

A PHYSICIAN'S HANDBOOK

# Childhood Nephrotic Syndrome

**Developed by**

Pediatric Nephrology Program  
British Columbia Children's Hospital  
British Columbia Provincial Renal Agency  
Vancouver, British Columbia, Canada

2nd EDITION • FEBRUARY 2017



## When and how to contact us

For pediatric nephrology advice, contact the Nephrology Program at British Columbia Children's Hospital.

During business hours, call **604 875 2272** and we will connect you with one of the team members.

Outside business hours, call the hospital switchboard at **604 875 2345** and ask for the nephrologist on call.

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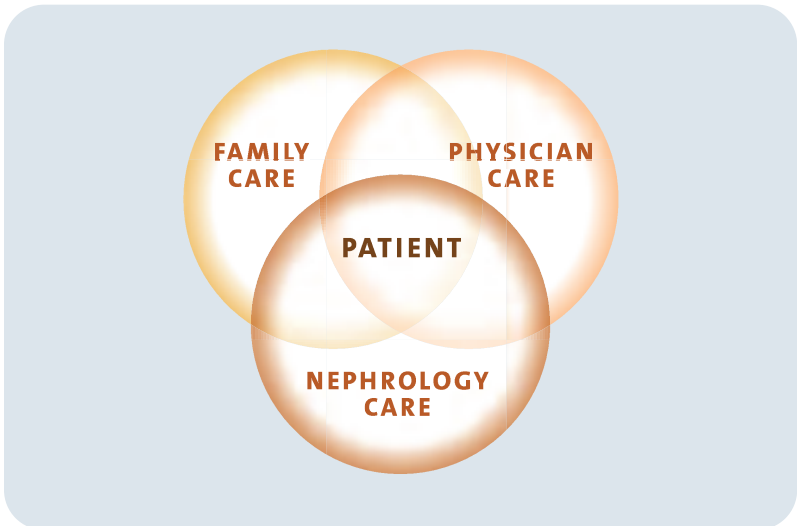
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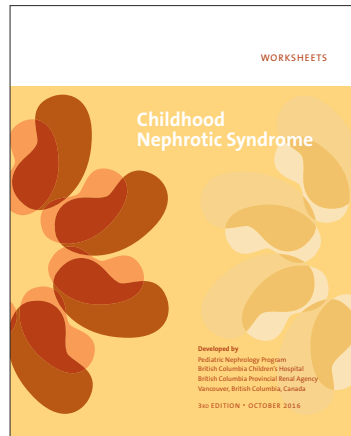
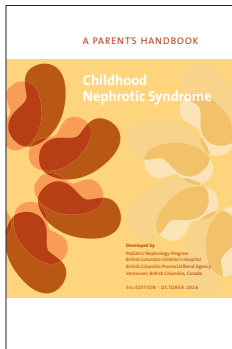
## Introduction

The purpose of this handbook is to present a summary of current and local recommendations for the evaluation and treatment of children with nephrotic syndrome (NS) by physicians in British Columbia. Children with NS require shared care among families, physicians, and nephrology teams. Some aspects of care, such as consultations and investigations, are unique to a specific type of care provider, such as nephrologists and other members of a specialized nephrology team including nurses, pharmacists, and dietitians. Other aspects, such as medication monitoring and education, require overlapping input from various types of care providers including families, physicians, and the patients themselves. Each type of care provider serves an equally important role, and it is the collective effort of ALL providers that has the most valuable impact on the health of children with NS. To facilitate the shared care of children with NS, we have therefore developed a childhood NS clinical pathway.



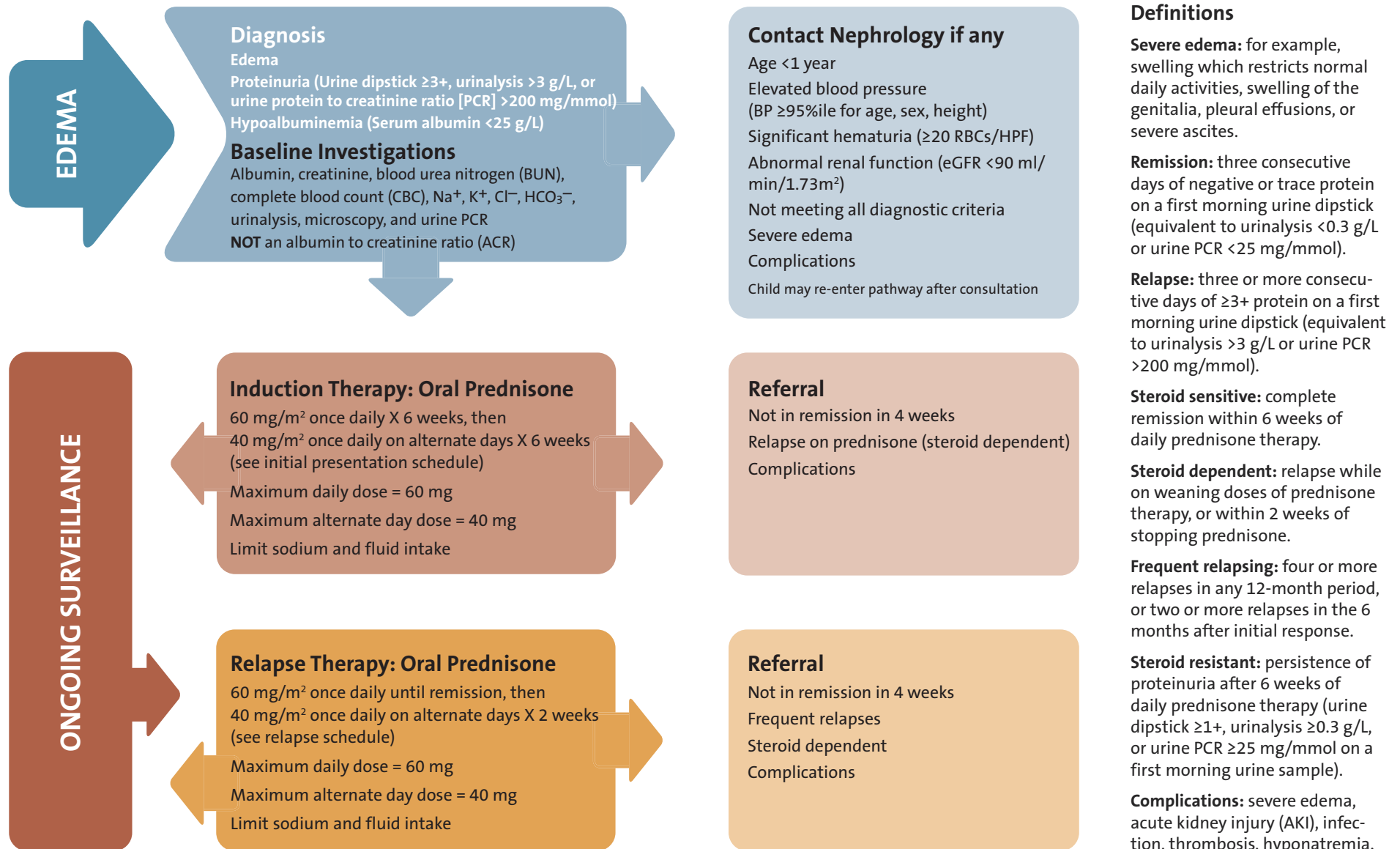
In its entirety, this clinical pathway is a structured, evidence-based, and multidisciplinary care plan detailing the essential steps undertaken by various care providers in the treatment of children with idiopathic and uncomplicated NS. It also provides a “roadmap” of the expected progress of these children through routine care.

This handbook incorporates the physician care portion of our clinical pathway and focuses on the steps to be taken by physicians, from the initial presentation of a child with NS up to one year of follow-up. We have developed a similar handbook (and accompanying worksheets) for the parents of children with NS which provides information about the disease, outcomes, and suggested treatments, as well as instructions on how to monitor for NS remission and relapses, side effects, and complications at home.



The recommendations outlined in our clinical pathway are based on the best-available evidence. In circumstances where evidence is lacking or conflicting, our clinical pathway team has come up with recommendations based on a thorough review of the available literature, detailed analysis of local data, and input from various members of our multidisciplinary team including nephrologists, nurses, dietitians, pharmacists, and local experts. As new evidence becomes available over time we will incorporate changes into practice and future editions of the handbook. The following is a schematic summary of the physician care portion of our childhood NS clinical pathway.

# Childhood nephrotic syndrome clinical pathway: physician care summary





## Childhood nephrotic syndrome clinical pathway: physician care summary

The physician care portion of the childhood nephrotic syndrome (NS) clinical pathway highlights the role of physicians in the evaluation and treatment of children with NS. Enclosed is a quick and concise visual reference of the steps to be taken by physicians, from initial presentation of a child with NS up to one year of follow-up.

### Useful calculators

Body surface area (BSA) in m<sup>2</sup>

$$BSA = \sqrt{\frac{\text{Height (cm)} \times \text{Ideal Body Weight* (kg)}}{3,600}}$$

\* To determine ideal body weight, plot the child's height on a growth chart, determine the percentile score for this height, then plot the child's weight using the same percentile score.

Estimated glomerular filtration rate (eGFR) in ml/min/1.73m<sup>2</sup>

$$eGFR = \frac{\text{Height (cm)} \times 36.5}{\text{Serum creatinine (umol/L)}}$$

### Recommended maximum calorie, sodium, and fluid intake

WEIGHT (kg)	CALORIE AND SODIUM (mg/day)*		FLUID (ml/day)**
	BOYS	GIRLS	
10	800	800	500
20	1,300	1,300	750
30	1,600	1,400	900
40	1,700	1,600	1,000
50	2,000	1,700	1,100
60	2,300	1,800	1,100
70	2,400	1,900	1,200

\* While on prednisone    \*\* While in relapse

### Pediatric Nephrology Program

Tel: 604 875 2272

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On call pager: 604 875 2161

## Schedule of ongoing care

Scheduled visits for the child during the first year

TEST/REVIEW	CLINIC VISIT						
	0 w*	4 w	6 w**	12 w	6 m	9 m	12 m
Confirm and explain diagnosis	✓						
<b>History</b>							
• History of swelling	✓						
• Review immunization status	✓	✓	✓	✓	✓	✓	✓
• Document date and time to remission		✓	✓				
• Review Handbook Worksheets		✓	✓	✓	✓	✓	✓
• Review prednisone schedule		✓	✓	✓	✓	✓	✓
• Review medication history	✓	✓	✓	✓	✓	✓	✓
<b>Physical examination</b>							
• Blood pressure, heart rate and temperature	✓	✓	✓	✓	✓	✓	✓
• Record growth (height, weight)	✓	✓	✓	✓	✓	✓	✓
• Check for swelling	✓	✓	✓	✓	✓	✓	✓
• Other signs of prednisone side effects (eyes, bone, skin)		✓	✓	✓	✓	✓	✓
<b>Lab testing</b>							
• CBC, albumin, urea, creatinine, Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup>	✓	No regular blood testing needed					
• Urinalysis, microscopy, and PCR	✓	✓	✓	✓	✓	✓	✓
<b>Monitoring</b>							
• Review fluid restriction	✓	✓					
• Review dietary recommendations	✓	✓		✓			✓
• Review home monitoring (urine dipsticks)	✓	✓	✓	✓	✓	✓	✓
• Eye clinic evaluation		✓					
• Family given handbook & worksheets	✓						
• Schedule follow-up appointment	✓	✓	✓	✓	✓	✓	✓

\* Visit at which prednisone is started. Contact the Nephrology Program at BCCH for support. A subsequent clinic visit within 1 week is likely needed to complete all necessary tests and teaching

\*\* A six-week visit is required if your child is not in remission at 4 weeks

## Diagnosis of nephrotic syndrome

Nephrotic syndrome (NS) is one of the most common kidney disorders in childhood. Most children will respond to standard steroid therapy (oral prednisone), outgrow their disease by the end of adolescence or early adulthood, and have a favorable long-term outcome with normal renal function. The reported international incidence and prevalence of NS is 2–7 cases per 100,000 and 16 cases per 100,000 children respectively, with a higher reported incidence in Asian populations. The median age of presentation is four years and more boys than girls are affected (2:1 male to female ratio).

Children are diagnosed as having NS if they have the triad of edema, proteinuria, and hypoalbuminemia. *Hyperlipidemia is an associated feature of NS, but is not required for diagnosis.*

### Edema

In NS, the retention of sodium and fluid results in fluid accumulation and edema. The onset of edema may be insidious, developing gradually over days to weeks. However, the severity of edema upon presentation can vary significantly depending on several factors including sodium and fluid intake, duration of illness prior to diagnosis, and the severity of the NS itself. Edema becomes clinically detectable when fluid retention exceeds 3–5% of body weight. Most children and their parents will notice periorbital edema first, which is often misdiagnosed as an allergic reaction (*Figure 1a*).



*Figure 1a.* Patient with moderate edema around the eyes.

Children with NS often have pitting edema of the lower legs, feet, and ankles (*Figure 1b*) and may also experience ascites, sacral edema, and in severe cases, scrotal or labial edema.



*Figure 1b.* Gentle pressure leaves a temporary imprint on the lower leg.

### Proteinuria

Heavy protein (albumin) loss in the urine is an important diagnostic feature of NS. Proteinuria helps distinguish NS from cardiac, gastrointestinal, and hepatic conditions commonly associated with edema and hypoalbuminemia alone.

A urine dipstick with  $\geq 3+$  protein or a urinalysis with  $>3$  g/L of protein is equivalent to “nephrotic range” proteinuria. A random urine measurement of the protein creatinine ratio (PCR)  $>200$  mg/mmol confirms “nephrotic range” proteinuria and therefore the diagnosis of NS.<sup>1</sup> A 24-hour urine collection is not necessary for diagnosis.

*Table 1* summarizes the interpretation of urinary protein findings.

TABLE 1

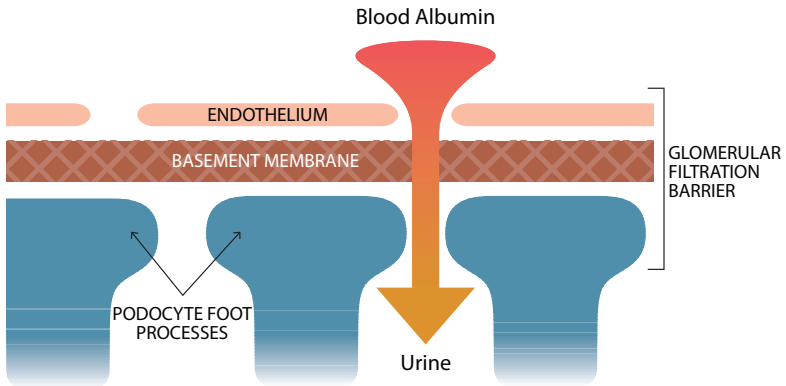
### Summary of urinary protein interpretation

	NORMAL	ABNORMAL	NEPHROTIC RANGE
Urine dipstick	Negative–trace	1+ or 2+	3+ or 4+
Urinalysis	$<0.3$ g/L	0.3–3 g/L	$>3$ g/L
Protein creatinine ratio (PCR)	$<25$ mg/mmol	25–200 mg/mmol	$>200$ mg/mmol

<sup>1</sup> Evidence for determining “nephrotic range” proteinuria from an albumin creatinine ratio (ACR) is lacking; therefore, its use in children with NS is not recommended.

## Hypoalbuminemia

In NS, low serum albumin results from heavy urinary losses of protein secondary to the disruption of the glomerular filtration barrier, which consists of the fenestrated endothelium, glomerular basement membrane, and podocyte foot processes (*Figure 2*). Hypoalbuminemia is defined as a serum albumin  $<25$  g/L (normal range 35–45 g/L). A serum albumin  $<25$  g/L is generally associated with edema formation, but many children with NS have significantly lower levels at presentation.



*Figure 2.* Disruption of the glomerular filtration barrier resulting in urinary protein losses.

## Hyperlipidemia

In NS, reactive hepatic protein synthesis from hypoalbuminemia and low oncotic pressure results in hyperlipidemia. Serum total cholesterol, triglycerides, and total lipids are all elevated in children with NS. However, documenting hyperlipidemia is not necessary to confirm the diagnosis of NS. Given that elevated cholesterol and triglyceride levels are often transient and will resolve once the child goes into remission, initial treatment with lipid-lowering agents is not recommended.

## Types of nephrotic syndrome

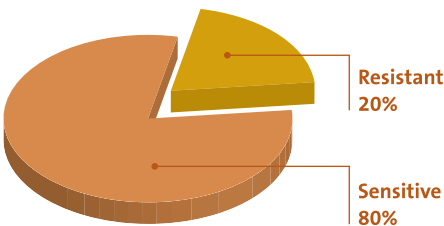
### Classifying nephrotic syndrome based on clinical course

The majority ( $\approx 80\%$ ) of children with nephrotic syndrome (NS) respond to prednisone therapy and are considered **steroid sensitive** (*Pie Chart 1*). At initial presentation,  $\approx 50\%$  of children who are steroid sensitive respond within 7–10 days of treatment,  $\approx 95\%$  by 4 weeks, and the remaining within 4–8 weeks. Even though most children with NS will respond to prednisone, the majority ( $>80\%$ ) will have a future relapse after the first episode. However, only  $\approx 5\%$  of children continue to experience relapses after the age of 18 years.

Overall,  $\approx 20\%$  of children with NS do not respond to prednisone therapy and are considered **steroid resistant** (*Pie Chart 1*). They have a higher risk of developing progressive chronic kidney disease (CKD) and end-stage renal disease (ESRD).

Childhood NS response to prednisone

PIE CHART 1



Documenting when and how often a child has a relapse is important to determine whether the child has a complicated disease course (**frequent relapsing or steroid dependent NS**). Children with a complicated course of NS should be monitored more closely as they often require repeated courses of daily prednisone, which puts them at higher risk of steroid side effects and increased need for other second-line therapies, such as cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors (tacrolimus, cyclosporine), and Ritixumab. *Table 2* summarizes the different clinical courses of childhood NS.

TABLE 2

### Clinical courses of childhood NS

<b>Remission</b>	Three consecutive days of negative or trace protein on a first morning urine dipstick (equivalent to urinalysis <0.3 g/L or urine PCR <25 mg/mmol)
<b>Relapse</b>	Three or more consecutive days of $\geq 3+$ protein on a first morning urine dipstick (equivalent to urinalysis >3 g/L or urine PCR >200 mg/mmol)
<b>Steroid sensitive</b>	Complete <i>remission</i> within 6 weeks of daily prednisone therapy
<b>Steroid resistant</b>	Persistence of proteinuria after 6 weeks of daily prednisone therapy (urine dipstick $\geq 1+$ , urinalysis $\geq 0.3$ g/L, or urine PCR $\geq 25$ mg/mmol on a first morning urine sample)
<b>Frequent relapsing</b>	Four or more <i>relapses</i> in any 12-month period, or two or more <i>relapses</i> in the 6 months after initial response
<b>Steroid dependent</b>	<i>Relapse</i> while on weaning doses of prednisone therapy, or within 2 weeks of stopping prednisone

### Classifying nephrotic syndrome based on histopathology

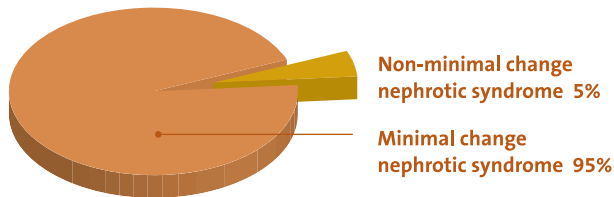
NS may be primary (often referred to as idiopathic), or secondary to other diseases.<sup>2</sup> This clinical pathway considers those children with primary NS, as they constitute the majority of children with NS. Distinguishing the type of NS based on histopathology obtained from a kidney biopsy may influence treatment and may help predict the long-term prognosis.

<sup>2</sup> Causes of secondary NS include systemic lupus erythematosus (SLE), Henoch-Schonlein purpura (HSP), malignancy, and infections such as hepatitis B, hepatitis C, and human immunodeficiency virus (HIV).

If all children with primary NS had a kidney biopsy, 75% would have **minimal change disease**. Minimal change disease refers to histologically “normal looking” kidney glomeruli by light microscopy on biopsy. The remaining 25% of cases would have other histological diagnoses, most commonly focal segmental glomerulosclerosis (FSGS), and others including mesangioproliferative glomerulonephritis, membranous nephropathy, and membranoproliferative glomerulonephritis (MPGN). We often refer to these conditions collectively as **non-minimal change disease**. Non-minimal change disease conditions are sometimes associated with a less favorable long-term renal prognosis with the development of progressive CKD and ESRD during childhood.

Previous studies have shown that 95% of patients who are steroid sensitive would have a diagnosis of minimal change disease if biopsied (*Pie Chart 2*), and for this reason kidney biopsy is not a routine test for those patients who respond to prednisone.

### Types of nephrotic syndrome in children who respond to prednisone



PIE CHART 2

# 4

## Evaluation at initial presentation

At the initial presentation of a child with nephrotic syndrome (NS), contact the Nephrology Program at British Columbia Children's Hospital (BCCH) to arrange access to patient/family resources and our multidisciplinary care team, medication coverage by the British Columbia Provincial Renal Agency, and possible follow-up with the BCCH team.

Obtaining a comprehensive clinical history, performing a thorough physical examination, and requesting relevant lab investigations are essential at the initial presentation of a child with NS. When done appropriately, these evaluations help confirm the diagnosis of NS, ensure that the child is well enough to start prednisone therapy, identify “red flags” or atypical features suggestive of secondary disease and/or possible complications, and provide a baseline against which to compare future visits.

### Cinical history

A comprehensive clinical history should include an evaluation of edema, possible atypical features, potential complications, possible secondary causes, and immunization status. *Table 3*, page 10, summarizes details.

### Physical examination

Determination of vital signs should include blood pressure (BP), respiratory rate (RR), heart rate (HR), and temperature. Obtaining an accurate weight and height is essential to calculate the child's body surface area (BSA) at the initial encounter. Given that children with NS can be several kilograms above their dry weight upon presentation depending on the severity of edema, it is important to determine their ideal body weight.<sup>3</sup> Height, weight and BSA are used to calculate

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3 To determine ideal body weight, plot the child's height on a growth chart, determine the percentile score for this height, then plot the child's weight using the same percentile score.



prednisone dosing, evaluate the response to therapy, and assess growth trends. The formula for calculating BSA is below:

$$BSA = \sqrt{\frac{\text{Height (cm)} \times \text{Ideal Body Weight (kg)}}{3,600}}$$

The child should then be evaluated for the presence, distribution, and severity of edema. Edema at presentation can sometimes be severe enough to require admission to hospital. Apart from peripheral and periorbital edema, many children with NS have ascites and pleural effusions. These are often mild, clinically silent, and rarely cause respiratory distress on their own. **If the child has severe edema (severe ascites, large and symptomatic pleural effusions and/or scrotal/labial edema), consultation with a pediatric nephrologist regarding possible admission to hospital is recommended.** *Table 4*, page 11, summarizes pertinent findings on physical examination.

TABLE 3

### Clinical history

#### Detailed history of edema

Location, duration, severity and weight gain

#### History of atypical features (possible “red flags”)

Age <1 year

Gross hematuria

#### Detailed history of possible complications

Severe edema: Respiratory distress, abdominal pain

Intravascular volume depletion: Thirst, dizziness, syncope, decreased urine output

Hypertension: Headaches, blurred vision, epistaxis

Infection: Abdominal pain, fever, respiratory distress

Deep vein thrombosis: Local tenderness, swelling, redness

#### History for possible secondary causes

Constitutional symptoms: Weight loss, fever, low appetite

Hair loss, photosensitivity, oral ulcers

Joint swelling or pains

Skin rash

Jaundice

#### Immunization status

Includes timing and doses of varicella and pneumococcal immunizations

## Physical examination

### Weight, height, BP, RR, HR, and temperature

#### Evaluation of edema

- Periorbital and peripheral edema
- Pleural effusion
- Ascites
- Labial or scrotal edema

#### Possible red flags

- Hypertension

#### Possible complications

- Severe edema: Respiratory distress, abdominal tenderness
- Intravascular volume depletion:
  - Dry mucous membranes, cold extremities
  - Decreased peripheral pulses, capillary refill >2 secs
  - Tachycardia and hypotension
  - Orthostatic changes in BP and HR
- Infection: Fever, rebound tenderness, tachypnea, cellulitis
- Deep vein thrombosis: Local tenderness, swelling, redness

#### Evaluation of possible secondary causes

- Arthritis
- Skin rash, petechiae, oral ulcers, alopecia
- Jaundice, liver enlargement and/or tenderness

## Initial lab investigations

Initial *urine tests* should include a standard urinalysis and microscopy, and a urine protein to creatinine ratio (PCR). These urine tests will be used to quantify the extent of proteinuria, to confirm the diagnosis of NS, and to document the presence of microscopic hematuria.

Initial *blood tests* should include serum albumin to confirm the diagnosis of NS. Obtaining urea, creatinine, and electrolyte levels (sodium [Na<sup>+</sup>], potassium [K<sup>+</sup>], chloride [Cl<sup>-</sup>], and bicarbonate [HCO<sub>3</sub><sup>-</sup>]) helps screen for acute kidney injury (AKI) and hyponatremia, which in children with NS can indicate intravascular volume depletion.

To determine kidney function, converting the child's serum creatinine into an estimated glomerular filtration rate (eGFR) using the Schwartz estimating formula is recommended. An abnormal eGFR is less than

90 ml/min/1.73m<sup>2</sup>. The Schwartz formula for calculating eGFR in ml/min/1.73m<sup>2</sup> is:

$$\text{eGFR} = \frac{\text{Height (cm)} \times 36.5}{\text{Serum creatinine } (\mu\text{mol/L})}$$

A complete blood count (CBC) helps identify signs of infection and an elevated hemoglobin value suggests hemoconcentration, often an indirect sign of volume depletion. The presence of anemia, thrombocytopenia and/or leukopenia may point towards an underlying auto-immune disease such as systemic lupus erythematosus (SLE).

Children with NS “at risk” for hepatitis B and C infections and those that have been exposed to human immunodeficiency virus (HIV) should be tested for these viruses since they are secondary causes of NS.

Complement C3 and C4 blood levels are markers for autoimmune disease. A low C3 level can point towards underlying diseases causing NS such as SLE nephritis, post-infectious glomerulonephritis, or membranoproliferative glomerulonephritis (MPGN). *Table 5* summarizes the recommended lab investigations for children presenting with NS.

TABLE 5

### Initial lab investigations

#### Urine tests

Urinalysis and microscopy (protein concentration in g/L and # of RBCs/HPF)  
Protein to creatinine ratio (PCR) (mg/mmol)

#### Blood tests

CBC  
Electrolytes (Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup>)  
Albumin, urea, creatinine

#### Additional blood tests as indicated

Viral risk factors: hepatitis B, hepatitis C, HIV  
Atypical features: C3, C4

### Typical versus atypical presentation

In children with NS, the clinical features and response to prednisone help predict histology and prognosis.

#### Typical features

Typical features of NS at presentation include onset at ≥1 year of age, normal blood pressure (<95%ile for age, sex, and height), normal renal function (eGFR ≥90 ml/min/1.73m<sup>2</sup>), and lack of or

mild hematuria (<20 red blood cells [RBCs]/high power field [HPF] by microscopy). A complete response to daily prednisone therapy by 6 weeks (complete remission) is also typical. For children presenting with typical features, a renal biopsy gives little additional information as there is a high probability that these children have **minimal change disease**.

### Atypical features or “red flags”

Atypical features of NS or “red flags” include onset at <1 year of age, hypertension ( $\geq 95$ th percentile for age, sex, and height on at least three different occasions), abnormal kidney function (eGFR <90 ml/min/1.73m<sup>2</sup>), gross and/or significant hematuria ( $\geq 20$  RBCs/HPF) at initial diagnosis or thereafter, and lack of a complete response after 6 weeks of daily prednisone. There is a higher probability of having **non-minimal change disease** with the presence of atypical features, especially when seen in combination. Some of these patients may require a kidney biopsy to confirm non-minimal change disease and to help with further treatment choices. *Table 6* summarizes the typical and atypical features of childhood NS.

TABLE 6

### Typical vs. atypical features of childhood NS

Typical features	Atypical features (red flags*)
Age $\geq 1$ year	Age <1 year
Transient hypertension or normal BP (BP <95th percentile for age, sex, and height)	Hypertension (BP $\geq 95$ th percentile for age, sex, and height)
Normal renal function (eGFR $\geq 90$ ml/min/1.73m <sup>2</sup> )	Abnormal renal function (eGFR <90 ml/min/1.73m <sup>2</sup> )
Lack of or mild hematuria (<20 RBCs/HPF)	Significant or gross hematuria ( $\geq 20$ RBCs/HPF)
Steroid sensitive NS	Steroid resistant NS

\* Atypical features are referred to as “red flags” and include features from the clinical history, physical examination, and initial lab testing at diagnosis which may suggest non-minimal change disease.

For children presenting with any atypical features or “red flags,” immediate consultation with a pediatric nephrologist is recommended to discuss therapy and possible referral.

**Age** Minimal change disease is the most common pathological diagnosis in children with NS who are <18 years of age. Both congenital NS (occurring within the first 3 months of life) and infantile NS (occurring between 3–12 months of age) are rare and often have a genetic basis. Children with congenital or infantile NS are typically unresponsive to treatment and have a poor long-term outcome. **An urgent referral to a pediatric nephrologist is recommended for any child <1 year of age presenting with NS.**

**Hypertension** In children, hypertension is defined as a BP  $\geq 95$ th percentile for age, sex, and height on at least three occasions. The child's BP should be measured on the right arm using an oscillometric instrument (Dynamap) or by sphygmomanometry (manual BP) with the appropriate sized cuff. If the BP readings by Dynamap are elevated, a manual BP should be obtained if possible. If initially elevated, the child's BP should be taken twice (at least five minutes apart) and the lowest BP recorded. Cuff bladders should measure at least  $\frac{2}{3}$  the circumference of the upper arm. A reference table for normal blood pressure ranges in children is available in *Appendix 1 (Boys)* and *Appendix 2 (Girls)*.

At initial presentation, many children with NS have mild to moderate elevations in BP. The reasons are varied and include anxiety, pain, and intravascular volume expansion. Most children with high BPs are asymptomatic. Therefore, it is important to repeat the BP when the child is calm and euvolemic. Hypertension may be related to the underlying form of NS or to the start of daily prednisone therapy. A child with high blood pressure at initial diagnosis and before starting prednisone requires repeat evaluation within a week, as the high BP may suggest more sinister forms of NS requiring prompt treatment.

**Abnormal kidney function** Many children with NS experience transient changes in kidney function related to intravascular volume depletion and acute kidney injury (AKI). However, persistently abnormal kidney function may indicate non-minimal change diagnoses.

**Hematuria** Children with NS presenting with a history of gross hematuria and/or significant microscopic hematuria ( $\geq 20$  RBCs/HPF on microscopic urinalysis) require careful attention. Hematuria can be initially identified from an abnormal urinary dipstick result (1+, 2+, and 3+ blood), but should be confirmed by the number of RBCs/HPF on urine microscopy.

### **Features suggesting secondary disease**

Children with secondary forms of NS may have clinical features at initial presentation which suggest a more systemic disease. For example, SLE is a disease that can present with NS. Other uncommon presentations of NS are those secondary to malignancy (leukemia, lymphoma) and infections (hepatitis B, hepatitis C, HIV). However, it is important to remember that these presentations are uncommon.

## Recognizing and treating complications

Prompt recognition and management of the complications of childhood nephrotic syndrome (NS) is important. Severe edema, acute kidney injury (AKI), infection, thrombo-embolic events, and hyponatremia are significant complications of NS that may require hospitalization and close monitoring. When these complications are mild and do not require immediate intervention, they may respond to treatment with the appropriate dosing of prednisone.

### Complication #1: Edema

Edema is the most common reason for parents to seek medical attention for their child with NS. When severe, edema may be associated with difficulty breathing (either because of large pleural effusions or severe ascites) and significant abdominal pain (due to bowel wall edema, ascites, poor splanchnic blood flow, and/or peritonitis). Severe generalized edema (anasarca) may also lead to skin breakdown, cellulitis, difficulty ambulating, and genital (scrotal or labial) edema.

#### Action: Sodium and fluid restriction

One of the most important and under-appreciated strategies for controlling edema is sodium restriction. Sodium restriction will also reduce thirst and thereby make fluid restriction more feasible.

Limiting sodium while the child is on prednisone and fluid intake while the child is in relapse is recommended, unless the child is volume depleted. For a detailed outline of this recommendation and the rationale for its use see *Section 7 Diet. Table 7* summarizes the recommended maximum daily calorie, sodium, and fluid intakes for children with NS.

TABLE 7

## Recommended maximum calorie, sodium, and fluid intake

WEIGHT (kg)	CALORIE AND SODIUM INTAKE (mg/day)*		FLUID (ml/day)**
	BOYS	GIRLS	
10	800	800	500
20	1,300	1,300	750
30	1,600	1,400	900
40	1,700	1,600	1,000
50	2,000	1,700	1,100
60	2,300	1,800	1,100
70	2,400	1,900	1,200

\* While on prednisone \*\* While in relapse

### Action: Albumin and furosemide therapy

If edema is severe enough to interfere with normal daily functions it may need to be treated with intravenous albumin (25%) and furosemide. Children with NS admitted to hospital with edema are often in a volume contracted state, sometimes reflected by symptoms of orthostatic hypotension and an elevated serum urea and creatinine. Orthostatic symptoms can be assessed by testing for a drop in blood pressure (BP) and a rise in heart rate (HR) with changes from the lying to standing position.<sup>4</sup>

Measuring the fractional excretion of sodium (FENa) in a child presenting with severe edema is recommended to differentiate whether the child's intravascular volume is contracted or expanded. A FENa <0.2% suggests volume contraction, while a FENa ≥0.2% suggests volume expansion. Those with a FENa ≥0.2% may require only diuretic therapy, such as oral or intravenous Lasix and/or fluid restriction. FENa is calculated as follows:

$$\%FENa = \frac{Urine_{Na} \times Plasma_{Cr}}{Urine_{Cr} \times Plasma_{Na}} \times 100$$

<sup>4</sup> To test for orthostatic changes measure BP while child is laying and standing and compare the measurements. Orthostatic hypotension is a 20 mmHg drop in systolic BP or a 10 mmHg drop in diastolic BP within three minutes of standing up. A significant orthostatic HR rise is defined as a rise of 20–30 beats per minute.



Intravascular volume contraction should improve with intravenous albumin and furosemide therapy; therefore, it is important to monitor trends in the child's renal function (urea, creatinine, electrolytes) throughout the hospital admission period.

The usual intravenous dosage of albumin is 1 g/kg given as a 25% solution over 3–4 hours with intravenous furosemide (1 mg/kg/dose) given halfway through and at the end of the infusion. Doses of intravenous albumin may be repeated during the day, but are often limited to two infusions daily. Vital signs should be recorded every 30 minutes during the infusion. Most children experience an asymptomatic and transient increase in BP during the first two hours of the infusion which does not require treatment. There is a small risk of pulmonary edema with use of albumin and Lasix particularly in the face of more significant renal injury and decreases in GFR. Most children with severe edema requiring admission to hospital need daily albumin infusions for several days, which should be continued until there is minimal edema. **If a child is swollen enough to require diuretics and/or admission to hospital for albumin therapy, and/or has AKI with decreased urine output, consultation with a pediatric nephrologist is recommended.**

### **Complication #2: Infection**

Children with NS are immunocompromised. They have impaired T-lymphocyte function and lose immunoglobulins and complement factors in their urine. Daily doses of prednisone worsen this immunocompromised state. Consequently, these children are at risk for severe infections including sepsis, cellulitis, and spontaneous bacterial peritonitis. Cellulitis is often caused by staphylococcal or streptococcus bacteria and peritonitis by *Streptococcus pneumoniae*. Other causes include *Escherichia coli* and *Haemophilus influenzae*. Despite a history of pneumococcal immunization, these children may require additional immunizations for pneumococcus. For more detail see *Section 8 Immunizations and infectious disease*.

Varicella-zoster virus (VZV) infections can also be severe in children with NS requiring the use of Varicella-zoster immunoglobulin (VariZIG) and acyclovir. It is essential to document the VZV status of all children presenting with NS including their history of previous disease or immunization. For more detail see *Section 8 Immunizations and infectious disease*.

### **Action**

Good hand hygiene, regular visits to the doctor and dentist, and ensuring that routine immunizations are up-to-date will help lower the risk of infection in children with NS. If a child with NS develops a persistent fever or any other signs of bacterial infection, they should be evaluated immediately and started promptly on antibiotics. **If a child with NS is exposed to an infectious agent/individual and/or they develop signs of infection, consultation with a pediatric nephrologist is recommended.**

### **Complication #3: Thrombo-embolic events**

Children with NS are at a higher risk of thrombosis. Factors contributing to an increased clotting risk include abnormalities of the clotting cascade and the loss of coagulation inhibitors such as antithrombin III in the urine. Other prothrombotic risks include hyperviscosity, increased platelet aggregation, and prolonged immobilization. Although rare, thrombo-embolic events in children with typical NS can be fatal. This occurs with sinus venous thrombosis and pulmonary embolism. The incidence of thrombo-embolic events in children with NS is as high as 5%, with the majority occurring in children with steroid resistant NS or secondary disease. The majority of events occur early in the course of the disease and correlate with severe proteinuria, the use of central venous catheters, age of onset >12 years, and a previous history of thrombo-embolism.

### **Action**

**When considering imaging studies and treatment for suspected clots in children with NS, consultation with a pediatric nephrologist and hematologist is recommended.**

Prophylactic anticoagulation such as daily aspirin is not routinely recommended in children with typical NS, but may be indicated in certain higher risk groups (age of onset >12 years, steroid resistant NS, secondary disease, and use of central venous catheters). **If you are considering the use of anticoagulation, consultation with a pediatric nephrologist is recommended.**

### **Complication #4: Hyponatremia**

Hyponatremia is defined as a serum sodium (Na<sup>+</sup>) <135 mmol/L. Children with NS can have hyponatremia at initial presentation and during relapses. These children usually have edema. This hyponatremia is due in part to the release of anti-diuretic hormone, particularly in

those children with intravascular volume depletion. Intake of hypotonic fluid will worsen this hyponatremia. Hyponatremia may warrant admission to hospital, especially if there are other features of intravascular volume depletion or AKI. Restoring the child's intravascular volume with intravenous albumin will usually reverse the hyponatremia. Correction of the hyponatremia at a slow rate (10–12 mmol/L daily) is unnecessary as the hyponatremia is often acute in nature.

### Action

**If a child with NS has a serum Na<sup>+</sup> level <135 mmol/L, consultation with a pediatric nephrologist is recommended.** The administration of sodium supplements or intravenous hypertonic (3%) saline solutions to correct the hyponatremia is not recommended in these children.

### Reasons for hospital admission

The majority of children presenting with NS and those experiencing a subsequent relapse can be treated as outpatients. There are however a number of concerning complications that require monitoring and treatment in the hospital setting. **Complications are signs of a more complex disease course and consultation with a pediatric nephrologist is recommended in these cases.** *Table 8* summarizes complications of NS that may necessitate hospital admission.

TABLE 8

### Possible reasons for hospital admission

#### Severe edema

Respiratory distress, massive ascites, genital edema, inability to ambulate

#### Impaired renal function

Estimated glomerular filtration rate (eGFR) <90 ml/min/1.73m<sup>2</sup>, oliguria, hyperkalemia

#### Severe infection

Suspected peritonitis, pneumonia, sepsis, meningitis, cellulitis, varicella

#### Thrombosis

Suspected deep vein thrombosis, pulmonary embolism, renal vein thrombosis, sinus venous thrombosis

#### Symptomatic hypertension

## Treatment

### Induction therapy with prednisone

After the initial diagnosis of childhood nephrotic syndrome (NS), a 12-week course of induction prednisone therapy is recommended. This induction therapy includes daily prednisone for 6 weeks followed by alternate day prednisone for an additional 6 weeks. If the child is hospitalized and not tolerating oral prednisone, an equivalent dose of intravenous methylprednisolone can be given. *Table 9* and *Figure 3* summarize prednisone dosing for induction therapy.

TABLE 9

### Prednisone dosing for the initial episode of NS\*

DURATION	DOSE BY CHILD'S SIZE (mg/m <sup>2</sup> )	DOSE (mg)	DATE
6 weeks	60 mg/m <sup>2</sup> daily (max 60 mg total)		
6 weeks	40 mg/m <sup>2</sup> alternate day (max 40 mg total)		
STOP			

\* Round to nearest 5 mg for total doses >10 mg

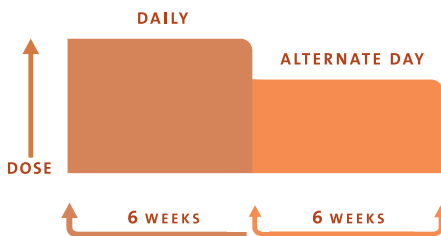


Figure 3. Time course of prednisone treatment for initial episode of NS.

Underdosing children with NS may predispose them to more frequent relapses; therefore, dosing based on body surface area (BSA) is recommended. Weight-based dosing of prednisone can be considerably less than that of BSA-based dosing, especially in children <30 kg.

To determine BSA all children require a weight and height measurement upon presentation. Because children with NS often have significant edema and weight gain upon presentation, BSA calculations based on ideal body weight for the child's age and height are recommended.<sup>5</sup>

Prednisone is dispensed in 1 mg, 5 mg, and 50 mg tablets. These are small tablets that are generally easy to swallow. Treating with a single daily dose rather than divided daily doses is recommended for reasons of convenience and optimal adherence. Rounding all doses to the nearest 5 mg for total doses >10 mg is recommended. Combining 50 mg and 5 mg tablets may be a more convenient dosing option for some families. For children who cannot swallow tablets, liquid prednisone (called prednisoLONE) is also available in most community pharmacies. The concentration of liquid prednisone can vary from 1 mg/ml to 5 mg/ml depending on the pharmacy, so it is important to be aware of the exact concentration being provided to families.

To help families keep track of their child's dosing schedule, the *Childhood Nephrotic Syndrome Parent Handbook* and accompanying *Worksheets* have been developed. All prednisone doses should be reviewed with the family. Further, all prednisone doses given should be recorded directly into the worksheets by families. The worksheets should also be used to record urine dipstick results, relapses, and possible side effects of complications.

### **Relapse therapy with prednisone**

Most children with NS have relapses that require repeated prednisone therapy. Most relapses are triggered by an infection, such as a cold or flu. Even very minor infections, dental cavities, or insect bites can sometimes trigger a relapse.

For NS relapses, starting daily prednisone at 60 mg/m<sup>2</sup> (to a maximum of 60 mg daily) until the child is in remission (urine protein is negative or trace on first morning dipstick for three consecutive mornings), followed by alternate day prednisone at 40 mg/m<sup>2</sup> (to a maximum of

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<sup>5</sup> To determine ideal body weight, plot the child's height on a growth chart, determine the percentile score for this height, then plot the child's weight using the same percentile score.

40 mg daily) for 2 weeks is recommended. Most children will receive approximately 1 month of prednisone for each relapse as they often go into remission within the first 2 weeks. *Table 10* and *Figure 4* summarize prednisone dosing for relapse therapy.

TABLE 10

### Prednisone dosing for relapses of NS\*

DURATION	DOSE BY CHILD'S SIZE (mg/m <sup>2</sup> )	RELAPSE #	
		DOSE (mg)	DATE
Until remission	60 mg/m <sup>2</sup> daily (max 60 mg)		
2 weeks	40 mg/m <sup>2</sup> alternate day (max 40 mg)		
STOP			

\* Round to nearest 5 mg for total doses >10 mg

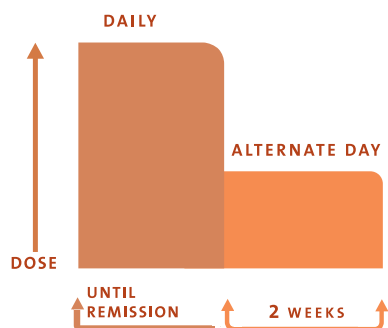


Figure 4. Time course of prednisone treatment for relapses of NS.

### Response to prednisone

Most children with NS will achieve remission by 4 weeks of starting prednisone treatment. Of those who respond, 80% do so by 2 weeks, 94% by 4 weeks, and almost 100% by 6 weeks. This is the typical and expected response. However, those children with NS who do not completely respond by 6 weeks, develop steroid dependence, or have a frequent relapsing disease course are most likely to require additional treatments. They are also most likely to develop complications from their disease and from the treatment of their disease. **If a child with NS is found to be steroid resistant, steroid dependent, or to have a frequent relapsing course, consultation with a pediatric nephrologist is recommended.**

## Prednisone side effects

The most common prednisone side effects seen in the treatment of NS are increased appetite, Cushingoid facies, acne, hirsutism, gastritis, mood instability, behavioral disturbances, sleep disturbances, headaches, and hypertension. Prednisone side effects are mainly observed when children are on daily therapy or when they experience frequent relapses, steroid dependence, or steroid resistance. *Table 11* summarizes various prednisone side effects.

TABLE 11

### Prednisone side effects

<b>Frequent</b>	Increased appetite and gain of body mass (fat) Cushingoid facial appearance Acne and hirsutism Gastritis/esophagitis Mood changes Insomnia Headaches Hypertension
<b>Occasionally</b>	Striae (seen most commonly on abdomen and legs) Myopathy/muscle loss/weakness Cataracts Glaucoma
<b>Rare/uncommon</b>	Glucose intolerance/insulin resistance Opportunistic infections Growth impairment Osteopenia/bone disease Pseudotumor cerebri/idiopathic intracranial hypertension

### Weight gain

Weight gain is a common side effect of prednisone treatment for children with NS. Increased appetite is commonly reported with higher doses of prednisone, but changes in appetite differ among children. Appetite increases generally subside as the doses are weaned and the child is off prednisone. Diet can play a role in avoiding excessive weight gain during prednisone therapy. See *Section 7 Diet* and *Appendices 3–5* for detailed dietary advice.

### Gastritis

Children with NS may experience abdominal pain due to gastritis or esophagitis during induction therapy with daily prednisone.

When symptoms are present, 2–4 mg/kg of oral ranitidine (H<sub>2</sub> blocker) divided twice daily is recommended to a maximum dose of 150 mg bid. If gastritis is more severe, a trial of a proton pump inhibitor may be warranted.

### **Hypertension**

One of the most common causes of elevated blood pressure (BP) is daily prednisone therapy. If a child's BP is persistently elevated ( $\geq 95$ th percentile on at least three different occasions) or confirmed by 24-hour ambulatory BP monitoring, anti-hypertensive therapy is warranted. The use of an oral calcium channel blocker such as Amlodipine is recommended (starting at 0.1 mg/kg/day and titrating up to 0.6 mg/kg/day with a maximum oral dose of 20 mg given once daily). Often, the hypertension resolves once the child is on lower doses of weaning prednisone. **If hypertension is severe, persistent, or requires multiple medications for optimal control, consultation with a pediatric nephrologist is recommended.**

### **Ocular complications**

Cataracts and glaucoma are the two ocular complications most often associated with prolonged prednisone therapy. **For all children with NS, an appointment with a pediatric ophthalmologist at 4 weeks after diagnosis is recommended, when prednisone exposure is highest.** The frequency of follow-up will be at the discretion of the pediatric ophthalmologist, but will likely occur once yearly in most children with NS.

### **Bone disease**

Children with NS may be at risk of developing decreased bone mass and decreased linear growth, especially in those with repeated courses of daily prednisone. Complications of bone disease include fractures, bone pain, and avascular necrosis. The risk of bone disease in children with NS has not been well established. Exposure to prednisone in this group has negative effects on bone mineral content and final height, with decreased lumbar spine bone mineral density.

Prophylactic doses of calcium and vitamin D may help reduce bone loss in children with NS. Therefore, during induction therapy for children with NS (the first 12 weeks), supplementing the child's daily dietary intake with calcium (500–1,000 mg elemental) and vitamin D (800–1,000 IU) is recommended.

Following successful induction, it is recommended that children continue to achieve intakes of calcium and vitamin D that meet the Daily Recommended Intakes (DRI) for age (*Table 12*). The intakes may be met with either diet or a combination of diet and supplementation.



In children exposed to more prolonged periods of prednisone therapy (frequent relapsing or steroid dependent NS), daily dietary calcium (500–1,000 mg) and supplemental vitamin D (800–1,000 IU) is recommended while on prednisone. *Table 12* summarizes recommended intakes of calcium and vitamin D in children with NS.

### Calcium and vitamin D recommendations

DRI	PATIENT	SUPPLEMENTAL DOSE
<b>Calcium:</b> 1–3 yr 700 mg 4–8 yr 1,000 mg 9–18 yr 1,300 mg	Newly diagnosed (Induction phase)	Calcium: 500–1,000 mg Vitamin D: 800–1,000 IU Supplement in addition to diet during first 24 weeks of prednisone treatment
	Infrequently relapsing*	No supplementation
	Frequently relapsing/steroid dependent	Calcium: 500–1,000 mg Vitamin D: 800–1,000 IU Supplement in addition to diet for duration of prednisone treatment
<b>Vitamin D:</b> 600 IU		

\* Less than four relapses per year

### Cosmetic Complications

While on prednisone, children with NS may experience hirsutism, hair thinning, acne, striae, abdominal distention, or Cushingoid facies. These are well known side effects that typically resolve as the prednisone dosing is decreased.

### Behavioural Complications

Prednisone is well known to cause labile mood, difficulty sleeping, and hyperactivity. These side effects usually fade as the prednisone dose is weaned.

### Adrenal Suppression

Prednisone may suppress adrenal function and impair the response to stressful events. Common symptoms of adrenal suppression include fatigue, decreased appetite, weight loss, and muscle weakness. These side effects typically improve once exposure is removed for a period of time. In cases of sustained adrenal suppression, consultation with a pediatric endocrinologist and further treatment may be required.

## Diet

Diet can have a profound impact on the clinical outcome of children with nephrotic syndrome (NS). As such, it is important that dietary intake and growth be monitored at regular intervals. Dietary recommendations are especially important around the time of diagnosis and during relapses, when symptoms are most severe and prednisone exposure is highest. Making healthy food choices at diagnosis and relapse can directly impact symptom severity and potential prednisone complications by minimizing edema, controlling blood pressure, preventing excessive weight, and maintaining bone health.

**For children with a typical presentation of NS, consultation with a dietician is recommended at four separate visits during the first year, including within the first week after initial diagnosis, then at 1 month, 3 months, and 12 months after diagnosis.** Additional visits may be required based on the disease course (steroid dependent or frequent relapsing NS). Each consultation should include a dietary history and evaluation, review of intake (calories, sodium, fluid), and patient/family education. Height and weight parameters should be checked at each visit to assess growth over time. A child with decreasing height velocity over consecutive visits may require consultation with a pediatric nephrologist as this may signal a significant prednisone side effect.

In situations where a dietitian is not available, parents should access dietary information for their child with NS from HealthLink BC (dial 8-1-1).

### Limiting sodium intake

One of the most important and under-appreciated factors in controlling edema is regulating sodium intake. Without controlling sodium intake, achieving fluid restriction becomes challenging. Limiting sodium intake will help to decrease thirst and thereby fluid intake. Careful adherence to age- and body size-appropriate intake of sodium is also recommended for the prevention of hypertension.

In light of the lack of evidence, we have developed a simple guideline for limiting sodium by linking it to a child's caloric requirements. **Specifically, children with NS should be limited to 1 mg of sodium for each calorie consumed while they are on prednisone.** *Table 7*, on page 17, summarizes the recommended maximum daily intake of calories, sodium, and fluid in children with NS. To help parents manage their child's sodium intake at home, *Appendices 3–5* outline common food items and their sodium content, a sample menu plan, and instructions on how to read food labels. Further information can be found in the *Childhood Nephrotic Syndrome Parent Handbook*.

### **Limiting fluid intake**

Recommended fluid intake is based on normal maintenance fluid requirements to compensate for insensible (skin and lung) and sensible (urine and stool) losses. Maintenance fluid requirements parallel energy needs with approximately 100 ml of fluid needed for every 100 kcal of energy required.

Excessive fluid intake increases the risk of severe edema and hyponatremia. **Therefore, limiting total fluid intake to 50% of normal maintenance fluid requirements is recommended until the child is in remission.** Once the child goes into remission, fluid restriction can be discontinued. In situations where the child is volume contracted, strict fluid restriction should be carefully evaluated.

### **Preventing excessive weight gain**

Children on daily prednisone are at risk of excessive weight gain. Our recommended caloric intake for children with NS while they are on prednisone is based on their height, estimated dry weight, and activity level (*Table 7*). Notably, the recommended sodium requirements for children with NS on daily prednisone closely parallel caloric intake: 1 mg of sodium for each calorie of energy.

Along with dietary management for the prevention of excessive weight gain, children with NS should be encouraged to remain physically active for the duration of prednisone therapy.

## **Maintaining bone health**

An important side effect of NS and being treated with prednisone is long-term bone problems such as osteopenia, osteoporosis, avascular necrosis, and bone fractures. The risk of bone problems increases with increasing prednisone exposure and is more common in those with frequent relapsing or steroid dependent NS. **To ensure children with NS get enough calcium and vitamin D, supplementing their regular diet with an additional 500 mg elemental calcium and 800–1,000 IU vitamin D is recommended while they are on prednisone.**

Further details about diet recommendations are also included in the *Childhood Nephrotic Syndrome Parent Handbook*.

## 8

## Immunizations and infectious disease

Children with nephrotic syndrome (NS) are at risk for developing severe infections. To mitigate this risk, careful attention should be paid to strict hand washing, regular visits to the doctor and dentist, and avoidance of sick contacts. All children with NS should also be immunized according to the provincial immunization schedule. To reduce the risk of infection in children with NS who are not fully immunized, immunizing all family members, if possible, is also recommended. At initial presentation, physicians should review the immunization history of children with NS in detail. As many parents do not recall exactly what immunizations were administered and at what time, it is recommended that the family bring their immunization records to all clinic visits. British Columbia's current immunization schedule can be found at: <http://www.immunizebc.ca>

Immunizations that require special consideration in children with NS include tuberculosis, influenza, varicella-zoster, and pneumococcal vaccines. Most children who present with NS are fully immunized by the time they are diagnosed. For children presenting with NS who are behind in their immunization schedule, immediate immunization is recommended. Following this, all children with NS should continue to receive their recommended immunizations at the scheduled time, except for the live vaccines.

### Live vaccines

Live vaccines are contraindicated in children who are significantly immunocompromised. This includes children who are either actively nephrotic (edema and/or urine dipstick protein  $\geq 3+$  or urinalysis protein  $>3$  g/L) and/or have been exposed to high doses of prednisone therapy for more than 14 days in the preceding month. High dose prednisone therapy is defined as  $\geq 60$  mg/m<sup>2</sup> or  $\geq 20$  mg per day. Live vaccines can be given 4 weeks after stopping high dose prednisone.

Table 13 highlights various live vaccines to be mindful of while caring for a child with NS.

### Live vaccines

MMR (Measles, Mumps, Rubella)	Yellow Fever*
Varicella	BCG (Bacillus Calmette-Guerin)*
Intranasal Influenza (FluMist®)*	Rotavirus**
Herpes zoster (shingles)*	Smallpox*
Typhoid*	

\* not part of routine British Columbia immunization schedule

\*\* administered before one year of age

Live vaccines are also contraindicated in children with NS receiving any steroid-sparing immunosuppressant agents, such as cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors (tacrolimus, cyclosporine), or monoclonal antibodies (Rituximab). Live vaccines should be deferred until the child has been off cyclophosphamide for more than 3 months and off other steroid-sparing agents for more than 1 month. Rituximab is likely not a risk factor for vaccine complications but because it depletes B cells there is no vaccine response. As such, we recommend that live vaccines be deferred until the child is off Rituximab for 6 months. Finally, live vaccines may need to be delayed for up to 1 year after intravenous immunoglobulin (IVIG) or other blood products containing immunoglobulin (such as varicella-zoster immunoglobulin [VariZIG] for varicella prophylaxis) because they decrease the effectiveness of vaccination. **When considering the immunization schedule of children with NS currently receiving and/or having received steroid-sparing immunosuppressive agents in the past year, consultation with a pediatric nephrologist and infectious disease specialist is recommended.**

### ***Mycobacterium tuberculosis***

Some children with NS are from communities with an increased risk of tuberculosis (TB). If a child belongs to a high risk group or has had contact with someone with possible TB, a Tuberculin skin test (TST or Mantoux) is recommended prior to initiating prednisone therapy. **In children with NS at high risk of TB exposure, consultation with a pediatric nephrologist and infectious disease specialist is recommended.**

## **Influenza virus**

Children with NS can have severe courses of seasonal influenza A. The Canadian flu season generally runs from November through April, but can vary from year-to-year. Influenza infections can often trigger episodes of NS. Annual influenza immunization is recommended in all children with NS. Immunizing with the influenza vaccine at initial presentation is recommended, regardless of NS activity or prednisone dose. Moreover, immunizing all family members whenever possible is also recommended to decrease the risk of transmission.

A live attenuated influenza vaccine (LAIV or FluMist®) is now available as a nasal spray; however, it is not recommended for use in children with NS.

We recommend active treatment of confirmed influenza with antiviral agents such as oseltamivir (Tamiflu) in children with NS. Please refer to the most recent Canadian Pediatric Society (CPS) statement for further information. **When considering the use of antiviral agents in children with NS, consultation with a pediatric nephrologist and an infectious disease specialist is recommended.**

## **Varicella-zoster virus**

In British Columbia, varicella-zoster virus (VZV) immunization is currently given at 12 months and 4–6 years of age. It was introduced in British Columbia in 2004; therefore, most children with NS will have had one or two doses of the vaccine at the time of presentation. Children who have received two doses of the vaccine are considered to be “safe/immunized,” whereas children who have received only one dose are considered to be “likely protected.”

### **VZV exposure**

Given the widespread immunization of VZV in British Columbia the chances of developing VZV are increasingly rare, but still pose a grave risk for all non-immunized children with NS. When a non-immunized or partially immunized child with NS is exposed to VZV, careful monitoring is required.

Exposure occurs through indirect contact with aerosolized droplets from nasopharyngeal secretions (likely resulting from face-to-face interaction with an infected individual for five or more minutes) or from direct cutaneous contact with vesicular fluid. Children are most contagious from 1–2 days before onset of the rash and continue to be

contagious until skin lesions have fully crusted. The incubation period of VZV is 21 days.

### **VZV immunization and exposure**

When a child presents with NS and has been *recently immunized* for VZV, a delay in prednisone induction therapy until 28 days after immunization is recommended, if at all possible. **If this situation arises, consultation with a pediatric nephrologist and infectious disease specialist is recommended.**

If a child presents with NS and has *not been immunized* or is *partially immunized* (received one out of two doses), immunizing when the child is in remission AND off prednisone for more than 4 weeks is recommended. A second dose can be given 4 weeks after the initial dose if they are due for their second dose.

VariZIG should be given only to children with NS who are *not fully immunized* and within 96 hours of exposure. No efficacy is reported after 96 hours of exposure.

The recommended dose of VariZIG is 125 units/10 kg intramuscular, with a maximum of 625 units. After VariZIG administration, children should be monitored for four weeks for symptoms of chickenpox (the incubation period of VZV is extended from 21 to 28 days in these cases). VZV immunization needs to be delayed for 5 months after the use of VariZIG.

### **VZV infection**

When a child with NS develops VZV infection, the disease may run a severe course. Children with NS receiving immunosuppressive therapy should be treated with intravenous acyclovir (30 mg/kg daily divided Q8H) for 7–14 days, depending on the severity of infection. While on acyclovir, it is important that the child is well-hydrated (1.5 X maintenance fluids) to avoid the nephrotoxicity associated with this drug. **If a child with NS develops a VZV infection, consultation with a pediatric nephrologist and infectious disease specialist is recommended.**

### ***Streptococcus pneumoniae***

British Columbia introduced pneumococcal immunization in 2003 using a 7-valent pneumococcal conjugate vaccine (PCV7). As of June 2010, this was changed to a 13-valent pneumococcal conjugate (PCV13 or Prevnar® 13) given at 2, 4, and 12 months of age; therefore, most



children with NS will have had three doses of the vaccine at the time of presentation.

However, due to the higher risk of infection with specific types of pneumococcus that are not covered by the standard British Columbia immunization schedule, an additional one time vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPSV23 or Pneumovax®) is recommended. PPSV23 offers protection against 23 different types of pneumococcal bacteria but is only effective in children  $\geq 2$  years of age.

For a child presenting with NS who is *not fully immunized* for pneumococcus (has not received three doses of PCV13), one dose of PCV13 followed by one dose of PPSV23 after 8 weeks is recommended. Children with NS can be safely and effectively immunized using PPSV23 while their NS is in relapse and/or while they are receiving prednisone therapy. No booster is required since they will have persistent protective levels of pneumococcal antibodies.

For a child presenting with NS who is *fully immunized* for pneumococcus (has received three doses of PCV13), one dose of PPSV23 is recommended.

## Follow-up after initial presentation

After their initial presentation, children with nephrotic syndrome (NS) will need to be followed closely over the first year. The goals of follow-up are to document their response to prednisone and to look for complications of NS or for possible side effects from prednisone treatment. Clinic visits within one week from initial diagnosis, then at 4 weeks, 12 weeks, 6 months, 9 months, and 12 months are recommended.

More visits may be required based on the individual child's needs (steroid resistant, steroid dependent, frequent relapsing NS). On occasion, while being treated for the initial presentation of their NS, children may develop complications and therefore may need to be seen earlier than the recommended 4 weeks. In cases where the child has not completely responded to prednisone therapy by 4 weeks, an additional clinic visit at 6 weeks after diagnosis may be needed.

Following remission, interim evaluations should include a review of the child's *Worksheets* (prednisone dosing, dipstick results), use of medications, complications from their disease or therapy, and immunization status. The date and time to remission for every relapse event should be documented to track the child's disease over time.

Follow-up physical examinations should include an evaluation of vital signs, height and weight (to calculate body surface area and body mass index), pulse, and blood pressure, as well as an investigation of possible disease-related (edema, infections) and prednisone-related (Cushingoid features, acne, striae, cataracts, glaucoma) complications.

Follow-up laboratory tests should be limited to a urinalysis for hematuria and proteinuria and a urine protein to creatinine ratio (PCR). This is especially relevant for children suspected of having relapses or steroid resistant NS.<sup>6</sup> In an uncomplicated course of NS, blood tests are generally not indicated for making the diagnosis of a relapse.

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<sup>6</sup> If the urinalysis or urine PCR suggests greater than expected protein levels, a first morning sample should be repeated to reduce the possible orthostatic effect on protein excretion.

Since children are treated with a lengthy course of prednisone for their first episode of NS (almost 3 months), evaluation preferably by the nephrology and ophthalmology services at British Columbia Children’s Hospital (BCCH) is recommended at four weeks after diagnosis for review of the child’s progress and evaluation of possible prednisone side effects (cataracts and glaucoma). Other tests may be required to review bone health or adrenal gland function, as needed.

Below is a comprehensive checklist on what needs to be reviewed at initial diagnosis and at each follow-up visit in the first year after diagnosis.

### Scheduled visits during the first year

TEST/REVIEW	CLINIC VISIT						
	0 w*	4 w	6 w**	12 w	6 m	9 m	12 m
<b>Confirm and explain diagnosis</b>	✓						
<b>History</b>							
• History of swelling	✓						
• Review immunization status	✓	✓	✓	✓	✓	✓	✓
• Document date and time to remission		✓	✓				
• Review Handbook Worksheets		✓	✓	✓	✓	✓	✓
• Review prednisone schedule		✓	✓	✓	✓	✓	✓
• Review medication history	✓	✓	✓	✓	✓	✓	✓
<b>Physical examination</b>							
• Blood pressure, heart rate and temperature	✓	✓	✓	✓	✓	✓	✓
• Record growth (height, weight)	✓	✓	✓	✓	✓	✓	✓
• Check for swelling	✓	✓	✓	✓	✓	✓	✓
• Other signs of prednisone side effects (eyes, bone, skin)		✓	✓	✓	✓	✓	✓
<b>Lab testing</b>							
• CBC, albumin, urea, creatinine, Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup>	✓	No regular blood testing needed					
• Urinalysis, microscopy, and PCR	✓	✓	✓	✓	✓	✓	✓
<b>Monitoring</b>							
• Review fluid restriction	✓	✓					
• Review dietary recommendations	✓	✓		✓			✓
• Review home monitoring (urine dipsticks)	✓	✓	✓	✓	✓	✓	✓
• Eye clinic evaluation		✓					
• Family given handbook & worksheets	✓						
• Schedule follow-up appointment	✓	✓	✓	✓	✓	✓	✓

\* Visit at which prednisone is started. Contact the Nephrology Program at BCCH for support. A subsequent clinic visit within 1 week is likely needed to complete all necessary tests and teaching

\*\* A six-week visit is required if your child is not in remission at 4 weeks

## **Follow-up after the first year**

Follow-up recommendations after the first year depend on the child's response to therapy and clinical course. Children should continue their regular follow-up with their family physician or pediatrician for ongoing medical problems. In most circumstances, relapses can be managed over the phone, without the need for extra laboratory testing other than urine dipstick monitoring at home.

As discussed, there are occasions when the child should be seen in the clinic or office, in particular if there is a lack of response after 2 weeks of relapse therapy or if the child has developed complications during their relapse such as severe edema. The timing of these clinic or office visits will be at the discretion of the child's qualified health care provider.

If a child continues to have relapses of their NS they will need to be seen more frequently to be sure they have responded properly to treatment and that they have not developed side effects of treatment. Regardless of course, most children with NS will need to be seen by a pediatric nephrologist at least once a year.

## Blood Pressure Nomogram 95%ile for Boys

95%ile BP for age and height percentile (Boys)														
Age	95%ile for Systolic BP (mm Hg) Percentile of Height							95%ile for Diastolic BP (mm Hg) Percentile of Height						
	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	125	126	127	128	130	131	132	82	82	83	84	85	85	86
17	125	126	127	129	130	131	132	82	83	83	84	85	85	86

## Blood Pressure Nomogram 95%ile for Girls

95%ile BP for age and height percentile (Girls)														
Age	95%ile for Systolic BP (mm Hg) Percentile of Height							95%ile for Diastolic BP (mm Hg) Percentile of Height						
	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	100	101	102	104	105	106	107	55	57	57	58	59	59	60
2	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	125	126	127	128	130	131	132	82	82	83	84	85	85	86
17	125	126	127	129	130	131	132	82	83	83	84	85	85	86

## Sodium Content of Foods

The table below illustrates how the sodium content of foods in their natural form increases as they are processed. As you move from left to right in the table you will notice that foods have increasing amounts of sodium. The preferred foods would be those on the left in the green boxes as they have less sodium. Foods listed on the far right in the red boxes contain the most amount of sodium and should be avoided.

HEALTHY CHOICE		LESS HEALTHY CHOICE		UNHEALTHY CHOICE	
Cucumber	<b>7 mg</b>	Cucumber with Ranch dressing	<b>145 mg</b>	Dill pickle 1 medium	<b>928 mg</b>
Tomato 1 small	<b>14 mg</b>	Tomato ketchup 2 packages	<b>140 mg</b>	Tomato sauce ½ cup	<b>640 mg</b>
Chicken ½ breast	<b>69 mg</b>	Chicken nuggets + sauce (4 nuggets)	<b>670 mg</b>	Chicken luncheon meat 3 ounces	<b>1059 mg</b>
Pork 3 ounces	<b>59 mg</b>	Bacon 4 slices	<b>548 mg</b>	Ham 3 ounces	<b>1,114 mg</b>
Roast beef 3 ounces	<b>54 mg</b>	Hot dog weiner 1 regular	<b>487 mg</b>	Pepperoni 3 ounces	<b>892 mg</b>
Cheddar cheese 1 ounce	<b>173 mg</b>	Processed cheese slice 1 slice	<b>390 mg</b>	Cheese spread 2 tablespoons	<b>540 mg</b>
Cooked oatmeal 1 cup	<b>&lt;1 mg</b>	Bread 2 slices	<b>298 mg</b>	Instant noodles 1 serving	<b>2,200 mg</b>
Shredded Wheat 1 round	<b>&lt;1 mg</b>	Rice Krispies® 1 cup	<b>298 mg</b>		
Steamed rice/cooked pasta 1 cup	<b>&lt;1 mg</b>				
Olive oil 1 tablespoon	<b>&lt;1 mg</b>	Salted butter/margarine 1 tablespoon	<b>81/70 mg</b>	Soy sauce 1 tablespoon	<b>1,029 mg</b>
Lemon juice 1 tablespoon	<b>1 mg</b>			Salt 1 teaspoon	<b>2,325 mg</b>
Unsalted butter/margarine 1 tablespoon	<b>2/0 mg</b>				

## Sample Menu

The table below illustrates a sample menu plan for a 10-year-old child being treated with prednisone for nephrotic syndrome (NS). The menu suggestions are low in sodium, relatively low in fat, and contain adequate calcium, all important recommendations for children with NS. A diet low in sodium can be healthy and enjoyable for ALL family members.

MEAL	LOW SODIUM SUGGESTION
Breakfast	1 cup Shredded Wheat/Mini Wheats® 1 cup 1% milk (½ on cereal + ½ to drink) 1 medium banana
Morning snack	1 orange
Lunch	1 jam sandwich 2 graham crackers ½ cup yogurt 1 small apple
Afternoon snack	3 cups unsalted popcorn Carrot sticks
Dinner	2 oz chicken breast 1 cup steamed rice 1 cup green salad 1 tablespoon oil + balsamic vinaigrette ½ cup steamed broccoli ½ cup corn niblets 1 cup of 1% milk
Evening snack	½ cup applesauce 1 cup 1% milk



## Reading Food Labels

In Canada, packaged foods are required to have a Nutrition Facts box on the label. By law, sodium is one of 13 items that is required to be reported on the package label. Below are simple instructions on how to read food labels and determine whether the food item is appropriate for children with NS:

- 1 Note the number of calories provided by the serving size listed.
- 2 Note the number of mg of sodium in the serving.
- 3 Choose food items that have LESS sodium mgs than calories.

Here are two examples where reading the labels helps make the right choice:

Nutrition Facts	
Per 125 mL (87 g)*	
Amount	% Daily Value*
<b>Calories 80</b>	
Fat 0.5 g	1%
Saturated 0 g + Trans 0 g	0%
Cholesterol 0 mg	
<b>Sodium 0 mg</b>	<b>0%</b>
Carbohydrate 18 g	6%
Fibre 2 g	8%
Sugars 2 g	
Protein 3 g	
Vitamin A 2%	Vitamin C 10%
Calcium 0%	Iron 2%

This nutrition label shows the food item provides 80 calories with 0 mg of sodium. The number of mg of sodium is less than the number calories, therefore, an appropriate low- sodium choice.


Nutrition Facts	
Valeur nutritive	
Per 1 tray (212 g) / Pour 1 plat (212 g)	
Amount	% Daily Value
Teneur	% valeur quotidienne
<b>Calories/Calories 170</b>	
Fat/Lipides 2.5 g	4%
Saturated/Saturés 0.5 g + Trans/Trans 0 g	3%
Cholesterol/Cholestérol 25 mg	8%
<b>Sodium/Sodium 620 mg</b>	<b>26%</b>
Carbohydrate/Glucides 25 g	8%
Fibre/Fibres 2 g	8%
Sugars/Sucres 2 g	
Protein/Protéines 12 g	
Vitamin A/Vitamine A	4%
Vitamin C/Vitamine C	15%
Calcium/Calcium	2%
Iron/Fer	8%

This nutrition label shows a food that contains 170 calories with 620 mg of sodium. The number of mg of sodium is nearly four times the number of calories, and is NOT an appropriate low-sodium choice.









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