Guideline for the Management of Idiopathic Nephrotic Syndrome of Childhood

Scottish Paediatric Renal and Urology Network (SPRUN)

Please note: This guideline is to be assessed using the AGREE (Appraisal of Guidelines for Research and Evaluation) criteria.
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1. **Guideline Development**

1.1 Membership of Guideline Development Group

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The views of the Scottish Paediatric Renal and Urology Network (SPRUN) were sought throughout. There was the opportunity to comment and feedback through the Managed Knowledge Network discussion pages of SPRUN.

1.2 Patient population and target audience

This document provides information on the investigation, treatment and management of nephrotic syndrome in children at initial presentation and in relapse of the condition. The guideline applies to children throughout Scotland with typical idiopathic nephrotic syndrome. The guideline may not be relevant to the management of children with atypical presentations and does not apply to children with congenital nephrotic syndrome, steroid resistant nephrotic syndrome and nephrotic syndrome secondary to other systemic disease (e.g. SLE) or other structural glomerular disease (e.g. Alport Syndrome).

This document is intended for use by all health professionals (for example, doctors, nurses, dieticians and pharmacists) who look after children with nephrotic syndrome within Scotland.

1.3 Objectives and clinical questions

Guideline objectives:
1. Describe typical and atypical presenting clinical features of idiopathic nephrotic syndrome of childhood likely to respond to treatment with steroids.
2. Provide guidance on the initial diagnostic approach in children presenting with typical idiopathic nephrotic syndrome to a general paediatric department.
3. Provide guidance for the safe and effective clinical management of the initial presentation of children with typical idiopathic nephrotic syndrome to a general paediatric department.
4. Provide guidance on the clinical management of complications of idiopathic nephrotic syndrome.
5. Provide guidance on the indications for early referral for specialist nephrology advice in children with atypical presenting clinical features.
6. Provide guidance on the indications for referral for specialist nephrology advice and review of complications of idiopathic nephrotic syndrome.
7. Provide guidance on the indications for referral for specialist nephrology advice and review of relapsing idiopathic nephrotic syndrome and its management.
8. Provide guidance on follow up in the general paediatric clinic setting.
9. Provide adequate information and training for children and their families on idiopathic nephrotic syndrome, its treatment (medication, dietary), home monitoring and planned follow up.

Clinical questions answered by the guideline:
1. What is the recommended approach to initial investigation and diagnosis?
2. What are the referral criteria for atypical cases?
3. What is an appropriate initial steroid treatment regimen?
4. What other management strategies are recommended at initial presentation?
5. What are the best-practice treatments of complications of nephrotic syndrome?
   a. Use of albumin infusion
   b. Management of hypertension
   c. Management of infection, including vaccination
   d. Venous thrombosis
6. What are the recommended management strategies for relapsing nephrotic syndrome?
7. What follow-up and monitoring do nephrotic syndrome patients require?

1.4 Methodology

This guideline was based on the RHSC, Glasgow “Guidelines on the Management of Nephrotic Syndrome” (2005). Best evidence was used to inform recommendations including Cochrane Collaboration reviews, literature searches of PubMed, using the terms “paediatric” / “children”, ”nephrotic syndrome”, and ”steroid sensitive”. Evidence based on double blind randomised control trials was deemed to be the best level of evidence, and expert opinion where no other form of evidence was available. Only articles written in English were included.

Recommendations were based on consensus of opinion from the working group. There were no areas of disagreement.
2. Definition and initial features of Nephrotic Syndrome

This document relates only to the management of idiopathic nephrotic syndrome in childhood. The features that characterise nephrotic syndrome result from a glomerular capillary leak causing heavy loss of protein traditionally defined as >1g/m$^2$/day, but currently quantified using urine protein (or albumin) creatinine ratio on a first early morning urine. Children who present with the typical features of nephrotic syndrome are generally responsive to steroid treatment and are likely to show minimal changes on histology, although biopsy is not usually indicated.

Children with typical features are started on steroids without renal biopsy. Steroid responsiveness is a better indicator than histology of long term outcome for renal function.

95% of patients with Minimal Change Nephrotic Syndrome (MCNS) and 20% with Focal Segmental Glomerulosclerosis (FSGS) achieve remission after an 8-week course of prednisone (60 mg/m$^2$ daily for 4 weeks then 40 mg/m$^2$ on alternate days for 4 weeks). For MCNS patients 75% achieve remission by 2 weeks.

Those with atypical features are more likely to be unresponsive to steroid treatment. Those with atypical features at presentation should be discussed early with a paediatric nephrologist. A renal biopsy may be indicated before receiving steroid treatment.

### Characteristic diagnostic features

- Nephrotic range proteinuria
  - Suspect for urine ‘stix’ testing ≥ ++.
  - Quantify as urine protein:creatinine (P:CR) >200mg/mmol.
- Hypoalbuminaemia
  - serum albumin <25 g/l
- Generalised oedema

### Initial presenting clinical features

Onset of oedema may be insidious. Features include

- Peri-orbital swelling
- Ankle and lower limb swelling – pitting oedema
- Abdominal swelling and scrotal/vulval oedema
- Less commonly
  - frank haematuria
  - frothy urine

The findings of fluid retention and heavy proteinuria in a child should lead to an urgent referral to the local general paediatric department.
Classification

- Idiopathic (primary) nephrotic syndrome
  - Minimal change (MCNS) (80-90%)
  - Focal segmental glomerulosclerosis (FSGS) (10-20%)
    An increased incidence of FSGS is reported over the last 3 decades.

- Secondary nephrotic syndrome (HSP, SLE, MPGN)
- Congenital nephrotic syndrome

For further reviews see
(1) Eddy and Symons. Nephrotic syndrome in childhood (Seminar) Lancet, 2003,
(2) Oxford Specialist Handbook Paediatric Nephrology.
3. Initial Assessment and Investigation at presentation

Confirm diagnostic and presenting features (see above).

**Initial clinical assessment to include:**
- Height, weight, surface area
- Volume status
  - Perfusion
  - Capillary refill
  - \(\text{CP}\Delta T\)
  - Heart rate and BP
  - JVP or hepatomegaly
- Urinary sodium

### 3.1 Hypovolaemia

- Assess intravascular volume. Oedematous patients may also be intravascularly depleted.
- Clinical signs
  - cool peripheries (capillary refill time > 2 secs)
  - core-peripheral temperature gap (\(\text{CP}\Delta T\)) of > 2°C
  - tachycardia
  - initial paradoxical hypertension before hypotension may be present.
  - hypotension is a late sign of hypovolaemia.
- Other symptoms: abdominal pain, dizziness, poor urine output
- A urinary sodium of < 10 mmol/l useful to confirm hypovolaemia, provided diuretics have not been administered.

- **Clinical shock:**
  - Emergency intravenous volume resuscitation with 4.5% albumin. Diuretics should **NOT** be given at this stage.
  - Give 10ml/kg 4.5% albumin IVI over 30-60 minutes.
  - Monitor closely using linked nursing care plan and initial management flowchart.

- **Hypovolaemia without shock or symptomatic oedema:**
  - For less severe hypovolaemia
  - or symptomatic oedema refractory to diuretics and fluids restriction
    - where there is skin compromise
    - scrotal or vulval oedema
    - cellulitis.
  - Give 1g/kg 20% albumin (5ml/kg) over 4 - 6 hours.
  - Give 1mg/kg IV furosemide mid-infusion
  - Repeat 1mg/kg IV furosemide at the end of albumin infusion.
Strict monitoring of vital signs to detect intravascular volume overload using linked 20% albumin infusion care plan. 

- Administer infusion during routine hours where possible.
- 20% albumin is not indicated to correct hypoalbuminaemia alone. Injudicious use can lead to either volume overload or intravascular depletion.

### 3.2 Hypertension

- Transient hypertension may be present at initial presentation in a minority of patients. However, if persistent it may be a feature of an atypical presentation. Clinical features of volume overload should be sought.
- Hypertension with clinical features of intravascular volume overload should be treated with a diuretic. IV furosemide (1mg/kg) for emergency management and oral furosemide 0.5-1mg/kg/dose once or twice daily.
- Severe or ‘urgent’ hypertension (systolic BP >99th centile + 5mmHg) can be treated with the use of hypotensive agents such as short acting nifedipine.
- Persistent hypertension (systolic BP >95th centile) can be treated with longer acting agents such as amlodipine with incremental dose increases
- Ca+ channel blocker
  - Short acting Nifedipine (BNF link) – 0.25 – 0.5 mg/kg per dose (‘bite and swallow’). Can be repeated
  - Long acting Amlodipine (BNF link) – 0.1mg/kg per day increasing in 0.1mg/kg increments every 48 hours to 0.4mg/kg/day.
- Paradoxical hypertension can be present due to intravascular volume depletion and other features of hypovolaemia should be sought (see above). If present give intravenous volume resuscitation using 4.5% albumin. Diuretics should **NOT** be given at this stage.

### 3.3 Infection

- Loss of complement components and immunoglobulins may result in an increased risk of infection. Prophylactic **Phenoxymethylpenicillin** (Pen. V) should be given whilst patients have significant proteinuria.
  - Phenoxymethylpenicillin by mouth
    - Child under 1 year 62.5 mg twice daily
    - Child 1–5 years 125 mg twice daily
    - Child 5–18 years 250 mg twice daily

### 3.4 Renal vein thrombosis

- Loss of proteins such as anti-thrombin III contributes to a pro-coagulant state. This can be exacerbated by hypovolaemia.
- Clinical features raising suspicion:
  - Macroscopic haematuria
  - Fall in Hb and platelets
  - Palpable kidney
  - Reduction in renal function
  - Hypertension
• Renal Doppler USS and specialist referral if suspicion.

3.5 Initial Investigations

Investigations to be performed in all children
- Blood: FBC, U+E’s; Creatinine; LFT’s; Varicella titres
- Urine: Urine culture and Urinary protein:creatinine ratio (PCR)
- Urinalysis including glucose
- Urinary sodium concentration in those at risk of hypovolaemia

Investigations to be performed in selected children
- ASOT – strep throat infection; anti-DNaseB – strep skin infection
- C3/C4 – post-strep GN; MPGN; SLE
- Hepatitis B status in children at high risk: FH of HBV; history of travel in endemic areas.

Initial assessment for atypical features

<table>
<thead>
<tr>
<th>Nephrotic Syndrome</th>
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<tbody>
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<td>Typical Features</td>
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<tr>
<td>Age 1-10 years</td>
</tr>
<tr>
<td>Normotensive</td>
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<tr>
<td>Normal Renal Function</td>
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<tr>
<td>Microscopic haematuria (in up to 25%)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Atypical Features</th>
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<tbody>
<tr>
<td>&lt;1yr, &gt;10years</td>
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<tr>
<td>Hypertensive</td>
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<tr>
<td>Elevated Creatinine</td>
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<tr>
<td>Macroscopic Haematuria</td>
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<tr>
<td>Systemic, extra-renal disease symptoms</td>
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<td>Positive family history of nephrotic syndrome</td>
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Patients with atypical features are more likely to be unresponsive to steroid treatment. Those with atypical features at presentation should be discussed early with a paediatric nephrologist. A renal biopsy may be indicated before receiving steroid treatment.
4. Initial Management of First Presentation of Typical Idiopathic Nephrotic Syndrome

4.1 Drug Treatment

Drug treatment in children with nephrotic syndrome can prove challenging. Pharmacy advice is helpful in many aspects of appropriate drug treatment in NS:

- drug dosing and administration
- appropriate formulation
- steroid treatment and tapering regimen
- antibiotic prophylaxis
- gastro-protection
- Renal Medication Information Booklet should be issued to all patients.

4.1.1 Prednisolone

On clinical diagnosis of nephrotic syndrome in children with typical features start prednisolone. In children with atypical features discuss with a paediatric nephrologist. A renal biopsy may be considered first.

Longer initial courses of prednisolone are associated with a lower incidence of relapse. Cochrane review (5). Further studies are in progress to identify any increased side effects and whether increased initial treatment reduces the use of second line treatments for relapsing steroid sensitive nephrotic syndrome.

Currently a 12-week initial course is recommended.

- 60 mg/m$^2$/day for 4 weeks (maximum 80 mg)
- 40 mg/m$^2$/on alternate days for 4 weeks (maximum 60mg)
- Reduce dose by 5-10mg/m$^2$ each week for another 4 weeks then stop

Prednisolone dose is based on body surface area.

(BSA = $\sqrt{(Ht \times Wt/3600}$). For BSA using weight only link to BNF for children.

Dosing regimen for initial presentation for ranges of BSA, with rounding of dose,

Prednisolone can be given as a single dose in the morning with food, or as divided doses during the day, particularly if the dose is large.

Patients should be issued with a steroid warning card.

Side effects and risks of steroid treatment should be discussed.

4.1.2 Antibiotic Prophylaxis – Penicillin V

Whilst nephrotic, children are at increased risk of infection, particularly with encapsulated organisms such as pneumococcus. Infection remains the main cause of death in children with nephrotic syndrome. Recommendations on the
use of antibiotic prophylaxis vary as there is no strong evidence of its benefit. Our policy is to give Penicillin V prophylaxis while there is proteinuria and discontinued when the child goes into remission. Grossly oedematous children are at particular risk of cellulitis and may benefit from antibiotic prophylaxis. See Section 3 Infection.

Pneumococcal vaccination is recommended for children with NS not previously vaccinated. Consider giving this at the time of diagnosis.

### 4.1.3 Gastroprotection

Protection against steroid induced gastric irritation should be considered for the duration of steroid treatment.

- **Ranitidine**
  - 2 – 4 mg (max. 150 mg) twice daily

- **Omeprazole**
  - For weight 10 – 20 kg 10mg once daily
  - For weight over 20 kg 20mg once daily

### 4.1.4 Albumin Infusion

**Clinical indications for albumin include**

- Clinical hypovolaemia (see earlier)
- Symptomatic oedema
  - skin compromise
    - cellulitis
    - scrotal or vulval oedema
  - Primary peritonitis
  - Respiratory compromise – pleural effusions

A low serum albumin alone is not an indication for intravenous albumin.

If clinically shocked give 10ml/kg 4.5% albumin without diuretic.

If there is evidence of hypovolaemia without shock or symptomatic oedema, give 1 g/kg as 20% albumin (5ml/kg) over 4 - 6 hours. Give 1mg/kg of IV furosemide mid-infusion and repeat at end unless good diuretic response in progress.

Children should be closely monitored following the linked 20% albumin infusion care plan and where possible it should be administered during working hours.

### 4.2 Dietary and Fluid Management

A low salt diet is used to try to prevent further fluid retention and oedema. Fluid restriction may also be helpful in limiting the increase in oedema. These restrictions are lifted once the child goes into remission. Dietetic advice regarding calorie control should be given while on steroids.
4.3 Complications

The main complications of nephrotic syndrome are hypovolaemia, infection and thrombosis.

4.3.1 Hypovolaemia without shock

The on-going assessment of children with nephrotic syndrome includes assessment of intravascular volume status. Children may be very oedematous, but may also have intravascular volume depletion. Clinical features are detailed above in Section 3 - Initial assessment and Investigation at presentation.

Hypotension is a late sign of hypovolaemia, but paradoxical hypertension may be present with hypovolaemia. A urinary sodium of < 10 mmol/l is a useful investigation to confirm hypovolaemia.

If there is evidence of hypovolaemia without shock or symptomatic oedema, give 1 g/kg as 20% albumin (5ml/kg) over 4 - 6 hours. Give 1mg/kg of IV furosemide mid-infusion and repeat at end unless good diuretic response in progress.

Children should be closely monitored following the linked 20% albumin infusion care plan and where possible it should be administered during working hours.

4.3.2 Hypertension

- Paradoxical: volume resuscitation
- Volume overload: diuretic
- Steroid induced
- Ca+ channel blocker
  - Short acting Nifedipine (BNF link) – 0.25 – 0.5 mg/kg per dose (‘bite and swallow’). Can be repeated
  - Long acting Amlodipine (BNF link) – 0.1mg/kg per day increasing in 0.1mg/kg increments every 48 hours to 0.4mg/kg/day.

Hypertension is unusual in the acute setting and if persistent should lead to reconsideration of other possible underlying glomerulonephritis.

4.3.3 Infection

Loss of complement components and immunoglobulins results in an increased risk of infection, particularly pneumococcal infection. Prophylactic Penicillin V (Phenoxy methylpenicillin) should be given whilst patients have significant proteinuria.
Cellulitis risk is increased and should be treated promptly. 20% IV albumin infusion with furosemide cover should be given to reduce oedema in the presence of cellulitis.

Varicella zoster (VZ) status should be documented clearly in the case notes and on any electronic patient record. Children with no previous exposure to VZV should receive VZIg if history of recent VZ exposure. Primary VZ infection should be treated aggressively with **IV Aciclovir** then p.o. **Valaciclovir** when no new crops of vesicles are appearing. Herpes Zoster infection (Shingles) also requires initial **IV Aciclovir** for immunosuppressed patients.

**Active immunisation with VZ vaccine** should be considered when off all immunosuppressive therapy. **Annual flu vaccination** should be administered.

See Appendix 2 & 3 of *Immunisation Guideline for Children with Chronic Kidney Disease* for further guidance.

### 4.3.4 Thrombosis

Loss of proteins such as anti-thrombin III contributes to a pro-coagulant state. This might be exacerbated by hypovolaemia. Clinical features raising suspicion include: macrohaematuria; fall in Hb and platelets; palpable kidney; reduction in renal function; hypertension.

Renal Doppler USS and specialist referral if venous thrombosis confirmed.

### 4.4 Monitoring and Observations

Admission and in-patient management is often necessary with the first presentation. Regular review to monitor for complications and to assess the onset of remission is needed. Parental teaching and education (see below) can take place at the same time.

### 4.4.1 Nursing

**Paediatric Nursing Care Plan**

- The ‘**Nursing Careplan Nephrotic Syndrome**’ can guide paediatric nursing care of nephrotic in-patients, at presentation or in relapse.

**During in patient admission**

- Monitoring progress
  - Daily weight
  - Fluid balance
  - Daily EMU ‘stix’/PC:R
  - BP

**Discharge planning (see sections 10 & 11 below)**

- Parent teaching
  - disease information
  - urine testing and recording
4.4.2 Laboratory monitoring

Daily urine P:CR
Renal biochemistry in patients requiring IV albumin and diuretics.
Renal biochemistry if evidence of impaired glomerular function.
Drug level monitoring if aminoglycoside/vancomycin therapy.

4.4.3 Response to treatment

Diuresis and weight reduction
Reduction in Albustix positive level
Reduction in daily urine P:CR

Most children with nephrotic syndrome will respond to steroid treatment within 2-4 weeks. A remission is defined as 3 or more days of trace or negative on dipstick testing. 80% of patients enter remission within 14 days on the dosing regimen used here. Treatment is continued for a total of 12 weeks. If proteinuria persists beyond the first 4 weeks of steroid treatment, then children should be referred for renal biopsy.

5. Indications for Referral to Paediatric Nephrology Service

5.1 Atypical Features

- Age < 1 yr
- Age > 10-12 yrs
- Persistent hypertension
- Elevated creatinine not associated with 'pre-renal' uraemia
- Macroscopic haematuria
- Low C3/C4
- Systemic disease symptoms and signs
- Failure to respond to steroids within 4 weeks

5.2 Complications

- Severe 'pre-renal' renal failure
- Renal vein thrombosis

5.3 Renal Biopsy

Renal biopsy is considered mandatory in children unresponsive to steroids following at least 28 days treatment with Prednisolone at a dose of
60mg/m$^2$/day. Histology appearances suggesting other underlying conditions may alter treatment options.

Those children with atypical features are more likely to be unresponsive to steroid treatment and a biopsy more likely to show FSGS or other forms of nephrotic syndrome. Those with atypical features should be discussed with a paediatric nephrologist as they may merit renal biopsy before receiving steroid treatment.
6. Management of Relapsing Nephrotic Syndrome

- Most important prognostic indicator - steroid responsiveness.
  - 60–80% of steroid-responsive nephrotic children will relapse.
  - 60% of these > five relapses.
- Predictors of fewer relapses
  - Age older than 4 years at presentation
  - Remission within 7–9 days of the start of steroid treatment in the absence of microhaematuria.
- Monitor urine regularly with Albustix® using a first morning urine sample.
- Relapses identified early by the appearance and persistence of proteinuria ≥ 2+ protein.

Typically relapses are triggered by intercurrent illnesses, particularly viral upper respiratory infections. Families should be more vigilant then. Low grade proteinuria (≤ 2+) may occur transiently and subside without steroid as the intercurrent illness settles. Studies suggesting low dose steroid ‘cover’ may reduce risk of full relapse await further research.

6.1 Diagnosis of Relapse Nephrotic Syndrome

Relapse diagnosed if > 2+ proteinuria on Albustix for 3 or more days. Urine should be checked initially 2 – 3 times weekly, then weekly after the first episode. Increase monitoring to daily with intercurrent infections.

Instruct families to make contact using a designated contact number if
- relapse of proteinuria occurs
- 2+ proteinuria is persistent for more than 1 week.

If uncertain whether there is a ‘full’ relapse
- clinical assessment (weight, BP) for fluid retention,
- quantitative uP:CR
- measurement of serum albumin

can be helpful in guiding management: intervention or expectant observation.

Patients often can be managed as an out patient with regular review while awaiting remission.

6.2 Drug treatment

6.2.1 Prednisolone

Prednisolone treatment should be restarted once a relapse has been diagnosed. Traditionally treatment has been based on the ISKDC relapse regimen:
- 60 mg/m²/day (maximum 80 mg) until urinary remission: negative or trace only for protein in first morning urine for 3 consecutive days
- 40 mg/m² (maximum 60 mg) on alternate days for 4 weeks then stop.

Individual patient care plans can include a taper over 4 to 8 weeks. **Steroid dosing regimens for relapse of nephrotic syndrome**
Further modifications aimed at minimising steroid exposure (e.g. limiting maximum daily dose or tapering more rapidly the alternate day dose) may be used for individual patients at the recommendation of a supervising nephrologist.

Treatment plans should be clearly documented in case records and the patient RMIB.

6.2.2 Antibiotic Prophylaxis – Penicillin V
Antibiotic prophylaxis in relapse follows guidance for prophylaxis at presentation – Section 4.1.2 above. While there is persistent proteinuria (> 2+) Penicillin V prophylaxis can be given. Penicillin V can be discontinued when the child goes into remission. Grossly oedematous children are at risk of cellulitis and should receive antibiotic prophylaxis. Pneumococcal vaccination is recommended for children with NS.

6.2.3 Gastroprotection
Protection against steroid induced gastric irritation should be considered for the duration of steroid treatment.

- **Ranitidine**
  - 2 – 4 mg (max. 150 mg) twice daily

- **Omeprazole**
  - For weight 10 – 20 kg 10mg once daily
  - For weight over 20 kg 20mg once daily

6.3 Dietary and Fluid management
Whilst there is proteinuria (> 2+) a no added salt diet is advised and advice on calorie control given. Advise on avoiding an excessively large fluid intake while awaiting remission. A modest fluid restriction may also be helpful in the clinically well child. These restrictions can be lifted as soon as the child enters remission.

6.4 Complications
The main complications of nephrotic syndrome are hypovolaemia, hypertension, infection and thrombosis. See above: section 4.3

6.5 Monitoring and Observations
Admission is often not necessary with relapse. Early clinic review to monitor for complications and to assess the onset of remission is needed.

Parental support for the first relapse is often welcome and allows teaching to be reinforced.
6.5.1 Nursing

Role of nurse specialist link or CCNs in local paediatric service
Monitoring and clinical support of patients in relapse may be carried out by local paediatric nurse specialists or community children’s nurses with support from the paediatric clinical team.

- Monitoring progress
  - Clinical assessment – fluid retention; complications
  - Weight
  - BP
  - Daily EMU Albustix (uP:CR – see below)
  - Fluid balance advice

6.5.2 Laboratory

Where clinical uncertainty on relapse status:

- urine P:CR
- Renal biochemistry including serum albumin.

7. Further management of patients with Frequent Relapses or Steroid Dependency

7.1 Diagnosis of frequent relapse

Frequent relapses are defined as:

- 2 or more relapses within the first 6 months of presentation
- 4 or more relapses within any 12 month period

This becomes steroid dependency if relapses occur while still on steroids or within 2 weeks of ceasing steroids.

If children have frequent relapses, strategies should be adopted to reduce the amount of steroid required. This should be discussed and agreed with a paediatric nephrologist.

A Cochrane systematic review (5) concluded that eight week courses of cyclophosphamide or chlorambucil and prolonged courses of ciclosporin or levamisole substantially reduce the incidence of relapse in children with NS in comparison with corticosteroids alone.

7.2 Drug treatment

Unfortunately, around 60% of steroid-responsive patients who relapse experience five or more relapses. Some can be successfully managed with low-
dose alternate day steroids. Many will still relapse, often with intercurrent infections. Steroid-induced side-effects develop in a high proportion. Currently there are no data on the preferred second-line immunosuppression (IS). Use of cyclophosphamide, chlorambucil, ciclosporin, and levamisole to reduce the risk of relapses is supported by a systematic review of randomised controlled trials and by evidence-based recommendations (5). More recently mycophenolate mofetil has been used successfully and appears to have a more favourable side effect profile (8, 9, 10). Rituximab is a B cell depleting antibody which has been successfully used to achieve remission with reduced IS requirements (12, 13). Its ‘off-label’ use is still considered experimental.

### 7.2.1 Low Dose Alternate Day Prednisolone

Low dose alternate day steroid treatment (< 0.5 mg/kg/alt days) may prevent relapses, and result in less steroid being given overall.

\[(0.5 \text{ mg/kg/alt day} = \sim 45 \text{ mg/kg/year}. \text{ 1 relapse of 14 days (60mg/m}^2/\text{day and 4 weeks 40mg/m}^2/\text{alt day}) = \sim 46 \text{ mg/kg/year})\]

Referral for discussion of second line therapy with a Paediatric Nephrologist is indicated in children with
- Frequent relapses
- Steroid dependency
- Steroid toxicity

**Intercurrent viral URTI**

For children controlled on low dose alternate day steroid the strategy of increasing alternate day steroid to daily steroid for a total 6 days treatment during viral URTIs may reduce the risk of relapse (4). Parents can be instructed to adopt this approach. Its use should be documented and reviewed at follow up. Further clinical research on this intervention is proposed.

### 7.2.2 Levamisole

Levamisole may be beneficial for children with frequent relapses. It is less useful if steroid dependent (5).

**Dose** 2.5 mg/kg/ on alternate days rounded to 25mg doses to max. 150mg.

After treatment established for 4 weeks steroids can be tapered.

If successful, treatment can continue for up to 3 years.

**Side effects** are rare and limited

‘Idiosyncratic’ neutropenia reversible on discontinuing drug.

Rash (‘erythema multiforme’-like)

GI intolerance.

**Monitoring**

FBC check monthly for first 3 months, at 6 months and 4-6 monthly thereafter. This drug is not licensed in the UK, and is imported. Community pharmacists can access the drug by special order. Families are advised to give adequate notice for repeat prescriptions.

[Levamisole – BNF link](#)
7.2.3 Cyclophosphamide

For children with frequently relapsing or steroid dependent NS, cyclophosphamide can induce longer lasting remissions (5).

- Frequently relapsing SSNS: ~50% remission at 5 years
- Steroid dependent: ~30% remission at 5 years

**Dose** 2.5 - 3 mg/kg/day for 8 weeks or equivalent. Maximum cumulative dose 168mg/kg. It is best to avoid cutting the tablets. Liquid extemporaneous preparations are available. Discuss with pharmacist re handling and disposal.

**Side effects** to be discussed

- Neutropenia and infection. FBC monitoring and dose reduction.
- Hair thinning – uncommon
- Haemorrhagic cystitis – rare. Encourage fluids for 6 hours post dose
- Gonadal toxicity – associated with cumulative dose >200-300mg/kg.
- Malignancy – rare and felt that there is not a clinically significant increased risk compared with the general paediatric population

**Monitoring**

FBC check weekly throughout treatment.

- Reduce dose to 50-75% if neutrophils 1.0 – 1.5x10⁹/L.
- Stop if neutrophils <1.0x10⁹/L and restart at 50-75% dose on neutrophil recovery >1.5x10⁹/L.

*Cyclophosphamide* – BNF link.

7.2.4 Calcineurin Inhibitors – Ciclosporin (or Tacrolimus)

*Ciclosporin (CsA) (Neoral®)* is useful as a steroid sparing agent (5).

**Dose** 2.5 mg/kg 12 hourly adjusted to achieve target trough level (see below).

If successful, treatment continued for at least 1 year initially. It can be continued for up to 3 years before a trial off therapy if relapse free. For children less than 5 yrs of age, three times daily dosing may be necessary. Parent advised to withhold morning dose until after trough level check.

**Monitoring**

12 hour trough level checked 1 week after treatment introduction.

Check 12 hour trough 1-2 weeks after any dose changes.

Therapeutic range for nephrotic syndrome is lower than for transplant patients. Aim for a 12 hour CsA trough of 50 – 100 nmol/l initially. Higher CsA trough levels up to a maximum of 150 nmol/l. Consider in patients relapsing at lower trough levels where renal function, blood pressure remain normal.

Monitor BP, urine P:CR and renal biochemical function at review for features suggesting possible drug nephrotoxicity.

If successful, CsA treatment can be continued, with careful monitoring for 3 years, or more if clinically indicated (6). When stable on treatment frequency of review can reduce to 2-3 monthly.

*Tacrolimus (Prograf®)* has been used in similar manner, in preference to ciclosporin, in children with SSNS but less frequently. However, there are few
data examining its efficacy (7) and no controlled trials comparing it with ciclosporin.

### 7.2.5 Mycophenolate Mofetil (MMF)

MMF has been used successfully as a second line steroid sparing agent in frequently relapsing and steroid dependent NS (8, 9, 10). Advantages include the absence of nephrotoxicity and no need for routine drug level monitoring.

**Dose** Up to 600mg/m²/dose twice daily. The GI intolerance may be reduced by a gradual introduction of MMF with stepwise dose increases over 4 – 8 weeks.

**Side effects**
- GI upset mainly diarrhoea.
- Leucopenia.
- Bone marrow suppression: Children and their carers should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding

**Monitoring**
- FBC monitored for leucopenia.
- If successful, MMF treatment can be continued, with careful monitoring for 3 years, or more if clinically indicated

[**Mycophenolate Mofetil** – BNF link](#)

### 7.2.6 Rituximab

Rituximab is a chimeric monoclonal antibody directly linked to the depletion of CD20 B cells. It has been used as experimental therapy to resolve cases of difficult nephrotic syndrome when other treatment modalities have failed (12, 13).

Patients with difficult to control NS despite use of recognised second line therapies may be considered for this treatment. Patients must be referred and reviewed by a paediatric nephrologist before treatment is initiated.

### 8. Dietary and Nutritional management

Increased exposure to steroids of children with frequent relapses or steroid dependence may lead to problems with weight and blood pressure control. Dietary advice should be repeated where clinically indicated.

[Nephrotic Syndrome Dietetic Guidelines](#)

### 9. Vaccination Advice

All children with NS should receive all routine childhood vaccinations. The timing of these may be interrupted if the child is treated with high dose steroids or
immunosuppressant therapies; see Appendix II of Vaccine Guideline for a list of vaccines that can be given safely. Vaccinations should be documented in the individual patient record, and recorded in the case notes (see Appendix III of Vaccine Guideline).

Refer DH Green Book for further guidance on the administration of vaccines in nephrotic syndrome and in patients on immunosuppression.

Other vaccines required include:

### 9.1 Pneumococcal

- Confirm status
- **Recommended for all unvaccinated children with NS.**
- Repeat vaccination every 5 years
- If not administered
  - Administer with first admission OR
  - Refer to GP to administer on discharge

### 9.2 Varicella

- **Varicella status confirmed non-immune**
  - For all children confirmed VZIGG negative, consider active immunisation with VZV when off all immunosuppressive therapy (14). (Appendix II of Vaccine guideline or DH Green Book)
  - ZIG (passive immunity) for exposure prophylaxis DH Green Book

- **Varicella - active disease**
  - And see 4.3.3 Varicella zoster (VZ) status

- Consider repeat Varicella status 6 - 12 monthly in the non-immune child.

### 9.3 Seasonal Influenza and H1N1

- **Annual seasonal flu vaccination** including H1N1 should be administered
  - Inform GP of recommendation in clinic letter
10. Patient and Family Preparation

Discharge planning and parent education should begin soon after admission and diagnosis.

This should include family support needs. Local psychology support can be sought. Information is also available on the SPRUN Managed Knowledge Network for children, siblings and parents. This can be adapted according for local arrangements.

10.1 Patient and Family Education

Corticosteroid use in nephrotic syndrome

Children with nephrotic syndrome lose excessive amounts of protein from their blood stream into their urine. This loss of protein causes tissue swelling, especially in the face, stomach and legs. The risk of infection also increases because important proteins used by their immune system have been lost.

When it is untreated, children can often die from infections. Corticosteroid drugs (steroids) such as prednisolone are used to induce a remission of the nephrotic syndrome and so reduce the risk of these infections. Steroids can have a number of serious side effects. A review of trials found that increasing the use of steroids for several months after the first episode reduces the risk of relapses, without an increase in serious side effects.

Second line treatment in nephrotic syndrome

Most children who experience this syndrome do have repeat episodes - relapses. Steroids such as prednisolone can stop the protein leak but the leak frequently recurs and further steroids can have adverse effects of poor growth, cataracts, osteoporosis and high blood pressure. Loss of protein in children with nephrotic syndrome can also be reduced with non-corticosteroid drugs. These drugs can reduce relapses and the need for more steroids.

A review of trials compared several drugs and found that cyclophosphamide, ciclosporin and levamisole are more effective than prednisolone alone in preventing relapses of the nephrotic syndrome. Newer drugs have also been used. There is less evidence of their benefit but they may be considered for individual children.
10.2 Patient and Family Information Provision and Links

Web links for patient information on Nephrotic Syndrome (NS)

EdREN Info - Edinburgh Renal Unit’s website information on NS.

The 3 links below are all from the UK National Kidney Foundation (NKF) website. The 3rd link is about a renal biopsy.

A guide to the treatment of Childhood Nephrotic syndrome. A more detailed description for parents and families

Nephrotic syndrome in Children – a brief description.

Rebecca has a Renal Biopsy describes for children what a renal biopsy involves.

Kids Kidney Research (adapted from a Great Ormond Street Hospital info sheet)

BKPA website PDF link: more suitable for adult NS than childhood

BBC website - information on childhood nephrotic syndrome.

Wikipedia link to nephrotic syndrome
11. Pre-discharge checklist

Discharge planning and parent education should begin soon after admission and diagnosis. A checklist can be used and a [printed copy (link here)](link) provided to the patient and family at discharge (below).

<table>
<thead>
<tr>
<th>Nephrotic Syndrome Discharge Planning Checklist</th>
<th>Date complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotic syndrome info sheet/website links</td>
<td></td>
</tr>
<tr>
<td>Renal Medication Information Booklet</td>
<td></td>
</tr>
<tr>
<td>• Prednisolone dose and reducing regimen</td>
<td></td>
</tr>
<tr>
<td>• Steroid card</td>
<td></td>
</tr>
<tr>
<td>• Penicillin prophylaxis regimen</td>
<td></td>
</tr>
<tr>
<td>• Omeprazole/Ranitidine regimen</td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
</tr>
<tr>
<td>• Parent/carer education complete</td>
<td></td>
</tr>
<tr>
<td>• Diary record</td>
<td></td>
</tr>
<tr>
<td>• Albustix® provided</td>
<td></td>
</tr>
<tr>
<td>Dietetic referral</td>
<td></td>
</tr>
<tr>
<td>• Diet information sheet</td>
<td></td>
</tr>
<tr>
<td>• Fluid restriction during relapse discussed</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>• Pneumococcal vaccination confirmed/arranged</td>
<td></td>
</tr>
<tr>
<td>• Varicella status: positive □ negative □</td>
<td></td>
</tr>
<tr>
<td>• Advice given for VZ seronegative</td>
<td></td>
</tr>
<tr>
<td>Follow up</td>
<td></td>
</tr>
<tr>
<td>• Out patient appointment issued</td>
<td></td>
</tr>
<tr>
<td>• Contact number/details issued</td>
<td></td>
</tr>
</tbody>
</table>
12. Out-patient management and follow-up

In a natural-history study of 398 children, the proportion that became non-relapsers rose from 44% at 1 year to 69% at 5 years, and 84% at 10 years (15).

The frequency of follow up will be dictated by the clinical course. For patients first presenting or having only an infrequent relapse a suggested course might comprise:

<table>
<thead>
<tr>
<th>Follow up</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks after starting steroids</td>
<td>Confirm steroid reduction plan. Review side effects. Information giving</td>
</tr>
<tr>
<td>3 mo. after starting steroids</td>
<td>Confirm steroid completion. Review side effects. Vaccine advice - influenza. Varicella status (see clinical monitoring below)</td>
</tr>
<tr>
<td>6 mo. from presentation/last relapse</td>
<td>Review. Information giving. Vaccine advice – influenza; VZ vaccine if seronegative</td>
</tr>
<tr>
<td>12 mo. from presentation/last relapse</td>
<td>Review. Vaccine advice - influenza.</td>
</tr>
<tr>
<td>24 mo. from presentation/last relapse</td>
<td>Review. Discharge to see again if relapse. Intermittent monitoring of urine up to 5 years.</td>
</tr>
</tbody>
</table>

For patients with a history of frequent relapses or previously treated with second line therapy and no longer relapsing, follow up is suggested for 2 years from last relapse or from completion of second line therapy without further relapse. A suggested course might comprise:

<table>
<thead>
<tr>
<th>Follow up</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 mo. from completion of 2nd line treatment or last relapse.</td>
<td>Review. Confirm relapse free.</td>
</tr>
<tr>
<td>3-6 mo. from completion of 2nd line treatment or last relapse.</td>
<td>Confirm relapse free. Vaccine advice - influenza.</td>
</tr>
<tr>
<td>6-12 mo. from completion of 2nd line treatment or last relapse.</td>
<td>Review. Confirm relapse free. Vaccine advice - influenza. VZ vaccine if seronegative.</td>
</tr>
<tr>
<td>12-24 mo. from completion of 2nd line treatment or last relapse.</td>
<td>Review. Vaccine advice - influenza.</td>
</tr>
<tr>
<td>24 mo. from completion of 2nd line treatment or last relapse.</td>
<td>Review. Discharge to see again if relapse. Intermittent monitoring of urine up to 5 years.</td>
</tr>
</tbody>
</table>
12.1 Clinical monitoring

For children on long-term steroids monitor for side effects:

1. Monitor BP at each clinic visit and chart against ‘casual’ BP centile chart.
2. Monitor growth (including bone age and pubertal stage where appropriate)
3. Monitor weight – dietetic review where appropriate
4. Glycosuria / HbA1c if clinical concerns about glycaemic control.
5. Monitor Varicella status 6 - 12 monthly if seronegative. Consider vaccination if still seronegative and having completed immunosuppressive therapy.
6. Patients who receive prolonged steroid treatment (continuously for over 12 months)
   • consider modified Synacthen test to identify risk of adrenal suppression on stopping treatment (16).
   • consider ophthalmology review
7. Patients on second line therapy require monitoring as specified for treatment regimen above (section 7).

13. Future guideline development

Future review of this guideline is due every 2 years (February 2014) or at an earlier date to incorporate clinically significant changes in practice. This guideline will be audited prior to its review to assess the impact of implementation of the guideline, and to determine changes required to improve patient outcomes.

Audit of the guideline should cover areas outlined in Table 3 in “Improving the standard of care of children with kidney disease through paediatric nephrology networks” (RCPCH 2011) (17).
14. References

   An excellent review article of nephrotic syndrome.

   An excellent and concise resource providing practical management advice.

   Meta-analysis indicates prolonged courses of steroid therapy should be administered in the first episode of SSNS to reduce the risk of early relapse and that this regimen, by reducing relapses, may result in a net reduction in steroid exposure compared with shorter courses.

   In children with steroid-dependent NS, a viral URTI triggers a relapse in nearly 50% of cases. A short-term modest increase in the dose of prednisolone during viral URTI can reduce this risk significantly.

   This updated Cochrane review concludes that eight week courses of cyclophosphamide or chlorambucil and prolonged courses of cyclosporin and levamisole reduce the risk of relapse in children with relapsing SSNS compared with corticosteroids alone.

   Long-term follow-up of 20 patients with proven SSNS treated with CsA for a median of 5 years. Initially, GFR dropped but remained stable afterwards. None developed chronic renal failure. The analysis demonstrates that even long-term therapy with CsA for more than 5 years in children with MCNS is safe and does not impair renal function.

   A retrospective study of 10 children with steroid-dependent SSNS. The number of relapses, cumulative dose of prednisolone, reduction of GFR and number of children requiring antihypertensive agents did not differ significantly between ciclosporin and tacrolimus treatment periods.
   The first randomized controlled trial of MMF in children with SSNS, comparing MMF and cyclosporin. The results suggest that MMF could be less effective than cyclosporin but no statistically significant difference was detected in this small study.

   Phase II trial of 23 children with SDNS showing that MMF in combination with low-dose alternate-day prednisone is effective to maintain long-term remission and allows decreasing prednisone dose in a homogeneous population of children with severe steroid dependency

    MMF therapy results in significant CsA and/or steroid sparing and reduction in relapse rates in children with CsA-dependent NS.

    A meta-analysis of cyclophosphamide (CYC) and chlorambucil (CHL) treatment. Side effects rates quoted: fatality rate was approximately 1%; leukopenia in one-third of patients with either drug; severe bacterial infections developed in 1.5% on CYC and in 6.8% on CHL; Seizures in 3.6% with CHL; malignancies observed in 14 children after high doses of either drug. Females rarely developed permanent gonadal damage. No safe threshold for a cumulative amount of CYC was found in males, but there was a marked increase in the risk of oligo- or azoospermia with higher cumulative doses. From this meta-analysis CYC 2–3 mg/kg body weight for 8–12 weeks as the standard scheme was recommended. CHL has higher rates of severe side effects and should be considered a second-line drug.

    First prospective, open series on the effective use of RTX in patients with severe SDNS.

    Series of 22 children with very early onset and long-lasting SDNS treated with Rituximab. Complete B cell depletion in all patients. Initial B cell depletion proved efficient to prevent relapse of NS and allowed decrease or withdrawal of steroids and immunosuppressive drugs. Tolerance of the treatment was good with no major side effects. At last follow-up, 9 patients displayed sustained remission.

    A study in 20 patients reports that immunization with a single dose of VZV vaccine is safe and effective in children with SSNS in remission.
A natural-history study of 398 children.

A study of 32 children with NS receiving alternate day prednisolone therapy for >12 months shown to be at risk of developing HPA suppression and should be evaluated using the modified synacthen test. Children with evidence of HPA suppression are at a greater risk of relapse.

17. *Improving the standard of care of children with kidney disease through paediatric nephrology networks (RCPCH 2011)*
The RCPCH in collaboration with NHS KidneyCare and the British Association of Paediatric Nephrology has published a report on paediatric nephrology networks, setting out the core requirements for success and standards for commissioning and provision of services.