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Managment of Childhood Onset Nephrotic Syndrome

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**KEY WORDS**
proteinurina, pediatric, nephrosis, kidney disease

**ABBREVIATIONS**
ISKDC—International Study of Kidney Disease in Children
MCNS—minimal-change nephrotic syndrome
FSGS—focal segmental glomerulosclerosis
Up/c—urine protein/creatinine ratio
BID—twice daily
ACEI—angiotensin-converting enzyme inhibitor
ARB—angiotensin receptor blocker
HMG-CoA—3-hydroxy-3-methylglutaryl coenzyme A

**abstract**
The therapeutic approach to childhood nephrotic syndrome is based on a series of studies that began with an international collaborative effort sponsored by the International Study of Kidney Disease in Children in 1967. The characteristics of children presenting with nephrotic syndrome have changed over recent decades with greater frequency of the challenging condition focal segmental glomerulosclerosis and a greater prevalence of obesity and diabetes mellitus, which may be resistant to glucocorticoids in the former and exacerbated by long-term glucocorticoid therapy in the latter 2 conditions. The Children’s Nephrotic Syndrome Consensus Conference was formed to systematically review the published literature and generate a children’s primary nephrotic syndrome guideline for use in educational, therapeutic, and research venues. Pediatrics 2009;124:747–757

Idiopathic nephrotic syndrome affects 16 in 100 000 children, making this condition one of the more common childhood kidney diseases. The therapeutic approach to childhood nephrotic syndrome is based on studies that began with the International Study of Kidney Disease in Children (ISKDC). Between 1967 and 1974, 521 children with nephrotic syndrome entered into this study with a histologic classification of minimal change (MCNS) (77.1%), focal segmental glomerulosclerosis (FSGS) (7.9%), membranoproliferative glomerulonephritis (6.2%), and others (8.8%).1,2 Normalization of urine protein levels with 8 weeks of glucocorticoid therapy was predictive of MCNS with a sensitivity of 93.1% and specificity of 72.2%.2 Consequently, pediatricians began using therapeutic response to glucocorticoids for evaluation and therapy for incident patients.

The sentinel work of the ISKDC followed by a series of studies by the Arbeitsgemeinschaft fur Padiatrische Nephrologie (APN) formed the foundation for management of children with nephrotic syndrome.3–5 The characteristics of children presenting with nephrotic syndrome have changed over recent decades. Contemporary literature has documented an increasing incidence of FSGS-induced nephrotic syndrome in the 1990s compared with that of the 1970s.6 FSGS is less responsive to glucocorticoids and has greater risk for progressive kidney failure compared with the MCNS that dominated the ISKDC cohort.2,7 Furthermore, children in the United States have a greater prevalence of obesity and diabetes mellitus compared with children of previous decades, which may be exacerbated by long-term glucocorticoid therapy.3,9 The Children’s Nephrotic Syndrome Consensus Conference was formed to assess current evaluation and management practices for children with nephrotic syndrome among North American Pediatric
Nephrologists, systematically review the published literature, and generate a children’s primary nephrotic syndrome guideline for use in educational, therapeutic, and research venues.

METHODS

Participating sites were gathered from the Southeast and Midwest Pediatric Nephrology study groups. One representative from each center was asked to represent the institution for the consensus conference and subsequent meetings by conference call. Participants (along with their institutions) are listed as authors.

A literature search was conducted by using the PubMed search engine. English-language literature generated from North America, Europe, and Asia was identified by using the key words “nephrotic syndrome,” “proteinuria,” and “child.” A total of 709 articles were identified. Simultaneously, members of the consensus group were asked to submit a list of key articles relevant to the topic of childhood nephrotic syndrome that were used to validate and augment the PubMed search. Articles with original scientific investigation, clinical trials, cohorts, and case-control studies were retained for a total of 344 articles.

The consensus study group was divided into working groups to review the literature and present guideline recommendations to the full study group for discussion at the June 21, 2007, Children’s Nephrotic Syndrome Study Group Consensus Conference held in Chapel Hill, North Carolina, and during subsequent conference calls through July 30, 2007. The charge to the consensus participants was to create a consensus document and educational module for childhood nephrotic syndrome on the basis of literature when available and with expert opinion when the literature was insufficient. All recommendations were generated by the physician participants and were not subject to previous review by the funding agency.

This document was designed for physicians who manage children 1 to 18 years old with:

- a urine protein/creatinine ratio (Up/c) of ≥2; and
- a serum albumin level of ≤2.5 mg/dL.

On presentation, the evaluation of a child with proteinuria includes a thorough review for signs and symptoms that may suggest that the nephrotic syndrome is a secondary condition. Malaise, rash, adenopathy, arthritis, fevers and weight loss may be signs of systemic lupus erythematosus, and diffuse lymphadenopathy and hepatosplenomegaly may suggest lymphoma. These disorders require a different evaluation and management approach and will not be considered within this document.

EVALUATION OF CHILDREN WITH NEPHROTIC SYNDROME

Recommendations for initial evaluation include:

- urinalysis;
- first morning Up/c;
- serum electrolytes, serum urea nitrogen, creatinine, and glucose;
- cholesterol level;
- serum albumin level;
- complement 3 level;
- antinuclear antibody level (for children aged ≥10 years or with any other signs of systemic lupus erythematosus);
- hepatitis B, hepatitis C, and HIV serology in high-risk populations;
- purified protein derivative level; and
- kidney biopsy for children aged ≥12 years.

A urinalysis with microscopy is recommended for identifying hematuria, cellular casts, or other evidence of nephritis, which should precipitate evaluation for glomerulonephritis rather than primary nephrotic syndrome. First morning Up/c will establish the degree of proteinuria without the contribution of benign orthostatic increases in urinary protein excretion. Complement 3 and antinuclear antibody screen for proteinuric diseases associated with hypocomplementemia, including membranoproliferative glomerulonephritis and systemic lupus erythematosus, which require additional investigation with laboratory tests and kidney biopsy.

A kidney biopsy for children over the age of 12 is recommended because of the frequency of diagnoses other than minimal-change disease. Figure 1 presents a summary of 223 kidney biopsies obtained between 2001 and 2006 from a southeast regional referral center showing that FSGS accounts for the majority of kidney diseases in children undergoing biopsy for proteinuria in this region.

DEFINITIONS

The following are terms commonly used for nephrotic syndrome management.

Remission: Up/c < 0.2 or Albustix negative (Albustix, Miles, Inc, Diagnostics Division, Elkhart, IN) or trace for 3 days.

Relapse: After remission, an increase in the first morning Up/c to ≥2 or Albustix reading of ≥2 for 3 of 5 consecutive days. Frequently relapsing: 2 or more relapses within 6 months after initial therapy or ≥4 relapses in any 12-month period.

Steroid dependent: Relapse during taper or within 2 weeks of discontinuation of steroid therapy.

Steroid resistant: Inability to induce a remission with 4 weeks of daily steroid therapy.
Discrepancies in the definition of steroid-resistant nephrotic syndrome create difficulties for comparing outcomes for reported treatment strategies. On the basis of the ISKDC study, 95% of children with steroid-responsive nephrotic syndrome will demonstrate resolution of proteinuria with 4 weeks of daily glucocorticoid therapy and 100% after an additional 3 weeks of alternate-day therapy. This consensus guideline uses a 4-week oral glucocorticoid limit to define steroid resistance; however, therapy may be continued during the subsequent evaluation for steroid-resistant nephrotic syndrome, allowing the capture of late responders. Glucocorticoid dosing is presented as mg/kg and mg/m². Published studies in childhood nephrotic syndrome have included glucocorticoid dosing with either mg/kg or mg/m² regimens. Actual prescribed dose will vary on the basis of the standard used, especially at the extremes of weight, but no literature exists to prove that 1 scheme is more effective than the other.

**THERAPY**

**Initial Therapy for Childhood Nephrotic Syndrome**
- prednisone 2 mg/kg per day for 6 weeks (maximum: 60 mg);
- then prednisone 1.5 mg/kg on alternate days for 6 weeks (maximum: 40 mg);
- no steroid taper is required at the conclusion of this initial therapy.

The initial therapy for nephrotic syndrome in children is based on the studies summarized in Fig 2. This series of studies evaluated initial prednisone exposure ranging from 4 to 28 weeks. The 12-week treatment regimen including 6 weeks of prednisone at 60 mg/m² per day (2 mg/kg per day) plus 6 weeks at 40 mg/m² (1.5 mg/kg) on alternate days is recommended by this consensus panel because of maximum effect and minimization of glucocorticoid-related adverse effects. Results of several studies in India, Europe, and Japan have challenged this course of therapy with a long treatment taper, addition of cyclosporine, and lower initial daily prednisone doses of 40 mg/m² per day but have not demonstrated significant improvements in sustained remission over the traditional 12-week regimen.

**Initial or Infrequent-Relapse Therapy**
- prednisone 2 mg/kg per day until urine protein test results are negative or trace for 3 consecutive days;
- then prednisone 1.5 mg/kg on alternate days for 4 weeks.
Treatment of the nephrotic syndrome initial or infrequent relapse requires considerably less glucocorticoids than initial therapy. Glucocorticoids (2 mg/kg per day prednisone equivalent) continue until urine protein levels normalize for 3 days. The dose is then reduced to alternate days for 4 weeks.\(^20\)

**Frequently Relapsing Nephrotic Syndrome Therapy Options**

- prednisone 2 mg/kg per day until proteinuria normalizes for 3 days, 1.5 mg/kg on alternate days for 4 weeks, and then taper over 2 months by 0.5 mg/kg on alternate days (total: 3–4 months);
- oral cyclophosphamide 2 mg/kg per day for 12 weeks (cumulative dose: 168 mg/kg) based on ideal body weight started during prednison (2 mg/kg per day) induced remission, decrease prednison dose to 1.5 mg/kg on alternate days for 4 weeks, and then taper over 4 weeks;
- mycophenolate mofetil 25 to 36 mg/kg per day (maximum: 2 g/day) divided twice daily (BID) for 1 to 2 years with a tapering dose of prednison; and
- cyclosporine A 3 to 5 mg/kg per day divided BID for an average of 2 to 5 years.

Patients with frequently relapsing nephrotic syndrome have treatment options that include extended dosing of glucocorticoids, cytotoxic agents, mycophenolate mofetil, or calcineurin inhibitors. When glucocorticoids have not produced signs of toxicity, this therapy may be continued with an extended dosing regimen. Clear data regarding the optimal extended course of prednison or, indeed, any other of the therapeutic options for frequently relapsing nephrotic syndrome have not been published; consequently, these recommendations are largely based on opinion.

Cytotoxic agents, including cyclophosphamide or chlorambucil, used in combination with glucocorticoids have been demonstrated to induce a sustained remission of 72% at 2 years and 36% at 5 years in frequently relapsing nephrotic syndrome.\(^21\) On the basis of a meta-analysis from pediatric nephrotic syndrome studies, cytotoxic agents have a significant toxicity profile including 1% fatality, 1.5% severe bacterial infections, and 0.2% to 0.6% late malignancy. Up to 3% of patients receiving chlorambucil have reported seizures. Reduced fertility after cytotoxic therapy has been described. Compared with cyclophosphamide, chlorambucil is associated with a slightly greater toxicity profile and no improvement in efficacy.\(^21\)

A 6-month course of mycophenolate mofetil with a tapering dose of alternate-day prednison induced remission in 75% of 33 patients during therapy and maintained in 25% after therapy was discontinued.\(^22\) The relapse rate in these patients improved from 1 episode every 2 months before mycophenolate mofetil to 1 every 14.7 months during therapy.\(^22\)

Cyclosporine for 2 to 5 years has resulted in 60% remission during the initial year of therapy.\(^23,24\) Remission was maintained in only 28% of children during the second year of cyclosporine.\(^25\) Up to 40% of patients may need additional alternate-day prednison to maintain remission. There is a high rate of relapse after cyclosporine withdrawal.\(^25\) The nephrotoxic effects of cyclosporine warrant careful monitoring of kidney function and blood drug levels. Tacrolimus, an alternative calcineurin inhibitor, provides no advantage regarding nephrotoxicity profile. The risk for nephrotoxicity attributable to calcineurin inhibitors makes this a third-line option for frequently relapsing nephrotic syndrome.\(^25,26\)

**Steroid-Dependent Nephrotic Syndrome Therapy**

- glucocorticoids are preferred in the absence of significant steroid toxicity;
- secondary alternatives should be chosen on the basis of risk/benefit ratio;
- cyclosporine A 3 to 5 mg/kg per day divided BID;
- tacrolimus 0.05 to 0.1 mg/kg per day divided BID; and
- mycophenolate mofetil 24 to 36 mg/kg per day or 1200 mg/m² per day divided BID (maximum: 2 g/day).

Steroid-dependent nephrotic syndrome occurs in ~24% of children with nephrotic syndrome.\(^27\) Some children can maintain a remission with low-dose glucocorticoids given daily or on alternate days, but many continue to relapse. Steroid-induced adverse effects, such as obesity, hypertension, and cataracts, develop in a significant proportion of patients and prompt clinicians to search for steroid-sparing therapies.

There have been no randomized, controlled trials reported in the English-language literature that address steroid-free protocols for steroid-dependent nephrotic syndrome. For 1 European study an improved outcome with the glucocorticoid deflazacort compared with prednisone in 40 children was reported.\(^28\) Deflazacort is not available in the United States. Use of cyclosporine, levamisole, mycophenolate mofetil, mizoribine (not available in the United States), cyclophosphamide, or chlorambucil may reduce the risk of relapses without glucocorticoids.\(^21,29–32\) Oral cyclophosphamide 2 to 3 mg/kg per day for 8 to 12 weeks in steroid-dependent children induces remission in 40% at 2 years, 24% at 5 years, and 17% in long-term follow-up.\(^21,32\) Given the severity of cyclophosphamide-associated adverse events, cytotoxic agents are considered a third-line choice for steroid-dependent nephrotic syndrome therapy.

**Steroid-Resistant Nephrotic Syndrome Management**

- kidney biopsy;
- tailor therapeutic regimen according to kidney histology; and
- provide optimal supportive therapy.
Steroid resistance places a patient at increased risk for both the development of complications of nephrotic syndrome and progression to end-stage kidney disease. The goal of therapy for steroid-resistant nephrotic syndrome is complete resolution of proteinuria and preservation of kidney function. However, pediatric and adult studies have documented an improved kidney survival rate for patients with a partial remission, defined as 50% reduction in proteinuria from baseline, compared with those without control of proteinuria. Because of this risk for end-stage kidney disease and the potential utility of histology for therapeutic decision-making, nephrologists perform a kidney biopsy before initiation of therapy for patients with steroid resistance.

The optimal therapy for steroid-resistant nephrotic syndrome remains poorly defined but requires a complete understanding of the armamentarium of therapeutic options and a fully engaged pediatric nephrologist to promote an optimal outcome. Clear evidence-based guidelines for the treatment of steroid-resistant nephrotic syndrome are not possible on the basis of a lack of sufficient randomized, controlled trials. There are 3 major categories of therapy for steroid-resistant nephrotic syndrome: (1) immunosuppressive; (2) immunostimulatory; and (3) non-immunosuppressive. The more commonly used immunosuppressive therapies include calcineurin inhibitors, mycophenolate mofetil, pulse intravenous methylprednisolone, and cytoxic agents. Other less commonly used or controversial treatments include plasma exchange and immunoadsorption. Novel agents are under investigation, but their safety and efficacy have not yet been determined. The only reported immunostimulatory agent in use is levamisole. However, this agent is not universally available. Last, nonimmunosuppressive treatments are commonly considered to be conservative therapy and include angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and vitamin E. Disease-based therapeutic recommendations are beyond the scope of these guidelines.

**ACE-I and ARB Therapy**
- ACE-I or ARB therapy is recommended for steroid-resistant nephrotic syndrome;
- consider use of ACE-Is or ARBs with steroid-dependent or frequently relapsing nephrotic syndrome; and
- counsel regarding contraindications of ACE-I or ARB therapy during pregnancy.

Blockade of the renin-angiotensin system has been shown to blunt the evolution of kidney disease, especially those associated with marked proteinuria. Several studies have demonstrated a reduction in proteinuria with ACE-I or ARB therapy. These drugs are generally well tolerated but also have documented adverse effects including hyperkalemia, angioedema, cough (ACE-Is), and, rarely, acute renal failure. Combination therapy with ACE-Is plus ARBs may simultaneously increase efficacy and adverse-effect potential. Women of childbearing age must be counseled regarding the teratogenic effects of ACE-I and ARB therapy.

**Hypertension Management**
- control blood pressure to <90th percentile of norma;
- recommend low-salt diet, exercise, and weight reduction if obesity is present; and
- ACE-Is and/or ARBs for chronic pharmacologic management.

Hypertension is present in 13% to 51% of children with nephrotic syndrome. Blood pressure generally improves with remission of nephrotic syndrome. When antihypertensive therapy is indicated, the expected reduction in proteinuria and blood pressure with ACE-I or ARB agents make them first-line agents.

**Edema Management**
- counsel caregivers regarding potential complications of edema; and
- consider treatment with low-sodium diet, modest fluid restriction, diuretics, and albumin infusions.

Edema is one of the cardinal symptoms of nephrotic syndrome. Immediate physician involvement is warranted if the patient develops respiratory distress, which may be secondary to pleural effusions or pulmonary edema. Sodium restriction to a level of 1500 to 2000 mg daily is commonly recommended. Severe edema associated with weeping tissues should be monitored for secondary infection. Severe edema may require pharmacologic intervention including loop diuretics, thiazide diuretics, and 25% albumin infusion. At a high dose or with chronic administration, diuretics may cause hypokalemia, exacerbate hyponatremia, cause intravascular volume depletion, and increase the risk for acute renal failure. Although only a temporizing measure, treatment with 25% albumin infusions and diuretics may be prescribed for children with severe edema. Albumin infusion may produce acute expansion of intravascular volume leading to hypertension, pulmonary edema, and congestive heart failure.

**COMPLICATIONS**

The complications of childhood nephrotic syndrome are associated with disease activity and therapy. Active nephrotic syndrome increases the risk for therapy-associated growth complications, dyslipidemia, infections, and thromboembolism.
**Obesity and Growth**
- monitor BMI and linear growth;
- provide counseling on weight control; and
- consider glucocorticoid alternatives when short stature or obesity is present.

Glucocorticoids may impair growth and increase BMI, with these effects proportional to dose and duration of the disease and therapy. Steroid-sparing treatment strategies may improve linear growth. Glucocorticoid therapy may increase BMI. Children who are overweight at initiation of steroid therapy are more likely to remain overweight after treatment for nephrotic syndrome. Steroid-sparing treatment strategies have been associated with a lower BMI. Anticipatory dietary counseling is recommended for children with nephrotic syndrome.

**Dyslipidemia**
- low-fat diet;
- consider low-density lipoprotein cholesterol-lowering drug therapy when fasting low-density lipoprotein cholesterol levels are persistently >160 to 190 mg/dL; and
- counsel regarding contraindications of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors during pregnancy.

Dyslipidemia is an expected finding in children with nephrotic syndrome and may resolve when patients are in remission. Children who have refractory nephrosis often have persistent dyslipidemia. In adult studies, persistent nephrotic syndrome is associated with atherosclerosis and an increased risk of coronary artery disease. One retrospective study, however, suggested that relapsing nephrotic syndrome in childhood does not lead to increase in risk for cardiovascular disease. Treatment includes dietary counseling to limit dietary fat to <30% of calories, saturated fat to <10% of calories, and <300 mg/day dietary cholesterol.

Treatment with HMG-CoA reductase inhibitors in adults with nephrotic syndrome have demonstrated a beneficial effect on dyslipidemia and may impact the progression of chronic kidney disease. Treatment of children with steroid-resistant nephrotic syndrome and persistent dyslipidemia with HMG-CoA reductase inhibitors has been proposed in childhood dyslipidemia care guidelines, but randomized studies are lacking.

**Infection**
- counsel regarding signs and symptoms of infections such as cellulitis, peritonitis, and bacteremia; and
- provide empiric therapy for peritonitis until culture results are available.

Infection is a common complication in children with nephrotic syndrome and an important cause of mortality. Edema associated with weeping tissues should be monitored carefully for development of secondary infectious complications including cellulitis. Spontaneous bacterial peritonitis, presenting with fever, severe abdominal pain, peritoneal signs, and, occasionally, signs of sepsis, is a well-described complication associated with morbidity and mortality. Thrombocytosis and coagulopathy; and thromboembolism.

**Thromboembolism**
- evaluate children with a thromboembolism for an underlying hypercoagulopathy; and
- provide anticoagulation therapy for children with nephrotic syndrome and thromboembolism.

Two percent to 5% of children with nephrotic syndrome develop thromboembolism. The risk seems higher in children with steroid-resistant compared with steroid-sensitive disease. Potential sites for thromboembolism include deep vein, central sinus, and renal vein thrombosis, pulmonary embolism, and arterial sites. Multiple factors are postulated to cause the increased risk of thromboembolism in nephrotic syndrome. There are urinary losses of factors that inhibit clot formation (eg, antithrombin III) and increased levels of factors that promote clot formation (eg, fibrinogen). Thrombocytosis and platelet hyperaggregability are common with nephrotic syndrome. Furthermore, volume depletion caused by dehydration or diuretic therapy may increase the risk of clot formation.

Although there have been no placebo-controlled studies, anticoagulation seems to be effective in children with nephrotic syndrome. Heparin, low molecular weight heparin, and oral anticoagulation with warfarin are therapeutic options. Fibrinolytic therapy has been effectively used in some children, but its use must be balanced by the increased risk of complications.
During periods of disease activity and increased thromboembolic risk, children should be encouraged to continue physical activity and avoid prolonged bed rest. The role of prophylactic anticoagulation medication such as low-dose aspirin is unclear. Prophylactic anticoagulation may be indicated in the setting of thromboembolism history, an underlying hypercoagulable condition beyond nephrotic syndrome, steroid-resistant nephrotic syndrome, and the presence of a central venous catheter.88 The potential benefits and risks of such therapy must be evaluated individually.

**Vaccinations**
- immunize with the 23-valent and heptavalent conjugated pneumococcal vaccines;
- immunize the immunosuppressed or actively nephrotic patient and household contacts with inactivated influenza vaccine yearly;
- defer immunization with live vaccines:
  - until prednisone dose is <2 mg/kg per day (maximum: 20 mg);
  - for 3 months from completion of therapy with cytotoxic agents; or
  - for 1 month from completion of other daily immunosuppression;
- provide varicella immunization if nonimmune, on the basis of immunization history, disease history, or serologic evaluation;
- provide postexposure immunoglobulin for nonimmune immunocompromised patients; and
- consider intravenous acyclovir for immunosuppressed children at the onset of chicken pox lesions.

Vaccination is especially important for children with nephrotic syndrome. They are at risk for more severe infections because of the impact of nephrotic syndrome and the effects of immunosuppression.89 Moreover, children with nephrotic syndrome are especially susceptible to pneumococcal disease.75 Varicella infection may lead to life-threatening disease in children receiving immunosuppressive medications.89 Varicella vaccination, proven to be safe and effective in children with nephrotic syndrome, should be administered on the basis of the recommended guidelines for live vaccines.90–93

**Monitoring**

Table 1 sets forth a summary of monitoring recommendations according to nephrotic syndrome severity and treatment regimen.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Home Urine Protein</th>
<th>Weight, Growth, BMI</th>
<th>Blood Pressure</th>
<th>Creatinine</th>
<th>Electrolytes</th>
<th>Serum Glucose</th>
<th>CBC</th>
<th>Lipid Profile</th>
<th>Drug Levels</th>
<th>Liver Function</th>
<th>Urinalysis</th>
<th>CPK</th>
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<td>Mild (steroid responsive)</td>
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<td>Moderate (frequent relapsing, steroid dependent)</td>
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<td>Severe (steroid resistant)</td>
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<td>Therapy</td>
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<td>Mycophenolate mofetil</td>
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<td>Calcineurin inhibitors</td>
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<td>ACE-Is/ARBs</td>
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<td>HMG-CoA reductase inhibitors</td>
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CBC indicates complete blood count; CPK, creatine kinase.
tors to infertility and potential for future malignancy with cytotoxic agents.

Patients with steroid-resistant nephrotic syndrome are at greatest risk for progressive kidney injury, complications of chronic nephrotic syndrome, and complications associated with pharmaceutical therapy. An individualized treatment plan based on kidney histology and response will require the involvement of a pediatric nephrologist to optimize control of nephrotic syndrome and minimize morbidity and mortality rates.

These guidelines are based on the best summary of available published data and opinion when data were insufficient. In addition to the development of these guidelines, the panel has identified opportunities for validation and improvement of this consensus document through collaborative research.

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