Systemic Lupus Nephritis

Pediatric Systemic Lupus Nephritis:
Current Research in Treatment and Outcomes

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By
Kathryn L. Ormsby

WASHINGTON STATE UNIVERSITY – SPOKANE, WA

College of Nursing

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Systemic Lupus Nephritis

To the Faculty of Washington State University:

The members of the Committee appointed to examine the master’s project of Kathryn L. Ormsby find it satisfactory and recommend that it be accepted.

Jacquelyn Banasik, Ph. D., Chair

Ruth Bindler, RNC, Ph.D

Debbie Brinker, MSN
Systemic Lupus Erythematosus (SLE) is a serious and devastating autoimmune rheumatic disease affecting 50 to 100 per 100,000 people in the United States and Europe. SLE has increased threefold over the past 2 decades. Childhood onset of disease (before 19 years) represents 15 to 20% of cases with higher rates of disease reported in females between 12 to 16 years (Paut, Piram, Guillaume, & Tran, 2007). Childhood-onset disease is more aggressive than adult-onset with large studies demonstrating mortality rates almost 8 times greater for patients less than 24 years.

The leading presenting symptoms of SLE are constitutional and non-specific such as fatigue, headache, weight loss or mood swings. These symptoms are also encountered in healthy adolescents, which is a primary reason for delay in diagnosis and treatment. Many children have
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long periods of illness before they receive appropriate treatment placing them at risk for advanced disease and poorer outcomes (Paut et al., 2007).

Lupus nephritis (LN) affects up to 80% of patients with SLE and is a main determinant of pediatric patient outcomes. End-stage renal disease develops in 10 to 15% of lupus nephritis patients with the remainder suffering from various stages of chronic renal impairment (Scheven & Bakkaloglu, 2009). Lupus nephritis is severe in childhood-onset SLE with aggressive renal disease and requirement for higher doses of steroid and immunosuppressive drug treatments. Longer life expectancy from improved chronic disease management has increased awareness of new long-term complications and chronic disease morbidity (Huang et al., 2010; Pogmarutani, Alpert, & Miller, 2006). Providers are challenged in delivering care to these adolescents given their disease severity, cumulative treatment toxicity, and the psychosocial consequences of a chronic illness that occurs during a time of adolescent physical, emotional, and social development (Paut et al., 2007).

Nurse practitioners need to maintain their role as primary care providers for children with SLE and LN to manage ongoing childhood medical care and chronic care of co-morbid conditions. Coordination of care by the NP in a multidisciplinary approach is critical to the management of the child with SLE. The NPs knowledge of the disease process, medications, and treatments utilized in acute management of SLE and LN are crucial to the on-going management of care along the illness trajectory. Nurse practitioners empower the child and family through education, counseling, and supportive care to promote maintenance of optimal function and quality of life.
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**Introduction**

Lupus nephritis is severe in childhood-onset systemic lupus erythematosus resulting in aggressive renal disease, chronic renal impairment, and end-stage renal disease. Chronic irreversible organ damage, accelerated atherosclerosis, and hypertension cause significant morbidity. The majority of children with SLE present to primary care practice with a chief complaint of recurring fevers and other constitutional symptoms of fatigue, headache, weight loss, mood swings and weakness. They are often misdiagnosed as having depression, anorexia nervosa or chronic fatigue syndrome rather than systemic lupus erythematosus (Paut et al., 2007). Nurse Practitioners in primary care are in key positions to identify and promptly diagnose early disease and implement referral and treatment that are critical to the disease outcomes in pediatric patients.

This paper reviews the etiology, pathophysiology, manifestations, and treatment outcomes of pediatric systemic lupus erythematosus and makes recommendations to improve the recognition and care of patients by primary care nurse practitioners. The review of systemic lupus nephritis in children is organized using the Chronic Illness Trajectory Framework by Corbin & Strauss (1991 & 1992). The first stage in the trajectory of illness is pre-trajectory occurring prior to diagnosis when the patient is asymptomatic. This stage emphasizes the importance of illness prevention within a chronic illness framework. Trajectory onset occurs when symptoms appear causing a threat to physical, psychological, or social stability of the individual creating a crisis phase. The period of illness (acute phase) may necessitate active intervention that in the setting of SLE nephritis could mean hospitalization, medication, and symptom management to prevent complications or worsening symptoms. Where interventions
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are successful, a period of stability (stable phase) ensues requiring various interventions aimed at maintaining stability. This would equate with maintenance drug therapy in SLE nephritis. Patients who face challenges to their recovery, either by relapse or failure to respond to treatment (unstable phase), require reappraisal and adaption of new interventions. Those who may at some point be unsuccessful in their recovery efforts experience deterioration in health (unstable & downward phase) to a point of terminal illness (dying phase). This framework is not rigid and each phase can have several subgroups allowing for movement in either direction over a considerable duration of time; however, this paper utilizes three of the eight phases of the Chronic Illness Trajectory Framework to illustrate the illness course of SLE (Burton, 2000).

This chronic illness trajectory framework is useful to describe the chronic relapsing and remitting course of pediatric SLE. Clinicians may utilize this structure to plan and implement necessary interventions according to the child’s illness trajectory stage. This trajectory serves as a reference to assist clinicians in adapting care of the child and family in order to best meet their current and future needs as they move through the illness trajectory stages. The chronic illness trajectory framework will be utilized throughout the literature review to illustrate pediatric SLE nephritis treatment through induction (unstable phase), maintenance (stable phase), and relapse (unstable/downward phase) in response to the trajectory stage of chronic SLE illness.
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Methods

A thorough search of PubMed and CINAHL was conducted looking at peer reviewed articles and meta-analyses from 2005 to 2011 with emphasis on random controlled trials with treatment and outcome data. Key search terms were pediatric systemic lupus, pediatric systemic lupus nephritis, lupus nephritis treatment (further refined using “pediatric”), then further refined using Mycophenolate, cyclophosphamide, and corticosteroid. Further search terms were African American systemic lupus nephritis, Asian lupus nephritis, Hispanic lupus nephritis all of which were further refined using the term “pediatric”. The World Health Organization website was searched to determine treatment guideline recommendations. Thirty-five articles were reviewed with twenty-nine articles selected based on their relevance to this subject. Additionally, eight reference textbooks were explored and one 2011 consensus report was retrieved and reviewed to help clarify the pathology and treatment of pediatric systemic lupus nephritis.
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**Etiology of Lupus Nephritis**

Lupus nephritis is more common in children with SLE than adults, with symptoms commonly manifesting within the first year of diagnosis. The severity and treatment requirements of pediatric lupus nephritis are determined by kidney biopsy and histological grading using the International Society of Nephrology/renal Pathology Society Classification (ISN/RPS) System (Table 1) (Mina et al., 2011). The initial presentation of lupus nephritis may be asymptomatic making the frequency of nephritis at disease onset undetermined. Clinically evident nephritis occurs in 75% of children with the most common initial clinical symptom being microscopic hematuria (79%) (Petty & Laxer, 2005). Variable proteinuria, including nephrotic syndrome is seen in most patients with nephritis (55%), as well as, decreased glomerular filtration (50%), hypertension (40%), and finally, renal failure (1.4%) (Petty & Laxer, 2005). Hypertension may be the initial presenting clinical symptom of glomerulonephritis and when present with peripheral edema, carries a more severe prognosis (Edgerton, 2008). Lupus nephritis class may remit, recur, or change and evolve into a different class and severity over time.

Ethnicity is a risk factor for lupus nephritis. African-American and Hispanic populations with lupus nephritis (LN) have been reported to have poorer outcomes than Caucasians despite advances in immunosuppressive therapy, dialysis, and transplantation. The cause is controversial, but studies have indicated that African Americans and Hispanics with SLE have higher disease activity, risk for relapse, early mortality, and chronic renal disease. African Americans had higher systemic lupus activity scores and more rapid clinical disease progression than other ethnic groups. Additionally, studies have shown that both African Americans and Hispanics have more
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aggressive forms of lupus nephritis (WHO class IV); however, delay in diagnosis and low socioeconomic status are also predictors of diminished survival and poor outcomes (Alarcon, 2008; Burgos, McGwin, Pons-Estel et al., 2011; Contreras, G. et al., 2006). Studies have shown that African Americans have severe presentation of disease with higher serum creatinine, low complement levels (significant depression of C4), thrombocytopenia, anemia, hematuria, hypertension, and proliferative glomerulonephritis all of which are associated with end-stage renal disease. Texas-Hispanic adolescent patients have demonstrated lupus nephritis at a frequency comparable to African-Americans in the general population. Research has determined this association to be genetic (African-American and Amerindian ancestral genes); additionally, persistent proteinuria indicating end-stage renal disease also has a genetic basis in Hispanics (Alarcon, 2008). Asian children with systemic lupus erythematosus most often present clinically with cutaneous rashes, arthritis, hematological involvement, and nephritis (Huang et al. 2010). The occurrence of nephritis varies from 29% to 81% with the most common histopathology being diffuse proliferative glomerulonephritis (WHO Class IV). Studies have shown that Asian children with SLE are more subject to infection with gram negative bacilli bacteremia and have poorer outcomes as a consequence. Recurrent major infections are a predictor of poorer outcome in these children (Huang et al., 2010).

Clinically evident symptoms of pediatric systemic lupus nephritis may be absent or subtle with presenting symptoms in children of microscopic hematuria, variable degrees of proteinuria, or hypertension. Clinical presentation and aggressiveness of symptoms vary with ethnicity with studies indicating genetic, socioeconomic, as well as, diagnostic delays as predictors of poor outcomes in children.
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Pathophysiology of Systemic Lupus Erythematosus

Systemic lupus erythematosus is a systemic multi-system autoimmune disease with widespread inflammation of blood vessels and connective tissues. The presence of antinuclear antibodies (ANA) and double stranded DNA (anti-ds-DNA) are highly specific for SLE; additionally, anti-Smith antibodies are seen in 10% to 30% of patients with SLE. These antibodies are highly associated with lupus nephritis as is the consumption of complement proteins C3 and C4. Serum inflammatory markers are more discrepant with marked erythrocyte sedimentation rate elevation and slight elevation of C-reactive protein (CRP) except in cases of serositis or infection in which CRP elevation is marked (Paut et al., 2007). The etiopathogenesis involves abnormal antibodies and polyclonal B cells; however the disease etiology is not completely understood. Genetic propensity because of human leukocyte antigens, sex hormones, environmental exposure such as sun, infection, and certain drugs, such as sulfa antibiotics, are considered predisposing factors. The disease is characterized by disordered immunity involving auto-reactive B and T lymphocytes. Auto-antibodies form immune complexes with tissue antigens. These immune complexes accumulate in small vessels of organs where they stimulate local inflammation by activation of complement pathways and cause consumption of complement. Hypocomplementemia (C3 and C4 deficiency) is found in three quarters of SLE patients and if present may help with a lupus nephritis diagnosis. Mast cell degranulation and local infiltration of macrophages and neutrophils causes further tissue damage. Additionally, there is an inability of T-cells to suppress the B-cell clones because of T-cell dysregulation. Excess CD4+T-cell activity and deficient CD8+ cytotoxic/suppressor function are present. Another immune system defect in SLE involves abnormal control of apoptosis and defective
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clearance of cellular debris creating cellular antigen exposure and inciting further immune response. (Benseler & Silverman, 2005; Nester, Thomas, & Gipson, 2007; Petty & Laxer, 2005; Pongmarutani, Alpert, & Miller 2006; Paut et Al., 2007). Lupus nephritis is an immune complex-mediated disease that results from immune system disorder and dysregulation resulting in widespread inflammation and immune-complex induced kidney damage (Petty & Laxer, 2005).
Clinical Manifestations

The majority of children with SLE present to primary care practice with a chief complaint of recurring fever that is mild to moderate (99.5 to 101.5° F) with occasional high fevers ranging from 102.0 to 105.0° F. Other clinical features at presentation are constitutional symptoms that can include fatigue, weight loss, and anorexia; additionally, clinical features include photosensitivity, and evidence of diffuse inflammation such as lymphadenopathy and hepatosplenomegaly. Abdominal pain occurs frequently in children and is caused by serositis or vasculitis. Other symptoms include muscle pain and inflammation which can occur in the presence of systemic vasculitis (Pongmarutani et al., 2005).

Cutaneous symptoms include malar rash (butterfly) or discoid rash; additionally, scarring alopecia (chronic hair loss), and mucosal ulcerations are frequent in childhood SLE. The malar rash occurs in one third to one half of children at the onset of disease and is considered highly suggestive of SLE (Benseler & Silverman, 2005). The rash is usually raised and well demarcated with sparing of the nasolabial folds (Petty & Laxer, 2005). Maculopapular rashes in SLE can occur anywhere on the body as a manifestation of vasculitis. They frequently occur in sun exposed areas of the face and upper chest (Petty & Laxer, 2005).

Musculoskeletal symptoms affect most children with SLE and include polyarthralgias and deforming erosive arthritis involving the small joints of the hands, wrists, elbows, shoulders, knees, and ankles. Arthralgias, arthritis, myalgias, and myositis occur in nearly 86% of children (Nester, et al., 2007). Joint pain can be severe, persistent, and migratory resulting in the child’s loss of range-of-motion. Myalgia is characteristic of the acutely ill patient and is most prominent.
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proximally; additionally, it is related to presence of systemic vasculitis and involvement of the viscera (Petty & Laxer, 2005).

Common cardiovascular symptoms include accelerated atherosclerotic heart disease, hyperlipidemia, and dyslipidemia. These findings along with hypertension and elevated homocysteine levels result in increased risk of ischemic heart disease and myocardial infarction with disease onset often asymptomatic (Pongmarutani et al., 2006). Studies have demonstrated that patients with SLE can develop myocardial ischemia as early as 20-30 years of age (Von Scheven & Bakkaloglu, 2009). Other common vascular symptoms include small and medium blood vessel vasculitis and Raynaud’s phenomenon which is a vasospastic structural disease frequently found in childhood SLE. Thrombotic events occur in 54% of children with SLE and often involve the lower extremities (Petty & Laxer, 2005). Children with SLE thrombotic events may have antiphospholipid antibodies, yet another diagnostic criteria of SLE which requires life-long anticoagulation (Petty & Laxer, 2005). Pericarditis and pericardial effusion are the most common cardiac manifestations occurring in 30% of children with acute SLE. Pleuropulmonary disease occurs commonly with plural effusion from inflammatory pleuritis or nephrotic syndrome; additionally, pneumonia and chronic interstitial lung disease (pulmonary fibrosis and infarction), are frequent findings. Studies demonstrate respiratory symptoms occur in 77% of children with SLE. Symptoms include cough, chest pain, dyspnea, and orthopnea (Petty & Laxer, 2005).

Central nervous system disease occurs in 20% to 95% of children with SLE (Petty & Laxer, 2005). Neuropsychiatric manifestations that occur most frequently include depression, concentration difficulties, and memory deficits. Other CNS manifestations are cerebral vascular
accident, cognitive impairment, seizures, and chorea. Vascular or migraine-like headaches are the most common with pain that is severe and unremitting.

Hematologic manifestations of childhood SLE are leukocytosis, thrombocytopenia, and hemolytic anemia. Normochromic and normocytic anemia’s are also common. Petechiae and purpura rash may result from thrombocytopenia or as a consequence of SLE related vasculitis (Benseler & Silverman, 2005; Nester et al., 2007; Paut et al., 2007; Petty & Laxer, 2005; Pongmarutani et al., 2006).

Diagnosis of SLE is based on both clinical and laboratory findings and the exclusion of other autoimmune diseases. Most patients have at least 4 or more of the 11 classification criteria of the 1997 update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus (Table II). Patients who do not meet all 4 criteria should not be excluded because the majority of these patients with incomplete SLE (< 4 criteria) will likely fulfill these criteria in subsequent years. These criteria are not strict diagnostic criteria rather; they are classification criteria for research purposes. There are few studies that validate ACR criteria use in international/multiethnic populations; therefore, caution is needed when applying ACR criteria to multiethnic populations (Callender, 2012).
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**Treatment Modalities**

There are no large randomized controlled trials in children; therefore, no drug to date has received Food and Drug Administration approval for treatment of pediatric lupus nephritis (LN). The superiority, dosing, efficacy, and safety of SLE drugs in children have not been determined (Mina et al., 2011; Pereira et al., 2011). Treatment of children relies on the off-label use of medications that are approved for immunosuppression following pediatric kidney transplant, treatment of solid organ tumors, or drugs that have been found effective in adults (Mina et al., 2011; Pereira et al., 2011). The following treatment modalities are specific to the management of lupus nephritis.

Corticosteroids are the first line treatment for SLE nephritis because of their rapid immunosuppressive and anti-inflammatory effects. High doses of corticosteroids may be required during remission induction or for control of severe SLE symptoms of nephritis, CNS and pulmonary disease. Low dose therapy is usually sufficient to control constitutional symptoms, dermatitis, serositis, arthritis, and hemolytic anemia. However, reversal of erythrocyte sedimentation rate (ESR) elevation, anti-sdDNA antibodies, and complement deficiency may take months. Weaning steroids once disease is controlled, or the addition of aggressive steroid reducing immunosuppressants in refractory disease, is imperative to minimize glucocorticoid toxicity. The benefits of corticosteroids in children are balanced by adverse effects of long-term use. Children are at risk for profound linear growth retardation as well as increased risk of infection. Initial manifestations of infection are often masked. Adverse reactions to corticosteroids include Cushing’s syndrome, hypertension, diabetes mellitus, premature atherosclerosis, osteoporosis, avascular necrosis, psychosis, acne, hirsutism and striae. In
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adolescents, these cosmetically undesirable signs may result in medication non-compliance which can have life-threatening consequences (Adams, MacDermott, & Lehman, 2006; Petty & Laxer, 2005).

There remains debate over optimal route and dose of corticosteroids in lupus nephritis therapy. In n=15 pediatric patients with biopsy-proven diffuse proliferative glomerulonephritis treated with oral prednisone (2 mg/kg/day), compared with n=6 patients receiving six daily pulses of methylprednisone (30 mg/kg/day to maximum of 1 g/day) followed by the same oral dose of prednisone, a more rapid clinical improvement was seen in the IV pulse group. A later study compared IV methylprednisolone and low-dose daily prednisone to high-dose (2 mg/kg/day) prednisone in patients with SLE nephritis. High dose was weaned to 0.2 mg to 0.5 mg/kg/day after remission. Relapse patients were treated with 20 mg/kg on alternate days and continued the pre-pulse dose of prednisone. There was no significant difference between the patients in each phase of treatment. The study design was unusual in that patients served as their own controls and received different treatment regimens at different points in their clinical course making specific conclusions difficult to identify (Adams et al., 2006).

Cyclophosphamide (CYC) has been considered the gold standard therapy for WHO class IV diffuse proliferative glomerulonephritis. It is a cytotoxic alkylating immunosuppressant agent that affects all tissues that have high proliferative activity (skin, intestines, and neutrophils). It is an effective treatment for inducing remission in lupus nephritis. Whether oral or IV pulses are more effective remains inconclusive; however, IV pulses reduce cumulative exposure to cyclophosphamide decreasing frequency of cytopenias, enhances bladder protection, and avoids problems of non adherence (Bomback & Appel, 2010). Randomized controlled trials (n=90) at
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the National Institute of Health established that six pulses of IV cyclophosphamide (IVC) (0.5 to 1 g/m²) on consecutive months, followed by every third month follow-up pulses with low dose corticosteroids, was effective and prevented relapses better than a shorter regimen limited to six doses alone. A subsequent controlled trial established that pulse cyclophosphamide when given with monthly pulses of methylprednisolone led to better glomerular filtration rate (GFR) than either regimen alone. However, side effects were significant in both therapeutic arms of this study and included ischemic and valvular heart disease, avascular necrosis, osteoporosis, and gonadal failure. Major infections occurred in 33% of subjects treated with cyclophosphamide alone and 45% in subjects treated with cyclophosphamide and steroids (Adams et al., 2006; Bomback & Appel, 2010; Lee, Woo, Choi, Ji, & Song, 2010; Yildirim-Toruner & Diamond, 2010).

Other serious adverse affects to cyclophosphamide include hemorrhagic cystitis, gonadal toxicity, bone marrow suppression, syndrome of inappropriate antidiuretic hormone, nausea, vomiting, and teratogenic potential. Optimal dosing regimens in children have not been determined; however, the standard dosing is pulsed intravenous high-dose CYC therapy followed by quarterly doses in combination with steroids (Lee, Woo, Choi, Ji, & Song, 2010; Yildirim-Toruner & Diamond, 2010).

Mycophenolate mofetil (MMF) is an immunosuppressant that is a selective inhibitor of T cell and B cell proliferation. It has been used for years in human organ transplantation and is has been studied in severe LN to reduce therapy-related toxicities. MMF is considered as an alternative to IVC for induction therapy in severe lupus nephritis. Several recent controlled trials and subsequent meta-analyses, recommend MMF as a first-choice regimen for inducing a
remission in severe active proliferative lupus nephritis. Random controlled trials suggest MMF is more efficacious with a better safety profile; however, adverse reactions include nausea, vomiting, and diarrhea; minor infectious episodes and rare cases of leukopenia (Yildirim-Toruner & Diamond, 2010).

Rituximab is a chimeric anti-CD20 monoclonal antibody which was developed for the treatment of B cell lymphoma. Rituximab depletes B cells by binding to CD 20 antigen and mediating B cell depletion and preventing renewal of autoantibodies and antigen presentation by pathogenic B cells. It is useful in inducing remissions in some patients with severe lupus nephritis who have failed cyclophosphamide or MMF therapy; however, data from two randomized controlled trials in which rituximab or placebo were added to standard immunosuppressive regimens failed to show a benefit. The Lupus Nephritis Assessment with Rituximab trial randomized n=140 patients to rituximab or placebo added to a full dose of MMF (up to 3 g/day) and tapering doses of corticosteroids (gradual dose reduction over 24 weeks). More subjects in the rituximab group achieved remission or partial remission; however, there was no statistical significance in the primary clinical endpoint (remission) (Bomback & Appel, 2010). The role of rituximab remains unclear but it may be useful in treating resistant patients, preventing flares, or reducing the number of immunosuppressive doses required. Protocols for treatment in children are derived from adult data and are center specific (Bomback & Appel, 2010; Nwobi, Abithol, chaundar, et al. 2007; Trachana, Koutsonikoli, Farmaki, Printza, Tzimouli, & Papachristou, 2011).

Lupus nephritis is a condition of no single etiology, and there is no single cure. Corticosteroids are the first-line in treatment of pediatric LN, but they are being increasingly
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superseded by cytotoxic drugs and corticosparing agents. (Adams et al., 2006). Pediatric patients
with LN and chronic SLE present to primary care clinics to receive other wellness focused care;
therefore, primary care over-sight is imperative. Nurse practitioners, caring for these patients,
need to be increasingly aware of the potential long-term implications of chronic use of
corticosteroids, immunosuppressive agents, and immune modulator medications (disease-
modifying antirheumatic drugs). Knowledge of these agents and their long-term adverse effects
is critical to providing on-going wellness care to children who are now surviving until well into
their adult years with chronic kidney disease and other secondary morbidities related to SLE.
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Induction: Acute Phase Management

Treatment is divided into several phases, including induction; acute treatment of severe disease; maintenance; long-term management of chronic indolent disease; and treatment of relapses (Von Scheven et al., 2009). Acute phase management requires induction which utilizes intense immunosuppression aimed at achieving remission with resolution of active inflammatory changes (Mina et al., 2011; Pereira et al., 2011).

A 24 week randomized, open-label, non-inferiority trial comparing oral mycophenolate mofetil (MMF) (initial dose, 1000 mg per day, increased to 3000 mg per day) with monthly intravenous cyclophosphamide (0.5g per square meter of body-surface area, increased to 1.0 g per square meter) as induction therapy for active lupus nephritis. The study purpose was to determine if MMF is more effective in treating lupus nephritis. A change to the alternative regimen was allowed at 12 weeks for lack of early response. The study specified adjunctive care, and use of tapering corticosteroids. The end point was complete remission at 24 weeks (normalization of abnormal renal measurements and maintenance of baseline normal measurements). A secondary end point was partial remission at 24 weeks. The sample size (n=140) with (n=71) randomly assigned to MMF, and (n=69) assigned to cyclophosphamide. In the intention-to-treat analysis 16 of the 71 (22.5%) receiving MMF and 4 of the 69 (5.8%) receiving cyclophosphamide had complete remission. Partial remission occurred in 21 of the 71 (29.6%) patients receiving MMF and in 17 of the 69 (24.6%) patients receiving cyclophosphamide. Three patients assigned to cyclophosphamide group died, two during protocol. The MMF group had fewer severe infections and hospitalizations but more diarrhea. In conclusion, MMF was more effective than intravenous cyclophosphamide. Study limitations
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included non-blinded treatment assignment. Low rate of cyclophosphamide response may have been because of inability to reach NIH protocol dosing; additionally, the study duration was short with restriction to induction therapy (Ginzler et al., 2005).

Appel et al. (2008) conducted a 24 week randomized controlled trial comparing mycophenolate mofetil (MMF) to intravenous cyclophosphamide (IVC) for induction treatment for active lupus nephritis in a multi-national, two phase (induction and maintenance) study. The purpose of this study was to test whether MMF was superior to IVC for the primary end point of a decrease in urine protein/creatinine ratio and stabilization or improvement in serum creatinine. The sample of (n=370) ages 12 to 75 years with classes III through V glomerulonephritis were randomly assigned to open-label MMF (target dose 3 g/day) or IVC (0.5 to 1.0 g/m² in monthly pulses). Both groups received prednisone (60 mg/day maximum) dose taper with the primary end point pre-specified decrease in urine protein/creatinine ratio and stabilization or improvement in serum creatinine. Secondary end points were complete renal remission, systemic disease activity and disease damage (Systemic Lupus Erythematosus Disease Activity Index), and safety. No significant difference between the groups was found. One hundred four (56.2%) of 185 patients responded to MMF compared to 98 (53.0%) of 185 to IVC. Secondary end points were similar. There were nine deaths in the MMF group and five in the IVC group (seven due to infection none due to SLE) with no significant difference in rates of adverse events or infections. The most common adverse events in both groups were infection and gastrointestinal disorders. A sub-analysis of this study identified statistically significant number of patients who were Black, Latin American mixed race, or Hispanic who had less response to IVC than MMF. Overall, this study indicated that these drugs in combination with prednisone have a similar efficacy in short-term
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induction therapy. Complete remission rates were low for both groups. Study limitations included unavailable data from previous therapies and open label design due to adverse effect (AE) profiles of the two study drugs which would interfere with attempted blinding; however, the randomization of patients to treatment groups was thought to mitigate bias as a result of study design.

Lee, Woo, Shoi, Ji, and Song (2010) performed a meta-analysis of random controlled trials using data from MEDLINE and Cochrane Controlled Trials Register from 1990 to 2009. The aim was to assess the efficacies and toxicities of immunosuppressive treatments for LN versus cyclophosphamide (CYC). The meta analysis included MMF and CYC induction therapies, between MMF and azathioprine (AZA) as maintenance therapies, and between low-dose and high dose intravenous cyclophosphamide (IVC). Subjects were biopsy-proven LN class III, IV, or V. There were a total of ten studies with an experimental sample size (n=450) and control group size (n=441). Six studies addressed LN induction therapy, two addressed maintenance, and two were meta-analyses of low-dose versus high-dose IVC therapy in LN; additionally, six studies compared MMF and CYC induction therapies. Follow-up periods in induction therapy ranged from 6 to 12 months, in maintenance therapy from 39 to 72 months, and in low-dose IVC versus high-dose IVC therapy from 12 to 60 months. The results indicated that MMF did not increase complete or partial remission rates as compared to CYC; however, the relative risks (RR) of amenorrhea and leukopenia tended to be lower in the MMF group. Meta-analysis of MMF versus AZA in maintenance therapy showed no difference in response rates or risks in development of end-stage renal disease. Low dose IVC therapy had lower relapse rates than high-dose and was associated with lower risk of infection. Limitations of this meta-analysis
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are the small number of trials and small sample size. The possibility of publication bias exists; additionally, heterogeneities in clinical features such as race, age, sex, renal impairment, proportion of renal classification, and definition of remission confused the meta-analysis findings (Lee et al., 2010).

Acute phase management requires intense immunosuppression aimed at achieving remission. Corticosteroids are considered first-line therapy in achieving remission and are used in concert with immunosuppressive drugs. CYC is widely considered the gold standard immunosuppressive induction agent for lupus nephritis; however, optimal dose and duration of therapy remains uncertain in children (Adams et al., 2004). MMF is considered an alternative to CYC with demonstrated anti-inflammatory effects; however, its long-term efficacy in comparison with other regimens in the treatment of children is unclear (Adams et al., 2004). Currently, there are no recommendations for the use of immunosuppressive agents in the treatment of children, and the choice for the type and duration of use of immunosuppressants is also not standardized (Adams et al., 2006). These clinical trials are an attempt to maximize therapeutic drug regimens to achieve remission while minimizing their adverse effects to children.
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**Ethnicity: Acute Phase Management**

Pereira et al. (2011) conducted a retrospective analysis comparing renal and patient survival in a group of pediatric patients followed over three decades. The sample size was 138 patients with childhood onset SLE from 1980 to 2010. A core cohort included 95 with severe LN by biopsy with WHO class III or higher histology: 28 progressed to end-stage renal disease (ESRD group); 67 did not (no-ESRD group). Patients were stratified into four eras according to the primary immunosuppressive drug introduced. Era one was: Triple oral therapy with corticosteroids (CS) at 1 mg/kg/day, cyclophosphamide (CYC) at 1 mg/kg/day, and azathioprine (AZA) at 1 mg/kg/day. Patients were maintained on triple drugs with taper and discontinuation due to drug toxicity or recovery. Era two regimen was: Intravenous CYC at 500 mg/m² per dose, maximum of 1 g for six consecutive months and methylprednisolone (MP) at 15 to 30 mg/kg per dose X 3, maximum of 1 g. Era three was: Mycophenolate Mofetil (MMF) was used at the onset of nephritis and was maintained at 300 to 600 mg/m²/day in 31 patients ± CYC (for 17 of 31 patients) for six consecutive months. Era four was: Rituximab (RTX) at 187.5 mg/m² for one dose followed by 375 mg/m² for three weekly doses for (n=23) patients in combination with IVC and / or MMF. The mean age of diagnosis was 12.3 ± 2.9 years with the median follow up of five years. Poor renal function (GFR < 60 ml/min per 1.73 m²) and nephrotic proteinuria at diagnosis heralded poor prognosis. Increased proteinuria correlated with progression of kidney disease. Patients in all four areas received low-dose daily maintenance oral corticosteroids (0.25 mg/kg/day). After era 1 all patients received methylprednisolone at induction and with relapses. Patients in mid era 2 received angiotensin-converting enzyme inhibitors (ACE Is) or angiotensin receptor blockers (ARBs) along with hydroxychloroquine. The results were evident in era three with the
addition of MMF which improved 5-year renal survival from 52% to 91% and overall patient survival from 83% to 97%. Additionally, nearly 90% of the study group was of non-caucasian ethnicity with 56% African American, 29% Hispanic, and 4% Asian, and 11% Caucasian. Diffuse proliferative nephritis was the most common histology in 73% of participants. Given this unique patient population, the response to MMF was thought to be race/ethnicity related. The limitations of this study were the disproportionate ethnicity creating bias, as well as, inadequate examination of long-term consequences of treatment regimens.

The ALMS study was a prospective, randomized, open-label, parallel-group, multicenter clinical trial whose objective was to compare the efficacy and safety of MMF and IVC as induction treatment for lupus nephritis, by race, ethnicity, and geographical region. Study methods included a sample of 370 patients ages 12 to 75 years who fulfilled the American College of Rheumatology (ACR) criteria for active Class III-V LN (Table 3). Subjects received MMF (target dose 3.0 g/day) or IVC (0.5-1.0 g/m²/month), plus tapered prednisone, for 24 weeks. Renal function, global disease activity, complements (C3 and C4), and anti-dsDNA levels were the outcomes assessed. The results were similar to other studies in that MMF was not superior to IVC as induction treatment (primary objective). MMF and IVC response rates were similar for Asians (53 vs 63.9%) and Caucasians (56.0 vs 54.2%), but differed in the Black and other groups. Fewer patients in the Black (40 vs 53.9%) and Hispanic (38.8 vs 63.9%) groups responded to IVC. Latin American subjects responded even lower to IVC (32 vs 60.7%). Baseline disease was not predictive of response and the incidence of adverse events were similar across groups with the exception of Asians. Patients from Asia had fewer overall infections but those infections were more likely to result in hospitalization or death. This study was not
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powered to detect an effect of a specific region, race or ethnicity. Small sample size in each ethnic subgroup does not allow for generalization of findings to the larger population (Isenberg et al., 2010).

Ethnicity is a risk factor for lupus nephritis in disease presentation, aggressiveness, and responsiveness to treatment. Retrospective studies have examined the use of corticosteroids, CYC, RTX, and MMF as induction therapies in predominantly non-caucasian samples. The outcomes demonstrated different remission response rates to immunosuppressive agents by ethnicity; additionally, adverse drug effects were equally varied by ethnicity. These study designs and small sample sizes made study outcomes difficult to generalize; however, they have helped to guide future research and therapeutic treatments in pediatric ethnic populations.
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Maintenance: Stable Phase Management

Maintenance therapy is long-term management of indolent disease which requires less intense immunosuppression. Drug regimens are used to sustain remission of lupus nephritis while minimizing side effects associated with immunosuppression (Mina et al., 2011; Pereira et al., 2011).

Azathioprine (AZA) is a purine analog that suppresses cell-mediated immunity by interfering with DNA synthesis and is often used in maintenance therapy after initial control of lupus nephritis. AZA has had a major role in the treatment of SLE mainly as a corticosteroid-sparing agent. AZA is inactive until it is metabolized to mercaptopurine by the liver and erythrocytes, at which point it inhibits DNA synthesis and cell proliferation in the immune system. Toxicity to the gastrointestinal tract, oral ulcers, nausea, vomiting, diarrhea, and epigastric pain are the common adverse effects (Yildirim-Toruner & Diamond, 2010).

A retrospective study aimed to evaluate the efficacy of short-term intravenous (IV) CYC treatment as a remission induction treatment followed by AZA or MMF as a maintenance treatment. The sample included 25 patients with biopsy proven class III (n=5) and IV (n=15) lupus nephritis. The mean age was 16.11 ± 3.49 years with a mean duration of follow-up of 49.6 ± 27 months. All received three methylprednisolone (MP) IV pulses, followed by oral prednisone 0.5-1.0 mg per day and one IV pulse of CYC per month for six months. AZA was started as a remission-maintaining treatment. Ten of 20 patients were switched to MMF. Fourteen patients (79%) had complete remission, three (15%) had partial remission; one (5%) continued to have active disease and two (10%) progressed to end-stage renal disease. Nine of the patients (45%) with complete remission had received AZA. The result demonstrated that a short-term (6
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month) IV bolus CYC treatment followed by AZA is a safe and effective treatment in children with severe lupus nephritis and demonstrated overall improvement in serological and clinical disease manifestations. The main study limitation was lack of comparisons between possible different treatment groups. Other limitations were small sample size, relative short follow up, and lack of prospective randomized study comparing MMF and AZA as maintenance therapy (Baskin et al., 2010).

A recent 36 month prospective, randomized, double-blind, phase 3 study was conducted comparing MMF (2 g/day) with AZA (2 mg/kg/day), plus placebo in each group, for the maintenance of remission in patients with lupus nephritis. Up to 10 mg of prednisone per day or its equivalent was permitted. The primary efficacy end point was the time to treatment failure (defined as death, end-stage renal disease, doubling of the serum creatinine level, renal flare, or rescue therapy for lupus nephritis). Patients were 12 to 75 years with active class III, IV, or V lupus nephritis who had clinical response to either mycophenolate or cyclophosphamide during the induction study. Participants (n=227) were randomly assigned to one of two agents in the maintenance study (n=116 to MMF and n=111 to AZA). Observed rates of treatment failure were 16.4% (19 of 116 patients) in the MMF group and 32.4% (36 of 111) in the AZA group. Adverse events, most often minor infections and gastrointestinal disorders, occurred in more than 95% of subjects in both groups. Serious adverse events occurred in 33.3% of patients in the AZA group and 23.5% in the MMF group with the rate of withdrawal because of adverse events being higher in the AZA (39.6%) than in the MMF (25.2%) group. MMF was superior to AZA in maintaining a renal response to treatment and in preventing relapse in patients with lupus nephritis who had a response to induction therapy. Study limitations were that few repeat renal biopsies were
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performed during the study which limits the ability to draw conclusions about possible treatment benefits with respect to active or chronic disease. Additionally, the study was not powered to draw conclusions about subsets of patients (Dooley et al., 2011).

Azathioprine in doses of 1 to 2.5 mg/kg/day has proven safety over a long period of follow-up. Macrocytosis, leukopenia at high doses, and interaction with allopurinol are potential side effects; in addition to the, risk of infection from immunosuppression. AZA has a small oncogenic potential and is relatively safe during pregnancy as a maintenance drug in comparison to other immunosuppressive agents. MMF has a more favorable safety profile; however, it should not be given during pregnancy which is an important consideration given that many lupus nephritis patients are adolescent and young women (Bomback & Appel, 2010).

Antimalarial agents, hydroxychloroquine and chloroquine are both 4-amino-quinolines; hydroxychloroquine is an analog of chloroquine. Antimalarial agents are a part of the immunomodulatory regimen used to treat SLE due to their anti-inflammatory, immunosuppressive, and photo-protective ability. Specifically, these agents might alter lysosome stability, suppress antigen presentation, inhibit prostaglandin and cytokine synthesis, and influence both Toll-like receptor signaling and leukocyte activation. The Hopkins Lupus Cohort and the LUMINA (Lupus in Minorities: Nature Versus Nurture) nested control study in adult African American and Caucasian populations, showed hydroxychloroquine use was associated with a long-term protective effect on end-organ damage and improved survival. (Lee, Silverman, & Bargman, 2011). In LN, antimalarial use is associated with reduced corticosteroid use, reduced disease activity, and extended time to end-stage renal disease. Treatment during pregnancy is associated with reduction in risk of cardiac manifestations of neonatal SLE. Safety
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profile is good with the most common adverse effects being gastrointestinal symptoms and retinopathy risk for patients taking agents greater than five years (Lee et al., 2011).

Renin angiotensin aldosterone blockade is recommended by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative. Studies have shown drugs such as ACE inhibitors control blood pressure, delay renal disease, and reduce or eliminate inflammation in lupus nephritis. De Albuquerqu et al. (2004) treated lupus prone mice with captopril and found delayed onset of proteinuria. In vitro exposure to captopril reduced IL-4 and IL-10 suggesting an effect on the immune system. These results were not seen in the Verapamil control group. A recent experiment on aldosterone blockade and the development of glomerulonephritis in a murine model of lupus demonstrated that spironolactone significantly reduced the incidence of nephrotic range proteinuria and on histology showed far less severe glomerular injury. (Bomback & Appel, 2010).

Maintenance therapy is long-term management of indolent disease with less intensive immunosuppression than induction regimens, whereby immunosuppressive drugs are used to sustain remission of lupus nephritis while minimizing side effects associated with treatment. (Mina et al., 2011; Pereira et al., 2011). Maintenance also involves symptom control; specifically, blood pressure and immune modulation with the outcome of end organ preservation.

These studies both retrospective and prospective examined MMF, CYC, AZA, in combination with corticosteroids to determine which was superior in maintaining remission. The outcomes were that MMF was superior to AZA in remission maintenance and demonstrated fewer serious adverse drug effects. Additionally, AZA, and hydroxychloroquine have
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demonstrated relative safety during pregnancy which is an important treatment consideration
given the disproportionate number of adolescent females with SLE lupus nephritis.
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**Unstable and Downward Phase Management**

The prevalence and significance of disease remission and relapse in children with lupus nephritis in the United States is poorly understood. End-stage renal disease affects 10 to 50% of SLE patients with lupus nephritis; additionally, treatment resistance is highly predictive of end stage renal disease as are nephritic flares. Unfortunately, most studies are small, single-centered reports with outcome data that is difficult to generalize to demographically diverse populations (Gibson et al. 2009).

Gipson et al., (2009) conducted a retrospective study of predominantly African American children, adolescents, and young adult patients with proliferative stage III to V biopsy proven lupus nephritis (ACR criteria). Patients were compared for partial versus complete treatment response and predictors of relapse. Cox regression models were used to evaluate predictors. The sample size was 73 from 6 to 21 years with female to male ratio 5:1. The mean follow up time was 55.4 ± 51.6 months. African Americans represented nearly two-thirds of the participants. Among the African Americans 70% had ACR class IV compared with 17% with class III, and 13% with class V disease. Overall, 65 (89%) had response to induction, while 8 (11%) were treatment resistant. Among responders, partial response in 47 (72%), was more common than complete response in 18 (28%). Treatment resistant participants (n=8) were all African American who had significantly reduced GFR at presentation, supporting the likelihood of delayed diagnosis and increased chronicity at initial diagnosis. Treatment resistance among individuals of African American descent has been described in areas with universal access to health care, supporting the presence of risk factors independent of socioeconomic disparities (Gipson et al. 2009). Of the 65 who responded to therapy, 23 (35%) experienced a renal relapse, with over one-
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third relapsing within 5 years of diagnosis (mean time to first relapse episode 44.6 ± 32mo). This study was unable to identify statistically significant predictors of relapse; however, the risk of relapse in African American patients was 32% lower than in Caucasians. Kidney survival at 5 years was 77% with treatment resistance highly predictive (tenfold risk) of end-stage kidney disease.

The study strengths were sample size; additionally, the length of follow-up (55 ± 51mo) and the ability to capture relapses and end stage kidney disease. The study weaknesses were the retrospective study design creating possible biases and the use strict definitions for partial and complete remission creating potential for variance in patient classification (Gipson et al. 2009).

Major predictors of poor renal outcome remain African American ethnicity, low glomerular filtration rate (< 60 ml/min per 1.73 m²), and nephrotic-range proteinuria (urine protein/creatinine ratio > 1.0) at the time of diagnosis with persistent proteinuria correlating with progression of kidney disease (Pereira et al., 2011). Although studies demonstrate improved 5-year survival, the leading cause of death continues to be attributable to infection and presumably from overimmune suppression which occurs in as many as 70% of pediatric patients (Pereria et al., 2011). This could possibly reflect a continued misplaced emphasis on disease control in deference to patient safety. Additionally, other studies have shown that cardiovascular disease constitutes the second-leading cause of mortality (Pereria et al., 2011).

End stage renal disease effects up to 50% of children with SLE nephritis. Treatment resistance and frequency of nephritic flares (relapse) are highly predictive of end-stage renal disease; additionally, heavy proteinuria at the time of initial diagnosis as well as persistent proteinuria that is unresponsive to treatment correlates with disease progression (Pereira et al.,
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2011). Delays in diagnosis and treatment, as well as low socioeconomic status are also associated with advanced disease and poor outcomes. Research has determined that infection and cardiovascular disease remain the leading cause of mortality in pediatric SLE and LN patients.
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Implications for Nurse Practitioners

Acute Phase Management

Nurse practitioners are key in the timely diagnosis of SLE and LN by thorough expertise in history and physical examination, as well as use of a broad differential diagnosis. Although there is no gold standard for diagnosis of SLE, the NP can analyze the clinical presentation of symptoms, laboratory findings, and enlist the consultation of sub-specialists in rheumatology and nephrology to assist in the final diagnosis of SLE (Edgerton, 2008). Coordination of care by the NP in a multidisciplinary approach is critical to the management of the child with SLE. The NPs knowledge of the disease process, medications, and treatments utilized in acute management of SLE and LN are crucial to management of the ongoing adverse effects of disease and treatments.

Stable Phase Management

Nurse practitioners can maintain their role as primary care providers for children with SLE and LN to manage ongoing childhood medical care and chronic care of co-morbid conditions. Nurse practitioners are actively involved in the healthcare of children in the stable phase of remission due to disease/treatment damages which occur in children after the first 1 to 5 years of treatment. Additionally, children require monitoring and treatment for delayed puberty (11.3%) and growth failure (15.3%) (Paut et al., 2007). NPs monitor bone density and implement treatment for osteoporosis or avascular necrosis due to pubertal delay, renal failure, and sustained steroid use. NPs evaluate for growth and developmental milestones, cognitive difficulties, and impaired learning due to chronic disease and treatment outcome. Additionally, NPs will coordinate referrals of children to multidisciplinary services for nutrition, feeding, growth, occupational, and physical therapies to assist in growth and developmental milestones.
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NPs demonstrate expertise in comprehensive education of the patient and family on disease effects, treatments, and ongoing evaluation for disease flares and co-morbidities (Paut et al 2007). NP’s are experts in lifestyle education regarding avoidance of smoking, and promotion of healthy lifestyle through diet, exercise, and weight control, and ongoing immunizations. NPs need careful consultation of the Centers for Disease Control and Redbook guidelines for specific vaccination timing and current recommendations for immunosuppressed patients. Additionally, NP’s provide continued evaluation of medication compliance by spending time with the adolescent, communicating, educating, and assisting, with the often emotional devastation of steroid treatment, especially with young teenage girls (Paut et al. 2007). Medication compliance is key to prevention of relapse and disease exacerbation; therefore, NP’s must seek ways to improve adherence for children and adolescents.

NP providers manage and refer young adolescent females for fertility maintenance and concerns due to amenorrhea or irregular menses from SLE and LN treatments. Gonadotoxic effects of CYC are well documented and anticipated in post-pubertal females who are at risk for premature ovarian failure; additionally, adolescent males have even higher risk to fertility than females necessitating ongoing education, evaluation, and follow-up (Paut et al. 2007). NP’s provide sexual health education and contraception needs to adolescents with SLE. Contraceptives may be necessary to prevent hemorrhagic events in young females caused from severe thrombocytopenia or co-medication with anticoagulants; additionally, contraceptives are important to prevent risks related to pregnancy, such as disease flare and fetal teratogenicity (Paut et al. 2007).
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NP’s are important in the monitoring of adolescents for cardiovascular risks of accelerated atherosclerosis which is a direct phenomenon related to SLE and the metabolic effects of chronic corticosteroid use. Atherosclerosis has emerged as a leading cause of death in both adult and juvenile SLE; therefore, NP’s are needed to aggressively manage hypertension, hypercholesterolemia and dyslipidemia while working in concert with other sub-specialists (Pongmarutani et al., 2006) (Pereira et al., 2011).

Unstable Disease Management

The psychosocial needs of the child and family in relapse or the unstable stage of illness are significant. The time of diagnosis, as well as periods of illness exacerbation are viewed as a time of crisis and added stress. This added stress effects the emotional and psychological well-being of the child and family members (Brady, 2009). Nurse practitioners have a primary role in the healthcare management of children with end-stage SLE and LN by assessing, planning, and implementing comprehensive healthcare for both the physical and psychosocial needs of the child and family. NPs coordinate services and empower the child and family through education, counseling, and support. Addressing parent and child perceptions of quality of life, including physical and emotional pain and discomfort are paramount to their well-being. Healthcare management of children with chronic unstable disease is about empowering children and families to live their lives to their fullest potential (Brady, 2009).
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Conclusion

Pediatric systemic lupus nephritis is a major determinant of outcome in pediatric systemic lupus erythematosus due to a higher frequency of aggressive renal disease in this population. Long-term prognosis in children has improved with the introduction of corticosteroids, immunosuppressive drugs, and improved management of infections. Treatment strategies for children have been adopted from advances in research and therapeutic options for adults. Determination of treatment efficacy in children is difficult due to the absence of clinical trial data. Determination of safety in a developing child or adolescent cannot be extrapolated from adult studies; however, there are no FDA approved drugs for treatment of pediatric SLE making off-label treatment common place. More pediatric longitudinal random controlled studies are needed in the treatment and management of systemic lupus erythematosus and systemic lupus nephritis. Further research and scientific evidence is needed to add to the understanding of the pathology of SLE and to identify new drugs with fewer toxicities that are more efficacious in the treatment of children.

Nurse practitioners need to maintain their role as primary care providers for children with SLE and LN to manage ongoing childhood medical care and chronic care of co-morbid conditions. The NP role is crucial to maintaining the optimal function and quality of life of pediatric patients with SLE and LN through coordination services and ongoing empowerment of the child and family through education, counseling, and support.
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Table 1

International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis

**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. A few isolated subepithelial or subendothelial deposits may be 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 lesion: focal proliferative lupus nephritis

**Class III (A/C)**  Active and chronic lesions: focal proliferative and sclerosing lupus nephritis

**Class III (C)**  Chronic inactive lesions: focal proliferative and 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

**Class IV-G (A/C)**  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)**
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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 may show advanced sclerosis

**Class VI Advanced sclerotic lupus nephritis**
90% of glomeruli globally sclerosed without residual activity

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

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 (Nester & Gibson, 2007).
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Table 2

System Lupus International Collaborating Clinics/American College of Rheumatology

Damage Index for Systemic Lupus Erythematosus*

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular</strong> (either eye, by clinical assessment)</td>
<td></td>
</tr>
<tr>
<td>Any cataract ever</td>
<td>1</td>
</tr>
<tr>
<td>Retinal change or optic atrophy</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Neuropsychiatric</strong></td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment (e.g. memory deficit, difficulty with 1 calculation, poor concentration, difficulty in spoken or written language, impaired performance levels) or major psychosis</td>
<td>1</td>
</tr>
<tr>
<td>Seizures requiring therapy for 6 months</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular accident ever (score 2 &gt; 1) Cranial or peripheral neuropathy (excluding optic)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>1</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
</tr>
<tr>
<td>Estimated or measured glomerular filtration rate&lt;50%</td>
<td>1</td>
</tr>
<tr>
<td>Proteinuria &gt;3.5 gm/24hours</td>
<td>1</td>
</tr>
<tr>
<td>Or End-stage renal disease (regardless of dialysis or transplantation)</td>
<td>3</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension (right ventricular prominence, or loud P2)</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary fibrosis (physical and radiograph)</td>
<td>1</td>
</tr>
<tr>
<td>Shrinking lung (radiograph)</td>
<td>1</td>
</tr>
<tr>
<td>Pleural fibrosis (radiograph)</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary infarction (radiograph)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>Angina or coronary artery bypass</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction ever (score 2 if &gt; 1)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Cardiomyopathy (ventricular dysfunction)</td>
<td>1</td>
</tr>
<tr>
<td>Valvular disease (diastolic murmur, or systolic murmur &gt;3/6)</td>
<td>1</td>
</tr>
<tr>
<td>Pericarditis for 6 months, or pericardiectomy</td>
<td>1</td>
</tr>
<tr>
<td><strong>Peripheral vascular</strong></td>
<td></td>
</tr>
<tr>
<td>Claudication for 6 months</td>
<td>1</td>
</tr>
<tr>
<td>Minor tissue loss (pulp space)</td>
<td>1</td>
</tr>
<tr>
<td>Significant tissue loss ever (e.g. loss of digit or limb)(score 2 if &gt; 1 site)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Venous thrombosis with swelling, ulceration, or venous stasis</td>
<td>1</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Infarction or resection of bowel below duodenum spleen, liver, or gall bladder ever, for cause any (score 2 if &gt; 1 site)</td>
<td>1(2)</td>
</tr>
</tbody>
</table>
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- Mesenteric insufficiency 1
- Chronic peritonitis 1
- Stricture or upper gastrointestinal tract surgery ever 1

**Skin**

- Scarring chronic alopecia 1
- Extensive scarring or panniculum other than scalp and pulp space 1
- Skin ulceration (excluding thrombosis) for > 6 months 1

**Musculoskeletal**

- Muscle atrophy or weakness 1
- Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis) 1
- Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis) 1
- Avascular necrosis (score 2 if > 1) 1(2)
- Osteomyelitis 1

**Premature gonadal failure**

- Diabetes (regardless of treatment) 1
- Malignancy (exclude dysplasia) (score 2 if > 1 site) 1(2)

*Damage (nonreversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur 6 months apart to score 2. The same lesion cannot be scored twice (American College of Rheumatology (ACR).
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Table 3

1992 Revision of the 1982 American College of Rheumatology Criteria for the Classification of Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th><strong>ACR 1997 CRITERIA</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar (butterfly rash) rash</td>
</tr>
<tr>
<td>Discoid lupus rash</td>
</tr>
<tr>
<td>Photosensitivity</td>
</tr>
<tr>
<td>Oral or nasal mucocutaneous ulcerations</td>
</tr>
<tr>
<td>Non erosive arthritis</td>
</tr>
<tr>
<td>Nephritis:</td>
</tr>
<tr>
<td>Proteinuria &gt; 0.5g/day</td>
</tr>
<tr>
<td>Cellular casts</td>
</tr>
<tr>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>Psychosis</td>
</tr>
<tr>
<td>Pleuritis or Pericarditis</td>
</tr>
<tr>
<td>Cytopenia</td>
</tr>
<tr>
<td>Positive immunoserology</td>
</tr>
<tr>
<td>Antibodies to dsDNA</td>
</tr>
<tr>
<td>Antibodies to Sm nuclear antigen</td>
</tr>
<tr>
<td>Positive finding of antiphospholipid antibodies based on:</td>
</tr>
<tr>
<td>1. IgG or IgM anticardiolipin antibodies, or</td>
</tr>
<tr>
<td>2. Lupus anticoagulant, or</td>
</tr>
<tr>
<td>3. False positive serologic test for syphilis for at least 6 mo, confirmed by <em>Treponema pallidum</em> immobilization or fluorescent treponema antibody absorption test</td>
</tr>
<tr>
<td>Positive antinuclear antibody test</td>
</tr>
</tbody>
</table>
### Systemic Lupus Nephritis

#### Table 4

**Summary of Research Findings**

<table>
<thead>
<tr>
<th>Author(s) / Date / Study</th>
<th>Study/Subjects</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appel et al., 2008</td>
<td>RCT: MMF vs CYC Induction / Maintenance study</td>
<td>No significant difference was found. Subanalysis found African American &amp; Hispanic better response to MMF Adverse effects (AE): Infection, GI</td>
</tr>
<tr>
<td>Baskin et al., 2010</td>
<td>Retrospective study Induction / Maintenance IV CYC with MMF or AZA Mean age 16 ± 3.49</td>
<td>IV bolus CYC &amp; AZA 45% remission rate MMF increased remission 25% Limitations: small sample, lack of comparison</td>
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<td>Bomback &amp; Appel, 2010</td>
<td>Meta-analysis: MMF 3 g/day corticosteroid taper, and Rituximab or placebo n=140</td>
<td>More patients in the RTX group achieved full or partial remission Not statistically significant</td>
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<td>Bomback &amp; Appel, 2010</td>
<td>Meta-analysis: IV CYC (6) monthly pulses 0.5 g/m² followed by every 3 month 500 mg every 2 week X6 verses just 6 doses alone Corticosteroids</td>
<td>Effective and prevented relapse better than the 6 doses alone Adverse effects: Infection, heart disease, gonadal failure, bone density</td>
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<td>Bomback &amp; Appel, 2010</td>
<td>Lupus prone mice treated with Captopril; ACE I Verapamil control</td>
<td>Delayed onset proteinuria Reduced nephrotic proteinuria Reduced glomerular injury</td>
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<td>Dooley et al., 2011</td>
<td>36 month duration MMF 2 g/day + placebo; n=116 AZA 2 mg/kg/day + placebo; n=111 Class III-V LN</td>
<td>MMF superior to AZA for renal response, relapse prevention Adverse effects: GI, serious effects greater AZA Limitations: Few repeat biopsies, under powered</td>
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<tr>
<td>Author(s) / Date / Study</td>
<td>Study/Subjects</td>
<td>Major Findings</td>
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<td>Ginzler et al., 2005</td>
<td>24 week MMF 1000 to 3000 mg/day n=71 IV CYC 0.5 to 1.0 g /m²; n=69 Corticosteroid taper Primary end point remission in 24 weeks; secondary partial remission 24 weeks</td>
<td>MMF: 9 deaths due to infection CYC: 5 deaths due to infection MMF was more effective than CYC Adverse effects: MMF had fewer severe infections, more diarrhea Limitations: Short duration. Inability to reach NIH protocol for CYC dosing (low response rate)</td>
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<td>Gipson et al., 2009</td>
<td>Mean follow up time 55.4 ± 51.6 months Cox regression models to evaluate predictors sample size n=73 Class III to V Treatment resistant: sample n=8 African American predominant GFR significantly reduced at presentation (diagnosis)</td>
<td>Overall 65 (89%) responded to induction, 8 (11%) were treatment resistant Among responders: 4 (72%) were partial responders; 18 (28%) were complete responders, 23 (35%) relapsed within 5 years Treatment resistant: All 8 were African American, decreased GFR at presentation supporting delayed diagnosis</td>
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<td>Isenberg et al., 2010</td>
<td>Class III to V LN MMF 3 g/day target; or IVC 0.5 g/m²/month; plus Tapering prednisone for 24 weeks Renal function, global disease, complements, anti-dsDNA levels were the assessed outcomes</td>
<td>MMF not superior to IVC as induction treatment (primary) MMF &amp; IVC response similar Asians and IVC; good for Black and Hispanic Few Black &amp; Hispanics respond to IVC; fewer Latin Americans responded Adverse effects: Similar across groups. Asians had fewer infections but more lethal</td>
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## Systemic Lupus Nephritis

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<th>Author(s) / Date / Study</th>
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<tbody>
<tr>
<td>Lee, S., Silverman, E., &amp; Bargman, J. (2011) LUMINA: Nested Controlled Study in adults</td>
<td>Study in adults n= 203 LN patients given Hydroxychloroquine</td>
<td>Associated with reduced corticosteroid use, protected from end-organ damage, improved survival, reduced disease activity, extended time to end-stage kidney disease Safety profile is good Safe in pregnancy; reduced risk of neonatal SLE &amp; cardiac manifestations Adverse effects: GI, retinopathy risk after 5 years</td>
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<td>Lee, Y., Woo, J., Choi, S., Ji, J., &amp; Song, G. (2010) Meta-analysis of RCTs (MEDLINE, Cochrane Controlled Trials 1990-2009) Assess efficacy of CYC, AZA, IVC</td>
<td>Ten studies, n= 450 Class III-V; LN Induction: 6-12 months maintenance: 39-72 months</td>
<td>MMF did not increase complete or partial remission rates compared to CYC. MMF had less amenorrhea, and leukopenia MMF vs AZA maintenance: No difference in response rates (risk for end-stage kidney disease) Low dose IVC vs High dose: Low dose had fewer relapses, less infection Limitations: Small sample size, small number of trials</td>
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References


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