sathish Kumar, Rajniti K, Kirubakaran C , Danda D . Clinical features and outcomes of SLE. Indian Pediatr. 2009;46:711-15.
30. Cameron JS. Lupus nephritis in childhood and adolescence. Paediatr Nephrol. 1994;8:230-49.
31. Font J, Cervera R, Espinosa G, Pallares L, Ramos-Casals M, Jimenez S, et al. Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. Ann Rheum Dis 1998;57:456–9.
32. Sulaiman M. Al-Mayouf, Alhanouf AlSaleem , Turki Al-Hussain. The impact of antiphospholipid antibodies in children with lupus nephritis. International Journal of Pediatrics and Adolescent Medicine2015;2:147e151.
33. Sim_on JA, Cabiedes J, Ortiz E, et al. Anti-nucleosome antibodies in patients with systemic lupus erythematosus of recent onset. Potential utility as a diagnostic tool and disease activity marker. Rheumatology 2004;43(2):220–24.
34. Anup Manoharan, Michael P. Madaio. Biomarkers in Lupus Nephritis; Rheum Dis Clin N Am. 2010;36: 131–143 (rheumatic.theclinics.com).
35. Appenzeller S, Clark A, Pineau C, et al. Isolated pyuria in systemic lupus erythematosus. Lupus 2010;19:793–6.
36. Nossent H, Berden J, Swaak T. Renal immunofluorescence and the prediction of renal outcome in patients with proliferative lupus nephritis. Lupus 2000;9:504–10.
37. Hill GS, Delahousse M, Nochy D, et al. A new morphologic index for the evaluation of renal biopsies in lupus nephritis. Kidney Int 2000;58:1160–73.
38. Esdaile JM, Federgreen W, Quintal H, et al. Predictors of one year outcome in lupus nephritis: the importance of renal biopsy. Q JMed 1991;81:907–18.
39. Whiting-O'Keefe Q, Henke JE, Shearn MA, et al. The information content from renal biopsy in systemic lupus erythematosus. Ann Intern Med 1982;96: 718–23.
40. Whiting-O'Keefe Q, Riccardi PJ, Henke JE, et al. Recognition of information in renal biopsies of patients with lupus nephritis. Ann Intern Med 1982;96:723–7.
41. Evandro Mendes Klumba, Clovis Artur Almeida Silvab, Cristina Costa Duarte Lanna et al. Consensus of the Brazilian Society of Rheumatology for the diagnosis, management and treatment of lupus nephritis. Rev Bras Reumatol. 2015;55(1):1–21.
42. Marks SD, Tullus K. Lupus nephritis. In: Comphrehensive Pediatric Nephrology, Geary DF, Schaefer F, Eds, Mosby Elsevier, Phidelphia, 2008.p. 329-42.
43. Suzanne Wilhelmus1 , Ingeborg M. Bajema1 , George K. Bertsias et al. Lupus nephritis management guidelines compared. Nephrol Dial Transplant 2016; 31:904–913.
44. George K Bertsias, Maria Tektonidou, Zahir Amoura et al. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012; 71:1771–1782.
45. Bertsias G, Ioannidis JP, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2008;67:195–205.
46. Lee HS, Mujais SK, Kasinath BS, Spargo BH, Katz AI. Course of renal pathology in patients with SLE. Am J Med 1984;77(4):612-620.

47. Gourley MF, Austin III HA, Scott D et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med 1996; 125:549–557.

48. McKinley A, Park E, Spetie D et al. Oral cyclophosphamide for lupus glomerulonephritis: an underused therapeutic option. Clin J Am Soc Nephrol 2009;4:1754–1760.

49. Moroni G, Quaglini S, Gallelli B et al. The long-term outcome of 93 patients with proliferative lupus nephritis. Nephrol Dial Transplant 2007;22:2531–2539.

50. Grootscholten C, Ligtenberg G, Hagen EC et al. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. Kidney Int 2006;70: 732–742.

51. Chan TM, Tse KC, Tang CS et al. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol 2005;16:1076–1084.

52. Houssiau FA, Vasconcelos C, D'Cruz D et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis 2010;69:61–64.

53. Wilmer WA, Rovin BH, Hebert CJ et al. Management of glomerular proteinuria: a commentary. J Am Soc Nephrol 2003;14:3217–3232.

54. Jafar TH, Schmid CH, Landa M et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med 2001;135:73–87.

55. Rina Mina, Emily von Scheven, Stacy P. Ardoin et al. Consensus treatment plans for induction therapy of newly-diagnosed proliferative lupus nephritis in juvenile systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2012 March;64(3):375–383.

56. Abu – Shakra, M. ; Shoenfeld, Y. Azathioprine therapy for patient with SLE. Lupus, 2011;10(3):152-153.

57. Marks SD, Sebire NJ, Pilkington C, Tullus K. Clinicopathological correlations of paediatric lupus nephritis. Pediatr Nephrol 2007;22:77–83.

58. Hagelberg, S., Lee, Y., Bargman, J., Mah, G., Schneider, R., & Laskin, C. Long-term follow up of childhood lupus nephritis. Journal of Rheumatology, 2002;29:2635-2642.

59. Walsh M, James M, Jayne D, Tonelli M, Manns BJ, Hemmelgarn BR: Mycophenolate mofetil for induction therapy of lupus nephritis: A systematic review and meta-analysis. Clin J Am Soc Nephrol 2007;2:968–975.

60. Zhu B, Chen N, Lin Y, Ren H, Zhang W, Wang W, Pan X, Yu H: Mycophenolate mofetil in induction and maintenance therapy of severe lupus nephritis: A meta-analysis of randomized controlled trials. Nephrol Dial Transplant 2007;22:1933–1942.

61. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009;20:1103–12.

62. Hahn BH, McMahon M, Wilkinson A, et al. American College of Rheumatology Guidelines for Screening, Case Definition, Treatment and Management of Lupus Nephritis. Arthritis care & research. 2012;64(6): 797-808.

63. Trachana M,Koutsonikoli A,Farmaki E,Printza N,Tzimouli V, Papachristou F Safety and efficacy of Rituximab in refractory pediatric systemic lupus erythematosus nephritis: a single-center experience of Northern Greece. Rheumatology International. 2013;33:809-813.

64. Nwobi O, Abitbol CL, Chandar J, Seeherunvong W, Zilleruelo G. Rituximab therapy for juvenile-onset systemic lupus erythematosus. Pediatric Nephrology (Berlin, Germany). 2008;23:413-419.

65. Mok CC, Ying KY, Yim CW, Siu YP, Tong KH, To CH,Ng WL. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis annrheumdis-2014-206456 Published Online First: 30 December 2014 doi:10.1136/annrheumdis-2014-206456.

66. Yap DYH, Ma MKM, Mok MMY, Kwan LPY,Chan GCQ,Chan TM. Long-term data on tacrolimus treatment in lupus nephritis.Rheumatology 2014;53 (12):2232-2237 first published online July 4, 2014doi:10.1093/rheumatology/keu265.

67. Tanaka H, Tsuruga K, Aizawa-Yashiro T, Watanabe S, Imaizumi T. Treatment of young patients with lupus nephritis using calcineurin inhibitors. World Journal of Nephrology. 2012;1(6):177-183. doi:10.5527/wjn.v1.i6.177.

68. Marmor, MF; Kellner, U, Lai, TY, Lyons, JS, Mieler, WF, American Academy of, Ophthalmology "Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy". Ophthalmology 2011 Feb;118(2):415–22.

69. Thatayatikom A, White AJ. Rituximab: a promising therapy in systemic lupus erythematosus. Autoimmun Rev 2006;5:18–24.

70. Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA. An open study of B lymphocyte depletion in systemic lupus erythematosus. Arthritis Rheum 2002;46:2673–7.

71. Wright EC, Tullus K, Dillon MJ: Retrospective study of plasma exchange in children with systemic lupus erythematosus, Pediatr Nephrol, 2004;19(10):1108-14.

72. Marks SD, Tullus K. Modern therapeutic strategies for paediatric systemic lupus erythematosus and lupus ne-phritis. Acta Paediatr 2010;99:967-974.

73. Praga M. Slowing the progression of renal failure. Kidney IntSuppl. 2002;80:18–22.105.

74. Gordon C, Jayne D, Pusey C, Adu D, Amoura Z, Aringer M, et al. European consensus statement on the terminology used in the management of lupus glomerulonephritis. Lupus 2009;18:257–63.

75. Vachvanichsanong P, McNeil E. Pediatric lupus nephritis :more options, more chances? Lupus 2013; 22:545-553.

76. Siso A, Ramos-Casals M, Bove A, et al. Previous antimalarial therapy in patients diagnosed with lupus nephritis: influence on outcomes and survival. Lupus 2008;17(4):281–8.

77. E. von Scheven, A. Bakkaloglu .What's new in paediatric SLE. Best Practice & Research Clinical Rheumatology 2009;23:699–708.

78. Abu-Shakra M. Safety of vaccination of patients with systemic lupus erythematosus. Lupus. 2009;18: 1205–8.46.

79. Campos LM, Silva CA, Aikawa NE, Jesus AA, Moraes JC,Miraglia J, et al. High disease activity: an independent factor for reduced immunogenicity of the pandemic influenza avaccine in patients with juvenile systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2013;65:1121–7.47.

80. Silva CA, Aikawa NE, Bonfa E. Vaccinations in juvenilechronic inflammatory diseases: an update. Nat RevRheumatol. 2013;9:532–43.48.

81. Reich HN, Gladman DD, Urowitz MB, et al. Persistent proteinuria and dyslipidemia increase the risk of progressive chronic kidney disease in lupus erythematosus. Kidney Int 2011;79:914–20.

82. Lam GKV, Petri M. Assessment of systemic lupus erythematosus. Clin Exp Rheumatol 2005:23(Suppl. 39): S120-32.

83. Hiraki LT, Benseler SM, Tyrrell PN et al. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: a longitudinal study. J Pediatr. 2008 Apr;152(4):550-6. doi: 10.1016/j.jpeds.2007.09.019. Epub 2007 Nov 5.

84. Alsuwaida A, Husain S, Alghonaim M et al. Strategy for second kidney biopsy in patients with lupus nephritis. Nephrol Dial Transplant 2012;27:1472–1478.

85. Pagni F, Galimberti S, Goffredo P et al. The value of repeat biopsy in the management of lupus nephritis: an international multicentre study in a large cohort of patients. Nephrol Dial Transplant 2013;28: 3014–3023.

86. Grootscholten C, Ligtenberg G, Hagen EC et al. Azathioprine/ methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. Kidney Int 2006;70: 732–742.

87. Mok CC, Ho CT, Chan KW et al. Outcome and prognostic indicators of diffuse proliferative lupus glomerulonephritis treated with sequential oral cyclophosphamide and azathioprine. Arthritis Rheum 2002;46:1003–1013.

88. Chan TM, Tse KC, Tang CS et al. Long-term outcome of patients with diffuse proliferative lupus nephritis treated with prednisolone and oral cyclophosphamide followed by azathioprine. Lupus 2005;14: 265–272.

89. Dhir V, Aggarwal A, Lawrence A, Agarwal V, Misra R: Long-term outcome of lupus nephritis in Asian Indians. Arthritis Care Res (Hoboken) 2012;64: 713–720.