SYSTEMIC LUPUS ERYTHEMATOSUS
AND THE DEVELOPMENT OF LUPUS NEPHRITIS:
THE ROLE OF IMMUNOSUPPRESSANTS
AND ALTERNATIVE TREATMENT OPTIONS

By
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The members of the committee appointed to examine the manuscript of Teresa M. Colley find it satisfactory and recommend that it be accepted.

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ABSTRACT

Lupus Nephritis is the leading cause of morbidity and mortality in patients with Systemic Lupus Erythematosus. Lupus Nephritis is a common manifestation and a significant indicator of poor outcome for patients with this condition. Diagnosis and treatment is paramount for prevention of further renal destruction. Classically, treatment has involved various immunosuppressant therapies. These therapies however, are not without potential toxic side effects. Has current research into alternative therapies generated definitively improved treatment options? Is additional long-term research necessary?

This paper reviews laboratory and physical markers for disease and also reviews both benchmark treatment options and contemporary alternative treatments with the goal of increasing the nurse practitioner’s awareness and ability to diagnose this often-asymptomatic condition.
Introduction

Lupus Nephritis is one of the leading causes of death in patients with systemic lupus erythematosus (SLE). Fifty percent of patients with SLE develop lupus nephritis (LN). Patients present with variable clinical courses, dependent on the classification of the glomerulonephritis (Hahn, 1990). The increased morbidity and mortality for SLE patients with lupus nephritis, coupled with the controversy over the most beneficial form of treatment and the serious side effects associated with these treatments, fuels continuing research. Early diagnosis and treatment of this disease could save SLE patients from severe complications and, potentially, save their lives. The purpose of this paper is to discuss a means for early detection and optimal treatment for Lupus Nephritis.

Prevalence

Incidence and prevalence of lupus nephritis depends on the population studied and the diagnostic criteria used for defining SLE. Race, gender, and genetics influence the prevalence of SLE. Eighty-five percent of all SLE patients are women. African American and Asian women exhibit more severe disease and increased incidence of renal involvement. The incidence is 1:1000 in white women, but 1:250 in black women. Women develop SLE at a ratio of 13:1 over men (Appel & D’Agate, 2000). The daughter of a woman with SLE has a 1:40 chance of developing the disease, while her son has a 1:250 chance (Hellman & Stone, 2000). Age of onset is 16-55 years of age in 65% of the population. Twenty percent of the cases occur before 16 years of age and 15% after 55 years of age (Schur, 2000). Renal involvement is even more variable and dependent on whether involvement is defined by renal biopsy or clinical features (Appel & D’Agate, 2000).
Pathophysiology of Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem, inflammatory autoimmune disease thought to be elicited by the body’s identification of its own serum proteins, cells, and tissues as abnormal. Reduced suppressor T cell function, which would normally down regulate immune function, allows increased immune system B cell activity. This B cell hyperactivity causes increased amounts of self and non-self antigens and antibodies. The increased formation of antigen-antibody complexes which migrate to the capillary basement membrane, activates the complement pathway and thus the inflammatory response (Peterson, 2000). The inflammatory response leads to scarring, destruction of tissue, and continued immune reaction against already damaged tissue.

Systemic Lupus Erythematosus can also be drug induced, however just a few drugs cause SLE with any frequency: Chlorpromazine, Hydralazine, Isoniazid, Methyldopa, Procainamide, and Quinidine. There are five features of drug induced SLE that allow for its differentiation from autoimmune induced disease. 1) The ratio of men to women is nearly equal, 2) central nervous system and renal symptoms are not commonly found, 3) antibodies to native DNA and decreased levels of complement are absent, 4) frequent presence of anti-histone antibodies, 5) laboratory changes and clinical symptoms usually resolve when the drug is discontinued. (Hellman & Stone, 2000).

Pathophysiology of Lupus Nephritis

SLE causes a variety of clinical symptoms that include rash, fatigue, and organ-specific damage. Lupus nephritis is a common manifestation and a significant indicator
of poor outcome (Drug and Therapy, 1999). Laboratory evaluations of urine associated with LN include hematuria, red cell casts, proteinuria > 2 gm/24hr (nephritic range), and decreased renal function. Often the presenting symptom is proteinuria discovered during a routine exam. Hypertension can also alert the practitioner to renal disease (Figure 1). Edema occurs in patients with nephrotic-range proteinuria (>3 g/24hr). Late findings of uremic symptoms indicate irreversible renal disease (Hrick, Sedor, & Ganz, 1999).

The immune complexes (IC) of SLE; namely, anti-DNA, complement-fixing IgG anti-nuclear antibodies, and nuclear antigens deposit in the mesangial or subendothelial portion of the glomerular basement membrane. This deposition activates the alternative complement pathway system (C3 and C4 complement factors) and chemotactic factors which cause attraction and infiltration by mononuclear cells and leukocytes. The mononuclear cells and leukocytes phagocytize immune complement and release cytokines, such as TNF-alpha and IL-6. The release of these cytokines induce leukocytosis, increased activation of macrophages, and promote inflammation and activity of other white blood cells through cellular communication which causes continuing inflammation of the glomeruli. Chronic inflammation from perpetual immune complex deposition leads to increased permeability of the glomerular basement membrane to red blood cells and proteins. It may also lead to scarring, fibroid necrosis, and decreased renal function (Schur, 2000).

Renal Classifications of Lupus Nephritis

Renal biopsy is the definitive indicator of glomerular injury. However, the clinical utility of renal biopsy is controversial. A patient with active lupus serology, which would be increased ANA and anti-dsDNA, acute renal insufficiency, and active
sediment (hematuria, red cell casts, proteinuria) will almost always have significant disease. In the presence of this clear serological and clinical evidence of active LN, a biopsy may not be necessary. Some practitioners however request a confirmatory biopsy prior to cytotoxic therapy. Renal biopsy is sometimes indicated for a clinical presentation that is less severe. Biopsy of renal tissue will help establish a definitive diagnosis of SLE and treatment plan in the presence of only mild hematuria and proteinuria (Rose and Appel, 1999). Treatment may vary for different histologic presentations.

The classifications of lesions of LN are based upon pathological findings of significant disease according to the World Health Organization (WHO). These classes are reviewed and described in Table 1. Further refinements can be made for each class. In Class I, patients exhibit no evidence of renal disease and have an excellent prognosis. Class II is associated with mesangial widening with or without hypercellularity and does not extend along the glomerular capillary loops (mesangial glomerulonephritis). It has a good prognosis often, without any treatment. Patients in this group may have mild proteinuria and hematuria. Class III is associated with mild or moderate mesangial alterations with immune complex deposition in some capillaries (focal proliferative). This class has a moderately good prognosis with early and aggressive treatment. Class IV, the most common is often associated with severe mesangial, endocapillary, or mesangiocapillary proliferation and/or extensive subendothelial deposits. Mesangial deposits are almost invariably present and subepithelial deposits are frequently present as well (diffuse proliferative). The proliferative changes extend into most capillary loops and the patient has a poor prognosis without aggressive intervention. Class IV often progresses to end stage renal failure. Class V is purely membranous glomerulonephritis
with immune deposits being primarily subepithelial in the capillary basement membrane. This class of lupus nephritis disease is relatively rare and is often seen together with Class III or IV lupus nephritis. It has a moderately good prognosis when treated early.

Class VI is characterized by a mixed nephritis with membranous and proliferative disease (Hahn, 1990). There is no specific treatment, as glomerular scarring and not inflammation cause the disease. It has a poor prognosis as this class usually results in renal failure.

**Clinical Manifestations**

Many patients with LN are physically asymptomatic, so early detection is paramount as its presence is a predictor of poor outcome (Bieneik & Lahita, 1994). The diagnosis of LN is based on a combination of physical, laboratory, and pathology findings (see figure 1). The presence of edema in the legs, ankles, and/or fingers may be the first symptom that brings a patient to the office. Edema is caused by protein loss in the urine and signifies glomerular injury (Klippel, 2000). The loss of protein in the urine causes hypoalbuminemia with resultant vascular oncotic changes. These changes draw fluid from the vascular space into the interstitum, resulting in edema. With the loss of vascular fluid to the interstitum the kidney releases renin in an effort to increase blood flow which activates the renin-angiotension system. Hypertension is often seen due to this increased fluid volume. (Henshaw, 2000). SLE patients may experience nocturia due to the inability of the kidney to concentrate urine (Bieniek & Lathia, 1994), but may be reluctant to report this, so the practitioner should inquire regarding this symptom.
Laboratory Findings

Few practitioners will ever have the need to classify LN according to the WHO classifications, as this is generally the domain of the nephrologist. With the exception of renal biopsy, no one test is diagnostic for LN. There are several studies the practitioner should consider to evaluate for the presence of LN. The sensitivity and specificity of each test should help to determine its usefulness and help the practitioner to prioritize the order in which they are obtained (see Table 2). Indicators of lupus nephritis are leucocyturia, hematuria, red blood cell casts and white blood cell casts in the urine, proteinuria, increased serum creatinine and blood urea nitrogen (BUN).

Additional other findings include decreased glomerular filtration rate (GFR), hypoalbuminemia, hypercholesterolemia, increased anti-double stranded DNA antibodies, in addition to hypocomplementemia, especially low C3 levels (Drug and Therapy, 2000). These tests are reviewed in more detail below. Although the practitioner would want to consult with a nephrologist for definitive diagnosis, it would certainly be within the nurse practitioner’s realm to obtain the basic laboratory tests after consultation with the nephrologist. The practitioner must also be able to discuss with the patient the individual tests, clinical usefulness, and the preparation required for each test (see Table 3).

Urinalysis  The practitioner should perform a urine dipstick in the office and then send the specimen for microscopy, if not done in the office. Urine dipstick will give information on color, pH, specific gravity, protein, ketones, glucose, blood, and bilirubin. The quantitative measurement of protein in the urine necessitates a 24-hour urine
collection, coupled with a creatinine clearance. Microscopy is also indicated when any urine dipstick is positive for protein or hematuria.

_Hematuria_ found on dipstick may be due to interactions of reagents with myoglobin or hemoglobin in the absence of intact red blood cells (Kasinath, 1996). This makes the microscopic examination essential. Dysmorphic red blood cells are suggestive of glomerulonephritis due to distortion when passing through the abnormal glomerulus. If microscopic examination reveals red blood cells with the appearance of circulating red blood cells then they are considered non-glomerular in origin.

_Proteinuria_ may be found in a normal healthy patient. A small amount of protein is normally filtered across the glomerular basement membrane the proximal tubule reabsorbing the majority of it. Protein excretion for this type of patient would be 25-150 mg/day. Damage to the glomerular basement membrane or inability of the proximal tubule to reabsorb the proteins allows the protein to move across the membrane and be excreted in the urine. Proteinuria detected by urine dipstick at trace amounts only indicates protein loss of 150 mg/day. Proteinuria detected by urine dipstick of 1+ or greater should be cause for concern and further investigation in a patient with SLE. Proteinuria greater than 3 gm/day is virtually always glomerular (C. Wickre, personal communication, Nov 13, 2000).

_Leukocyturia_ can indicate inflammatory disease, but is not specific for LN.

_White cell casts_ are generally seen in pyelonephritis. They can however indicate tubular damage. If found with red cell casts and proteinuria they are diagnostic for LN (C. Wickre, personal communication, Sept 22, 2000).
Red cell casts suggest active glomerular disease and indicate the kidney as the origin of the hematuria. In the presence of SLE, red cell casts are indicative of LN (Peters, 1981). Fatty cells or Oval fat bodies are found in nephrotic syndrome that can be associated with LN. Fat droplets are produced when the renal tubular cells exceed their capacity to reabsorb proteins of glomerular origin (Jacobs, 1996). Oval fat bodies are thought to be renal tubule cells filled with fat droplets that have been reabsorbed from glomerular filtrate. The presence of proteinuria, pyuria, white blood cell casts, and red blood cell casts in combination, suggests both interstitial and glomerular injury. The presence of this combination should increase the suspicion of LN (C. Wickre, personal communication, Sept 22, 2000).

Twenty-four hour urine with creatinine clearance is more specific for the types of proteins being excreted in the urine and is an excellent predictor of renal disease and decreased glomerular filtration rate. Proteinuria > 3.0 gm/24hr is the clinical definition of nephrotic syndrome.

Serum Creatinine is not the most sensitive indicator of renal deficits as > 50% of nephrons must be non-functioning before a rise in serum creatinine will be detected. The benefit is that serum creatinine levels can provide a rough estimate of GFR (Jacobs, 1996). Serum creatinine is generally a very constant value since muscle metabolism does not change on a daily basis. So, if creatinine levels are rising the cause must be because it is not being cleared at the same rate, which would indicate decreased GFR. Increased serum creatinine can also be predictive of progressive renal dysfunction when serial creatinine levels are being assessed (Brennor and Rector, 2000).
**Blood urea nitrogen** (BUN) is best evaluated with serum creatinine to assess renal function. BUN is normally easily filtered by the glomeruli and reabsorbed by the distal tubule and is dependent on renal blood flow and urine flow rates. This makes it an excellent indicator of renal disease. The nurse practitioner should be aware that the corticosteroids used to treat SLE may increase BUN, due to increased protein catabolism (Jacobs, 1996) and that hydration status will affect the value.

*Serum albumin* will be decreased in glomerular renal disease, due to loss of protein in the urine (Klippel, 2000). Edema associated with hypoalbuminemia will not be seen until serum albumin levels drop below 3 g/dL (Salomon, 1989).

*Cholesterol and Triglycerides* will be elevated due to the loss of lipid carrier proteins and increased hepatic production of cholesterol in nephrotic syndrome. This is termed secondary hyperlipidemia.

Elevated *Anti-dsDNA* levels accompanied by low complement levels are helpful in evaluating and following SLE patients, as they correlate with severe or active renal disease (Wise, 1998). dsDNA has an affinity for the kidney basement membrane and when bound with antibodies these immune complexes are deposited in the kidney and create local inflammation by activating complement and chemotaxis of neutrophils (Drug and Therapy, 1999).

*Hypocomplementemia* is usually the result of activation of the alternative pathway (Ricker et al., 1991). Activation of the pathway consumes complement factors, C3 and C4 at a greater rate than their production, thus leading to decreased levels. For every C4 molecule consumed six molecules of C3 are consumed thus making C3 a more sensitive marker.
Renal Biopsy is important to ascertain the type and severity of disease and whether it is reversible or will respond to treatment (Couser, 1999). A baseline hematocrit, platelet count, prothrombin time, and partial thromboplastin time should be obtained.

General Management

There are a few common components in the management of patients with LN. These are:

a. Early referral to a nephrologist, if LN is suspected
b. Long-term follow-up is required on all LN patients
c. Exquisite blood pressure control (SBP <140, DBP <90) is required. The practitioner should consider adding an ACE inhibitor in LN patients with or without hypertension.
d. Medications for the reduction of lipids should be instituted
e. Avoidance of nephrotoxic drugs is paramount
f. Frequent communication between the practitioner and the nephrologist can prevent unnecessary admission, morbidity, and possibly mortality (Sizeland, 1997).

While the nurse practitioner may not prescribe most of the medications used to treat LN, they may very well manage them in conjunction with the nephrologist. At the very least the practitioner must have a thorough understanding of the medications and the options available for their use. This allows the practitioner to better educate patients on the expected side effects and course of therapy.

Treatments

Research studies conducted by Balow et al., (1983), Steinberg and Steinberg (1991), and Wallace et al., (1982) have greatly expanded the knowledge base for the treatment of lupus nephritis. With the knowledge that lupus nephritis is primarily an autoimmune disorder, treatment has focused primarily on anti-inflammatory, immunosuppressant, and alkylating agents. Table 4 reviews the different classifications and the traditional treatment methods. The most commonly used medications are
prednisolone, azathioprine (Imuran), and cyclophosphamide (Cytoxan) or some combination of these (D'Cruz et al., 1997). Each of these classes of drugs carry potentially life-threatening side effects that must be addressed.

**Prednisolone**

Glucocorticoids, like Prednisolone depress immune system function through a number of pathways. Neutrophils are less able to move across vascular endothelium to sites of injury, macrophage processing of antigens is inhibited, and the inflammatory response is depressed as the synthesis of interleukins, cytokines, and other mediators of the inflammatory response are inhibited (Shupnik, Chrousos, & Siragy, 1998).

Serious side effects associated with high doses (40 mg or higher, daily) of long-term (more than 30-60 days) prednisolone are thromboembolism, hypertension, edema, menstrual irregularities, osteoporosis, susceptibility to infection, hypokalemia, hyperglycemia, and adrenal suppression. Sudden withdrawal after prolonged use can be fatal (Nurse Practitioner Drug Handbook, 1998).

**Azathioprine**

The method of action of Azathioprine is decrease of cellular proliferation, suppression of cell-mediated hypersensitivity, and alteration of antibody production. This decreases the number of lymphocytes that can migrate to inflammatory sites and thus you see reduction in inflammation. Serious side effects associated with use of Azathioprine are leukopenia, bone marrow suppression, pancytopenia, thrombocytopenia, hepatotoxicity, infections, and increased risk of neoplasia such as lymphomas, and skin cancers (Nurse Practitioner Drug Handbook, 1998).
**Cyclophosphamide**

Cyclophosphamide is an alkylating agent with the therapeutic classification of antineoplastic. It is used in the treatment of lupus nephritis for its ability to significantly suppress immune system activity. Serious side effects are hemorrhagic cystitis, primary ovarian failure, thrombocytopenia, anemia, and secondary malignant disease. (Nurse Practitioner Drug Handbook, 1998).

**Newer Therapeutic Modalities**

Although the classic treatments for lupus nephritis do achieve therapeutic effect, the increased risk of premature ovarian failure, osteoporosis, secondary malignancy, hemorrhagic cystitis, and infection have compelled researchers to find less toxic methods of halting progression of renal involvement.

In addition to the above mentioned medications and therapies, there are also others that have either been explored or are currently undergoing clinical trials for additional data on their effectiveness. These include plasmapheresis, mycophenolate mofetil, cyclosporine A, and intravenous immunoglobulin.

**Plasmapheresis**

Despite the clinicians best attempts at appropriate treatment, some patients with lupus nephritis will progress to end stage renal disease (ESRD). A few studies on the efficacy of plasmapheresis in the treatment of LN have been done in the past, however Lewis et al., (1992) was the first to document a controlled study on this subject. The results of this study demonstrated no improvement in the course of the disease. This outcome was further reinforced by Wallace et al., (1998) in a study that again confirmed
no improvement of outcomes when plasmapheresis was added to a course of
cyclophosphamide in the treatment of WHO class III and IV lupus nephritis patients.

**Mycophenolate Mofetil**

Mycophenolate mofetil (Cellcept) is normally used as an immunosuppressant for
treatment after renal transplantation. Mycophenolate works by inhibiting T and B cell
proliferation and production of antibodies. It also leads to decreased recruitment of
lymphocytes and monocytes to sites of inflammation. Mycophenolate mofetil is
currently being used with some success to help reduce proteinuria and to stabilize serum
creatinine at a dose of 0.5-2.0 grams per day (Rose & Appel, 2000).

Dooley et al., (1999) studied 12 patients with proliferative LN who were offered
Mycophenolate as an alternative to continued cyclophosphamide therapy. The goal of the
study was to determine if Mycophenolate could suppress renal sediment activity and
improve serum creatinine. The outcome of the study was that serum creatinine values
remained normal or decreased if the patient had elevated levels at the beginning of the
study. There was significant decreased proteinuria. C3 levels and anti-dsDNA levels
improved in some, but not all patients. This study showed that mycophenolate could be a
viable alternative to the more toxic cyclophosphamide.

A drawback to Mycophenolate mofetil is its cost (Transplant News Network,
1998). The cost of a 250 mg dose is $2.36 and a 500 mg dose is $4.73 (R. Huffman,
personal communication, October 9, 2000).

**Cyclosporine A**

Tam et al., (1998) evaluated the efficacy of cyclosporine A (CSA) in the long-
term treatment of lupus nephritis. CSA works by inhibition of T-cells, suppression of the
production of helper factors including over-activity of B cells, and attenuates the
immune-mediated injury. By preventing induction of interleukin II, CSA inhibits the
induction phase of the immune response.

They found that treatment with CSA and low dose prednisolone provided
improvement in serum hemoglobin and albumin levels, while greatly reducing
proteinuria. The study did not monitor ANA, anti-dsDNA antibodies, or immunoglobulin
levels, which makes it difficult to compare these results with more classic treatment
modalities. There was no documented evidence of premature ovarian failure, which has
been a major concern with other treatments due to the majority of patients being females
of child bearing years. This gives CSA an added potential advantage and further research
is currently being pursued.

**Intravenous Immunoglobulin**

Intravenous immunoglobulin exerts its effect by modulating monocyte and
lymphocyte neutralization of autoantibodies and thus decreasing cytokine activity. A
prospective intervention described by Boletis, Ioannidis, Boki, & Moutsopoulos, (1999)
was the use of intravenous (IV) immunoglobulin compared with cyclophosphamide for
maintenance therapy. Findings of this study demonstrated that there were no substantial
differences in creatinine, creatinine clearance, or change in proteinuria between the two
groups being studied. They concluded that immunoglobulin was safe and effective for
maintenance therapy of lupus nephritis without the serious side effects of long-term
cyclophosphamide use. The dose of intravenous immunoglobulin in this study was
400mg/kg per month for a total of 18 months. A point to consider would be the cost and
availability of immunoglobulin for wide spread use. The cost of IV immunoglobulin is
$87.00 per gram (R. Huffman, personal communication, October 9, 2000).

End Stage Renal Disease

End stage renal disease (ESRD) will occur in 10-30% of LN patients (Rose and Appel, 1999). It presents an interesting phenomenon in that there is decreased lupus activity as the kidneys fail. The treatment for ESRD is dialysis and eventual transplantation.

Dialysis

Dialysis is achieved either with hemodialysis or continuous ambulatory peritoneal dialysis. If hemodialysis is chosen, then a permanent fistula is eventually placed to facilitate dialysis. Initially a temporary venous line may be placed, however patients should be advised that this will be replaced, as soon as medically prudent. Dialysis is continued for at least three to six months, and usually much longer to assure remission of lupus activity before transplantation is performed (Rose and Appel, 1999).

Renal Transplant

Survival rates of LN patients who have undergone renal transplantation is similar to patients with other systemic disease undergoing renal transplant at 5 and 10 years. However, LN patients experience improved 5-year survival rate, if the graft is living related versus a cadaver graft (89 vs. 41 percent), (Rose and Appel, 1999). Both dialysis and renal transplant would require management by a nephrologist skilled in this area.

Conclusion

Lupus nephritis is a frequent sequela of SLE and carries high morbidity and mortality rates. Treatment choices still need to be individualized to each patient and
should take into consideration factors such as the presence of urine abnormalities, edema, proteinuria, loss of renal function, and classification of kidney disease (Klippel, 2000). Use of immunosuppressant drugs substantially improves survival rates. However, the long-term use of such regimes is associated with significant side effects (Tumlin, 1999). The need for further research into immunosuppressive therapies with fewer side effects is clearly evident. Current alternative therapies show considerable promise over their more toxic conventional counterparts. Unfortunately, solutions to the high cost of these promising new treatments are still on the horizon. There is a need for long-term follow-up with each modality to establish clinical outcomes. Early detection and aggressive treatment of LN with proven therapies remains the hallmark of quality patient care.
References


Schur, P. (1999). Epidemiology and pathogenesis of systemic lupus erythematosus. Nephrology UpToDate, 7 Section 4, 1-8


Figure 1: Diagnosing LN

History and Physical

Vital signs

Include age, wt, ht.

Blood tests

Creatinine

BUN

Elevated

Albumin

Hypoalbuminemia

Hypercholesterolemia

Lipids

Hypertriglyceridemia

Urinalysis

Positive for:
hematuria, *proteinuria, *pyuria and leukocyturia

Microscopy

24 hour urine

*RBC casts

*WBC casts

Creatinine Clearance

Elevated Creatinine clearance and protein

Anti-dsDNA

Decreased C3

Decreased C4

Complement

Renal Biospy

*suggests both interstitial and glomerular injury and is diagnostic for LN
Table 1  

Classification of Lupus Nephritis Lesions according to World Health Organization

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DESCRIPTION</th>
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<tr>
<td>I</td>
<td>Normal glomeruli</td>
</tr>
<tr>
<td>II</td>
<td>Pure mesangial alterations (mesangial immune deposits)</td>
</tr>
<tr>
<td>III</td>
<td>Focal proliferative glomerulonephritis (changes in glomerular tufts)</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse proliferative glomerulonephritis (changes in all glomeruli)</td>
</tr>
<tr>
<td>V</td>
<td>Membranous glomerulonephritis (basement membrane deposits)</td>
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<tr>
<td>VI</td>
<td>Advanced sclerosing glomerulonephritis</td>
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<th>Sensitivity</th>
<th>and</th>
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<tr>
<td>Leukocyturia</td>
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</tr>
<tr>
<td>White cell casts</td>
<td>Low</td>
<td></td>
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</tr>
<tr>
<td>Red cells casts</td>
<td>High</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Fatty cells/oval fat bodies</td>
<td>Medium</td>
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<td>High</td>
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<td>24 hr urine with creatinine clearance</td>
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<tr>
<td>Serum creatinine</td>
<td>High</td>
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<tr>
<td>Blood urea nitrogen</td>
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<td>Serum albumin</td>
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<td>Cholesterol/Triglycerides</td>
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<tr>
<td>Anti-dsDNA</td>
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<tr>
<td>Decreased Complement C3-C4</td>
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<tr>
<td>Renal Biopsy</td>
<td>High</td>
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<td>High</td>
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<tr>
<td>Test</td>
<td>Instructions and Notes</td>
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<tr>
<td><strong>Serum Creatinine</strong></td>
<td>Serum creatinine is unaffected by most diet or activity. However, increased consumption of meat and ascorbic acid (Vitamin C) may falsely elevate levels. Use of cephalosporin antibiotics may increase levels. Serum creatinine has relative reliability in the presence of Cefoxitin (Jacobs, 1996).</td>
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<tr>
<td>(Male &lt; 1.2 mg/dL)</td>
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<td>(Female &lt; 1.1 mg/dL)</td>
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<td><strong>Blood Urea Nitrogen</strong></td>
<td>BUN may be increased by recent ingestion of a High protein meal so it is best to avoid at least 24 hours before blood work. Prednisone therapy as well as dehydration, GI bleed, and volume depletion may increase BUN level.</td>
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<td>(5-20 mg/dL)</td>
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<td><strong>Urinalysis</strong></td>
<td>Instruct patient on cleansing the urethral meatus. Obtain a clean catch, midstream specimen. A first morning urine is preferred as this is when red cell casts will most likely be found.</td>
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<td><strong>24 hour urine with creatinine clearance</strong></td>
<td>Instruct patient to discard first void of the morning and begin timing from that point. Instruct patient to collect all urine during the 24 hour time period and to keep urine refrigerated at all times. Urine is to be transported to the lab immediately on completion of the collection. Meat free diet is recommended. Instruct the patient to maintain good hydration during the test. Inform patient that serum creatinine will be drawn when they bring urine to the lab.</td>
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<td>(Protein 30-150 mg/24 hr)</td>
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<td><strong>Serum Albumin</strong></td>
<td>No specific patient preparation required.</td>
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<td>(3.5-5.0 g/dL)</td>
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<td><strong>Cholesterol and Triglycerides</strong></td>
<td>Instruct patient to fast for at least 10 hours before testing. If possible, a steady diet for at least 3 weeks before testing is desirable.</td>
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<td>(&lt;200)</td>
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<td>(&lt;200)</td>
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<tr>
<td><strong>Anti-dsDNA (negative)</strong></td>
<td>No specific patient preparation required. No fasting required.</td>
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<td>Table 3 continued</td>
<td>Patient teaching in preparation for Diagnostic Tests</td>
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<tr>
<td>Serum Complement</td>
<td>No specific patient preparation required. No fasting required.</td>
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<td>(C3 males 88-252 mg/dL)</td>
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<tr>
<td>(C3 females 88-206 mg/dL)</td>
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<tr>
<td>(C4 males 12-72 mg/dL)</td>
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<td>(C4 females 13-75 mg/dL)</td>
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<td>Renal Biopsy</td>
<td>Obtain informed consent. Inform the patient that Biopsy will be performed using ultrasound. There will be no contrast used. A mild general anesthetic or anxiolytic will be given. Inform the patient they will be laying on their back for approximately 6 hours after the procedure. All urine will be collected. Inform patient that 5% of patients experience blood in urine after the biopsy. Inform the patient they are to avoid strenuous or contact activity for 2-4 weeks after procedure.</td>
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### Table 4

*Treatment Methods According to Classification*

| Class I (normal)                  | No treatment required |
| Class II (mesangial)             | No treatment required. May use low dose Corticosteroid monotherapy. Treat extra-renal symptoms. Practitioner should closely monitor for transformation to Class III or IV (McLigeyo, 1998). |
| Class III (focal proliferative)  | Aggressive therapy with Cyclophosphamide and/or Azathioprine is often used in conjunction with Prednisone. This group of patients often Progresses to ESRD (McLigeyo, 1998). |
| Class IV (diffuse proliferative) | See Class III         |
| Class V (membranous)             | Often treated with prednisone only, if pure membranous nephritis. May combine prednisone and AZA. This type of nephritis is rare. Generally found in conjunction with Class III or IV types (Bienek, 1994). |
| Class VI (sclerosing)            | No benefit to treat. Irreversible. Treat extra-renal lupus manifestations. |