Nephrotic Syndrome Children's Guideline

NHS University Hospitals of Leicester NHS Trust

Trust Ref:E4/2019

1. Introduction and Who Guideline applies to

This guideline describes the assessment and management of children and young people with nephrotic syndrome

This guideline applies to Children and young people under 18 years of age with nephrotic syndrome within the EMEESY Children's Kidney Network (East Midlands, East of England and South Yorkshire) being managed by the Leicester Children's Hospital and the Paediatric Emergency Department.

Other related guidelines include:

Hypertension UHL E8/2020 **Hypertension UHL Childrens Medical Guideline**

Abnormal Glomerulofiltration Rate UHL E6/2020 **Abnormal Glomerular Filtration Rate UHL Childrens Medical Guideline**

Glomerulonephritis UHL E5/2019 **Glomerulonephritis UHL Childrens Hospital Guideline**

This EMEESY network guideline has been developed by clinicians from Nottingham Children's Renal Unit with consultation across the network including from the Leicester Royal Infirmary and has been ratified by the Leicester Children's Hospital guideline process.

IMPORTANT: Section 2.6.2. Gastro protection recommendations - RANITIDINE is not available at UHL.

Our local renal specialists are:

Dr Angela Hall Associate Specialist

Dr Pradeep Nagisetty Consultant Paediatrician with interest in Nephrology

Renal Nurse: Leigh Ellis-Cox

They can be contacted via UHL switchboard.

Nephrotic Syndrome

Title of Guideline (must include the word "Guideline" (not protocol, policy, procedure etc)	Guideline for the assessment and management of nephrotic syndrome in children and young people
Contact Name and Job Title (author)	Dr MT Christian, Consultant Paediatric Nephrologist, Nottingham University Hospitals, QMC Campus, Ext 83832
Directorate & Speciality	Family Health Paediatric Nephrology
Date of submission	March 2024
Date on which guideline must be reviewed (this should be one to three years)	March 2027
Guideline Number	2006
Explicit definition of patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis)	Children and young people under 18 years of age with nephrotic syndrome within the EMEESY Children's Kidney Network (East Midlands, East of England and South Yorkshire)
Abstract	This guideline describes the assessment and management of children and young people with nephrotic syndrome
Key Words	Nephrotic syndrome, oedema, renal, child, young person, paediatric
Statement of the evidence base of the guideline – has the guideline been peer reviewed by colleagues? **Evidence base: (1-5)**	Up to 1a

1a	**meta analysis of randomised controlled trials**
1b	at least one randomised controlled trial
2a	at least one well-designed controlled study without randomisation
2b	at least one other type of well-designed quasi-experimental study
3	well –designed non-experimental descriptive studies (ie comparative / correlation and case studies)
4	expert committee reports or opinions and / or clinical experiences of respected authorities

	5 recommended best practise based on the clinical experience of the guideline developer	
Consultation Process		Paediatric Nephrologists, EMEESY Network Steering Group, Paediatric Nephrology Guidelines Meeting, Paediatric Nephrology Liaison Nurse, Pharmacist. Child Health Guidelines SOP EMEESY guideline group – Chesterfield and Leicester hospitals
Target audience		Clinicians and healthcare professionals throughout EMEESY caring for children and young people with nephrotic syndrome

This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date.

Version number	Date produced	Author
1	December 2004	Dr Jonathan Evans
2	December 2008	Dr Martin Christian
3	November 2009	Dr Martin Christian
4	September 2010	Dr Martin Christian
5	May 2017	Dr Martin Christian
6	January 2023	Dr Martin Christian
6.1	March 2024	Dr Martin Christian
6.1.1	May 2024	Dr Martin Christian

Document history

Version	Amendments
4	1. Reformatted as a network guideline 2. Inclusion of flowsheet for recording relapses 3. Removed dosing of low-molecular heparin and referred to separate guideline 4. Included reference to PREDNOS2 study for patients with frequently relapsing disease 5. Removal of Prograf as recommended tacrolimus preparation in line with NUH policy to move to prescribing generic preparations 6. Inclusion of checking of hepatitis B status prior to giving first rituximab dose 7. Amendment to genetic investigations for children with steroid resistant nephrotic syndrome to amalgamate different tests as single sample for NGS of all known SRNS mutations
5	1. Insertion of relevant hyperlinks to the EMEESY website, InfoKID and other sources of public information 2. Removal of information on PREDNOS study (now completed but awaiting results)

	3. Re-insertion of information on metolazone as now available again. 4. Amendment of rituximab guidelines in line with NHS England commissioning policy for rituximab use in SSNS, including amendment of FRSSNS management algorithm. 5. Amendment of guidelines for investigation/management of SRNS in line with NHS England commissioning policy for rituximab use in SRNS.
6	Revised following publication of IPNA clinical practice guidelines [1]: 1. Removal of option for intensified initial steroid regime 2. Change of maximum prednisolone dose from 80 mg to 60 mg 3. Removal of routine option to use low-dose prednisolone at the time of URTI to prevent relapses 4. Change of emphasis for second-line treatment options 5. Introduced guidance on mycophenolic acid AUC monitoring
6.1	1. Minor adjustments including to antibiotics and Varicella sections
6.2	1. Minor adjustments for antimicrobial therapies and peritonitis section

Statement of Compliance with Child Health Guidelines SOP

Recent updates to this guideline refer to activities of only one specific team and consultation has taken place with relevant members of that team. Therefore this version has not been circulated for wider review.

Maria Moran

Clinical Guideline Lead

12th July 2017

Objectives of the guideline

With regard to initial presentation:

1. Describe presentation of typical and atypical nephrotic syndrome.
2. Know what investigations to carry out for a child presenting with nephrotic syndrome.
3. Recognise how to diagnose and manage hypovolaemia in the nephrotic state.
4. Know when and how to give intravenous albumin safely.
5. Know when to discuss with a paediatric nephrologist and when to refer.

6. Know how long children need to remain in hospital during the initial episode and what the purpose of the hospital admission is.
7. Be familiar with the information about nephrotic syndrome that parents need at discharge.
8. Know how to follow-up children with nephrotic syndrome in the out-patient clinic and what to do at each consultation.

With regard to relapsing disease:

1. How to define and manage a relapse.
2. What the role of the linked renal nurse is during the initial episode and following discharge.
3. Understand what other members of the multi-disciplinary team should be involved in the care of a child with nephrotic syndrome.
4. Know how to recognise and manage frequently relapsing nephrotic syndrome.
5. Know how to prevent and manage infective complications of nephrotic syndrome.
6. Know when to refer to a shared care clinic
7. Have knowledge of current evidence base for nephrotic syndrome care and knowledge of studies currently in progress.

Contents of the Guideline

1. Background

Nephrotic syndrome is characterised by heavy proteinuria (protein:creatinine ratio > 200 mg/mmol, hypoalbuminaemia (serum albumin <30 g/l) and oedema. It is an uncommon childhood condition with an annual incidence in the UK of only 2 per 100,000 children. It is more common in children of other ethnicities, particularly those of South Asian ancestry [2].

There are many different causes of nephrotic syndrome, but the majority of cases (over 90%) are primary and due to minimal change disease (MCD). Approximately 80% of children presenting with nephrotic syndrome will respond to prednisolone and this is the most important factor in terms of management and prognosis.

Nephrotic syndrome is thought of as a relatively benign condition; however the mortality rate remains around 0.5-1%. There is significant acute and long term morbidity and almost half children presenting with an initial episode will develop frequently relapsing disease, therefore it is appropriate to consider early referral of all patients to the paediatric renal team

Definition of nephrotic syndrome

- Heavy proteinuria (3+/4+ on dipstick or urine protein >200 mg/mmol creatinine)
- Hypoalbuminaemia (< 30 g/l but frequently <20 g/l)
- Oedema

2. Assessment and management of initial episode

2.1. Clinical history

To include history of:

- Atopy
- Immunisations
- Natural childhood infections (particularly varicella zoster)
- Family history (particularly renal disease and thrombophilia)

All children should be admitted.

2.2. Clinical examination

To include:

- Height, weight, estimated body surface area (NB – an estimate of dry weight will give a more accurate surface area estimate)
- Blood pressure
- Assessment of oedema (lower limb, sacral, ascites, scrotal, pleural effusions?)
- Cardiovascular status and perfusion (volume status):

- Indicators of fluid overload: tachycardia, hypertension, respiratory distress, warm peripheries, hepatomegaly, raised JVP
- Indicators of hypovolaemia: tachycardia, hypertension, cool peripheries, delayed capillary refill time

2.3. Baseline investigations

Children presenting with typical nephrotic syndrome are frequently over-investigated. Providing the history is consistent with typical nephrotic syndrome (see section 2.4 below), the following investigations are all that is required as a baseline assessment for diagnosis and surveillance for complications

Urine tests	Blood tests
Urinalysis for protein and blood	Electrolytes, urea and creatinine,
Protein:creatinine ratio (early morning sample if possible	Bone profile (including albumin)
	Full blood count
	Varicella zoster immunity status

Raised urea or haemoglobin may be markers of hypovolaemia. Elevated creatinine can indicate atypical nephrotic syndrome and is an indication for discussion with a paediatric nephrologist.

Plasma lipids, complement and hepatitis serology are not relevant investigations for a first episode of typical nephrotic syndrome.

Plan tests: single venepuncture is ideal in children who may be difficult to bleed because of oedema. Femoral stabs should never be performed as thrombosis is a described complication.

On-going blood tests are only necessary for children receiving albumin infusions, diuretics or to follow-up initial abnormal results.

2.4. Typical versus atypical nephrotic syndrome

Children with an atypical initial presentation of nephrotic syndrome are less likely to have minimal change disease and may not be responsive to steroids. They may require biopsy before initiating treatment and should always be discussed with a paediatric nephrologist.

Criteria	Typical nephrotic syndrome	Atypical nephrotic syndrome
Age	2-11 years	<2 or >11 years
Renal function	Normal creatinine	Elevated creatinine
Haematuria	Microscopic may occur	Macroscopic
Hypertension	Usually normotensive	Elevated
Family history of nephrotic syndrome	Usually absent	May be present

2.5. Indications for discussion with a paediatric nephrologist at presentation

The nephrotic state can be complicated by hypovolaemia, thrombosis and infection. If there are any of the following features during the initial presentation, the child should be discussed with a consultant paediatric nephrologist:

- Any atypical features as above
- Suspicion of hypovolaemia from clinical assessment or elevated haemoglobin/urea
- Before giving intravenous albumin

2.6. Management

Nephrotic syndrome treatment aims to induce remission with steroids (most patients respond within 7-14 days), and therefore promote diuresis. All other therapies are symptomatic and aimed at preventing complications. Children who do not respond to prednisolone within 28 days will require referral to paediatric nephrology for a renal biopsy.
Please consider recruiting children to the RaDaR rare disease registry if available if your local centre.

2.6.1. Corticosteroids

PREDNOS [3] has shown that a prolonged initial corticosteroid course has no influence on the future course of the disease and so all children should be treated with a standard prednisolone regimen:

- Prednisolone 60 mg/m^2/day in a single morning dose (maximum dose 60 mg) for 28 days. (Methylprednisolone 50 mg/m^2/day can be used intra-venously in the vomiting child as this is the equivalent dose to 60 mg/m^2/day oral prednisolone)
- After 28 days, the dose of prednisolone is reduced to 40 mg/m^2 on alternate days (maximum dose 40 mg) for the next 28 days and then stopped.

All doses should be rounded to the nearest 5 mg.
A "steroid warning card" should be provided for the patient to carry.

2.6.2. Gastroprotection

Despite large doses of steroids, few children experience gastritis symptoms. If necessary, children may be given gastro-protection whilst on high dose steroids according to local protocols.

2.6.3. Assessment of hypovolaemia

Hypovolaemia in the nephrotic state is a common but serious complication which increases the risk of thrombosis. Clinical indicators of hypovolaemia include tachycardia, hypertension, cool peripheries and delayed capillary refill time. Laboratory parameters suggesting hypovolaemia include elevated urea or haemoglobin.

Diuretics without albumin must not be given in hypovolaemia due to the risk of thrombosis.

If hypovolaemia is severe (such as with noticeably cool peripheries, abdominal pain or elevated urea) then consideration should be given to treatment with intravenous albumin (section 2.6.4.2) and to thromboprophylaxis (section 2.6.5). Normal saline or other isotonic crystalloid may be given if albumin is not immediately available.

2.6.4. Oedema and ascites

A gentle fluid restriction is may be beneficial to minimise oedema. Suggested fluid intake:

<5 yrs = 750 ml
>5 yrs = 1 litre

A "no added salt" diet is recommended (see section 2.7)

2.6.4.1 Diuretics

These must only be used if severe and worsening oedema/ascites in the absence of hypovolaemia. Furosemide alone may be tried initially but if oedema is severe, the synergistic action of furosemide with spironolactone may be required. Doses are:

- Furosemide 0.5-1 mg/kg twice daily
- Spironolactone 1 mg/kg twice daily

If oedema persists, a thiazide, metolazone, may be added under the guidance of a consultant paediatric nephrologist. The dose is:

1 m – 12 y: 100 microgram/kg once daily initially, increased if necessary to twice daily for resistant oedema.

12 – 17 y: 5 mg once daily initially, increased if necessary to twice daily for resistant oedema.

2.6.4.2 Albumin infusions

Albumin infusion is only indicated in symptomatic hypovolaemia or severe diuretic resistant oedema. It should be administered with great caution with frequent monitoring of vital signs until at least two hours after the infusion is completed.

Dose:

- Shock = 4.5 or 5% albumin 20 ml/kg over 30-60 mins repeated if necessary. If volume status remains depleted, discuss with regional paediatric intensive care before giving further boluses.
- Mild hypovolaemia + oedema = 20% albumin 5 ml/kg (1g/kg) over 4 hrs with IV furosemide 1 mg/kg halfway and/or at the end of the infusion provided signs of hypovolaemia have resolved (mid and end-point clinical evaluation should be carried out)
- Severe diuretic resistant oedema = 20% albumin 5 ml/kg (1g/kg) over 4 hrs with IV furosemide 1mg/kg half way through infusion

Ensure that your individual hospitals' transfusion policy will allow for infusion of 20% albumin over >3 hours.

Unless there is experience in giving 20% albumin and facilities for high-dependency monitoring, condition should be given to discussion with a paediatric nephrologist with a view to transfer to Nottingham or a more local critical care bed.

2.6.5. Risk of thrombosis

Thrombosis, either arterial or venous is relatively rare in the nephrotic state but the consequences can be devastating.

To decrease the risk of thrombosis:

- Avoid hypovolaemia
- Prevent sepsis
- Encourage mobilisation and avoid bedrest

For children with prolonged nephrotic states, a history of thrombosis, or a marked hypovolaemic state (with elevated/rising plasma urea or haemoglobin) the following additional measures may be considered:

- Compression stockings
- Low molecular weight heparin. Heparin is preferable to Aspirin for prevention of venous thrombosis but only available as sub-cutaneous injections. Enoxaparin is used in Nottingham but whichever LMW heparin is used in local formulary would be suitable. It may be given through an Insufflon (changed weekly) to avoid daily sub-cutaneous injections if this is local practice. For enoxaparin dosing, please see guidelines for Anti-coagulation in chronic kidney disease for dosing (also available via EMEESY website).

2.6.6. Hypertension

Check volume status. If euvolaemic:

- Atenolol initially 0.5-1 mg/kg/day in single daily dose
- Nifedipine (initially 200-300 microgram/kg three times daily) for rapid short term control. Risk of rebound hypertension therefore for medium/long term therapy, amlodipine is the preferred calcium channel blocker.
- Amlodipine initially 100-200 micrograms/kg/day (max 10 mg/day)

2.6.7. Infection prophylaxis

2.6.7.1. Antibiotics

Oral Penicillin V (62.5 mg twice a day <1 years or 125 mg twice daily if <6 years or 250 mg twice daily 6 years or older) for 10 days should be prescribed to oedematous/ascitic patients to protect against pneumococcal infection.

If Penicillin allergic use Clarithromycin:

Doses are as follows:

- 1 month – 11 yr (body-weight up to 8 kg) 7.5 mg/kg twice daily for 10 days
- 1 month – 11 yr (body-weight 8-11 kg) 62.5 mg twice daily for 10 days
- 1 month – 11 yr (body-weight 12-19 kg) 125 mg twice daily for 10 days
- 1 month – 11 yr (body-weight 20-29 kg) 187.5 mg twice daily for 10 days
- 1 month – 11 yr (body-weight 30-40 kg) 250 mg twice daily for 10 days
- 12 – 17 yr 250 mg twice daily for 10 days

2.6.7.2 Peritonitis

If peritonitis is suspected then treatment for Gram negative organisms is recommended in addition to pneumococcal infection until blood cultures are available. This should be as per local microbiology advice and standard peritonitis treatment.

2.6.7.3. Pneumococcal immunisation

All children should receive a dose of 23 valent Pneumococcal Polysaccharide Vaccine if not already given. Children who have received Prevenar 13 as part of the

routine vaccination schedule will be better covered against invasive pneumococcal disease by receiving an additional dose of the 23-valent Pneumococcal Polysaccharide Vaccine. It can be given from the age of 2 years.

2.7. Dietary advice

A dietitian should see the child and family. A balanced no added salt diet is recommended during the nephrotic state. The dietetic advice to achieve this is to reduce the intake of processed foods and to avoid the addition of salt in cooking and at the table.

To reduce the intake of processed foods parents should select foods which contain <0.5 g Na or <1.25 g salt per 100 g weight of food. This information is usually available on the packaging. Compliance with a no added salt diet will aid adherence to the fluid restriction and encourage good blood pressure control. The diet should be nutritionally balanced with an emphasis on a healthy intake of fruit, vegetables, wholegrains carbohydrates (bread, rice, pasta and cereal), pulses, meat, fish, milk and dairy.

As this disorder is characterised by heavy protein loss in the urine, some people might feel that counteract this loss by eating a protein-rich diet may be helpful. However, a high-protein diet is not recommended for nephrotic syndrome. Children should be encouraged to eat adequate protein to encourage good growth, this includes a portion of protein-rich food with each meal e.g. milk, cheese, yogurt, eggs, fish, chicken, meat, soya, nuts and seeds, beans and pulses.

If a dietitian is unavailable, advice about low salt foods is available on the EMEESY website.

2.8. Parental education

Nephrotic syndrome is a significant diagnosis. The family needs to be aware that the risk of relapse is >80% and they should know how to detect and treat it. Making adequate information available for the family is essential. All carers should receive the Childhood Nephrotic Syndrome booklet or be signposted to the infoKID website (www.infokid.org.uk) and be given a Nephrotic Diary or equivalent notebook or signposted to the nephrotic syndrome app when available (via NeST) to record daily urine results. They should be shown how to test urine and record in the diary before discharge. They should also be given a number for advice if urine tests suggest a relapse.

Referral to the paediatric nephrology liaison nurse or link paediatric nephrology nurse (if available) should be routine. For Nottingham patients, contact numbers are found at: www.emeesykidney.nhs.uk/contact. Local centres will have their own contact details.

Patient support information is available on the internet through. NeST (www.nstrust.co.uk) and Nephcure (www.nephcure.org). There is a good infographic on lifestyle issues for children with nephrotic syndrome produced by the Hospital for Sick Children, Toronto.

2.9. Discharge planning

Children will normally spend several days in hospital following a first presentation with nephrotic syndrome. Even if there is not significant oedema, a short admission will be necessary to teach children and their parents about nephrotic syndrome. For many children with their initial presentation, there is significant oedema and discharge date will be determined according to when the child is judged to be cardiovascularly stable.

Each day during their in-patient stay, children should have a thorough assessment of their fluid status including accurately completed fluid balance charts, regularly blood pressure monitoring and a daily weight. They should be examined daily for extent of oedema and signs of hypovolaemia.

2.10. Discharge checklist

Before discharge, parents/carers should know:

- how to dipstick the child's early morning urine and record this in a daily diary.
- how to recognise a relapse
- whom to contact for advice
- appropriate fluid and dietary advice
- steroid and immunosuppression advice

3. Out-patient management

3.1. Out-patient follow-up until remission

Most children will be discharged from their initial episode of nephrotic syndrome before they enter remission. All will be taking high-dose steroids and some will also be taking regular diuretics. Children not yet in remission should be reviewed in an out-patient clinic (review in a rapid access clinic or as a ward attender is also suitable) at least every week. Parents should be encouraged to bring urinalysis diaries to all out-patient appointments.

The consultation should include a review of medication and any side-effects experienced. Weight, blood pressure and urinalysis should be done before seeing the doctor. Examination should include an assessment of volume status as above.

3.2. Routine out-patient follow-up for the first 6 months

Children should be seen approximately 1-2 monthly for the first 6 months. The purpose of the regular review is:

- Assess for side-effects of steroids (weight gain, Cushingoid appearance, striae, hypertension, behavioural side-effects, growth)
- Review urinalysis diary and reinforce the importance of daily urine testing and recording
- Confirm steroid dosing
- Provide further education opportunities, especially the management of relapses

Parents are usually encouraged to test their child's urine daily until remission then three times weekly for the first six months. Frequency of routine monitoring after that depends on frequency of relapses, but testing at least weekly for the first few years

is good practice. If urine shows + or more, it should be retested the next day to detect a relapse early on. When there is intercurrent infection, urine should be tested daily for around a week as there is increased risk of relapse at this point.

3.3. Management of relapses

At least 80% of children will relapse within the first year but it can also occur years after the initial presentation. Relapse can follow viral infection or occasionally immunisation.

A relapse is defined as proteinuria of +++ or more for 3 consecutive days.

Standard treatment for a relapse is prednisolone 60 mg/m^2/day (maximum dose 60 mg) given once daily until remission, which is defined as urinary protein negative or trace for 3 consecutive days. This is followed by prednisolone 40 mg/m^2/alternate day (maximum dose 40 mg) for 28 days. Thereafter steroids are usually stopped but may taper slowly if this is not the first relapse or the relapse has occurred on steroid therapy.

It is suggested that children are assessed face to face for their first relapse to:

- Ensure that the relapse has been diagnosed correctly
- Check for hypovolaemia
- Confirm daily prednisolone dose and duration
- Give parameters to parents that should prompt further hospital review such as worsening oedema or the development of abdominal pain.
- Plan for further routine out-patient review within the next month.

For further relapses, it is not always necessary for a child to be seen but parents are encouraged to phone their local contact (e.g. paediatric nephrology liaison nurse, paediatric renal link nurse (if available), local SPIN paediatrician, paediatric ward out of hours) before initiating high dose prednisolone. Prednisolone treatment is frequently delayed for at least 5 days unless the child is becoming oedematous since a small number of children will remit spontaneously. Any children with abdominal pain or who are otherwise unwell should be reviewed by a doctor.

Some children have relapses that respond equally effectively to half-standard doses of prednisolone, i.e. 30 mg/m^2 daily until remission followed by 20 mg/m^2 on alternate days for 4 weeks [4,5]. Until there is clinical trial evidence to support, children may be offered this half-dose regimen unless there are clinical risk factors that caution against it, such as oedema or hypovolaemia complicating the relapse, failure to respond to a previous half-standard course or recent relapses that take >14 day to remit. If no response after 7 days or the child becomes oedematous before then, the dose should be increased to 60 mg/m^2 daily.

3.4. Routine immunisations in nephrotic syndrome

See separate guideline Immunisation in Renal Disease Short Title: Nottingham Children's Hospital guidelines - EMEESY

3.5. Chicken pox contact

Chicken pox whilst immunosuppressed can be a serious illness. Varicella zoster immunity status should be known (and documented) in each nephrotic patient.

Children who are non-immune and have close contact (household or same school class etc.) with chicken pox may require post-exposure prophylaxis with aciclovir or valaciclovir according to local policies.

All children with nephrotic syndrome who are varicella non-immune should be vaccinated against chicken pox at the first opportunity of their being non-immunosuppressed (as defined above). Consideration should also be given to immunising non-immune siblings. These issues should be raised with the parents and GP at the initial episode.

There is further information about chicken pox contact in the Immunisation in Renal Disease guideline.

3.6. Data collection

Careful recording of clinical information is key to guiding future treatment. Any relapses since the previous clinic should be recorded with the following information:

- Date of relapse
- Prednisolone dose at the time of relapse (also note if steroid dose reduced within two weeks of relapse)
- Treatment given
- Time until remission

4. Management of FRNS and SDNS

At least 40% of children will have regular relapses and have difficulty discontinuing steroid medication. These two sub-types of nephrotic syndrome and their management are described below.

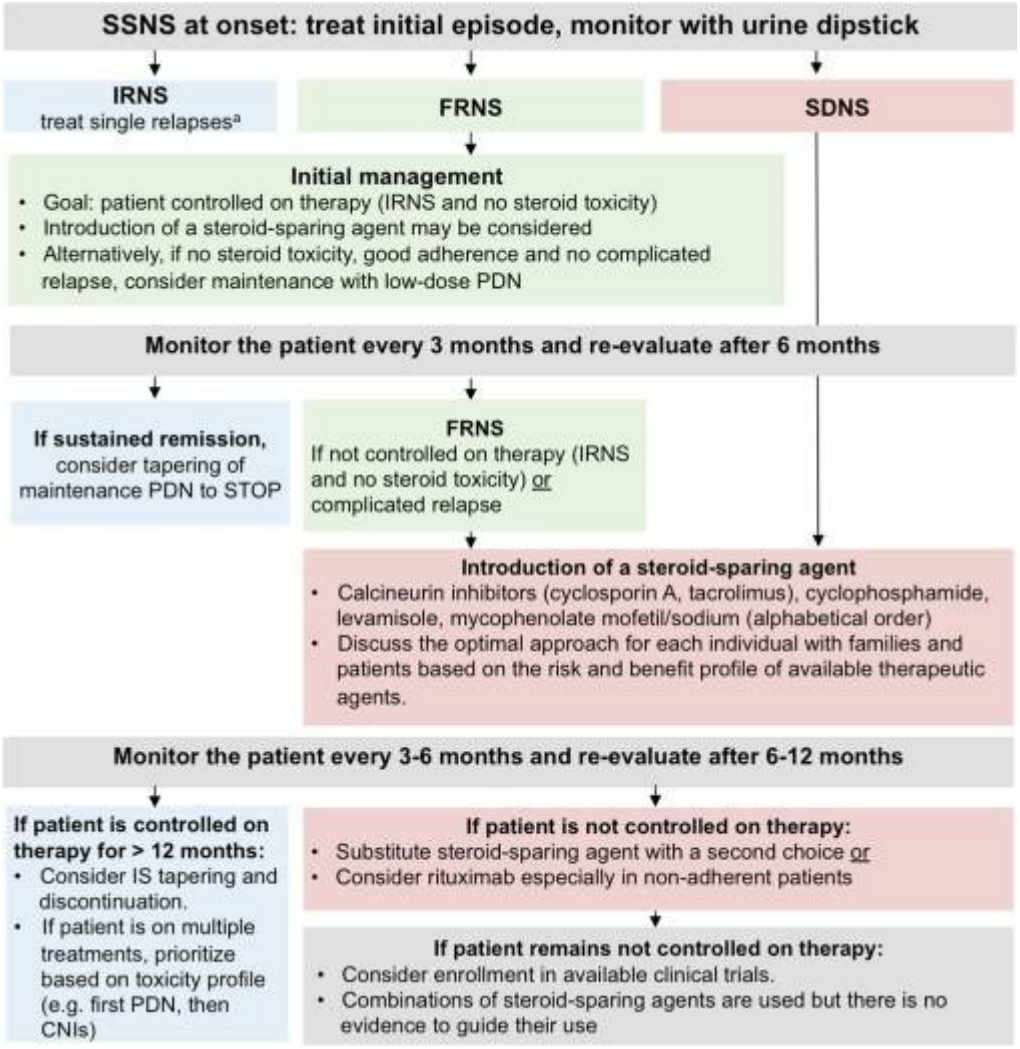
It is anticipated that children with frequently relapsing nephrotic syndrome (FRNS) and steroid dependent nephrotic syndrome (SDNS) will be managed by SPIN paediatricians or paediatric nephrologists.

FRNS is defined as three relapses (including the initial episode) within the first 6 months or three or more relapses in any 12 months thereafter [1]. SDNS occurs when children have two consecutive relapses on prednisolone treatment for a relapse or within two weeks of discontinuing it. Nephrotic syndrome which meets either of these definitions is a prompt that second-line, relapse-preventing medication should be considered.

Children with frequently-relapsing disease may be suitable for an initial trial of low-dose prednisolone as outlined below. In contrast, steroid-dependent disease is always an indication for a second-line, steroid-sparing treatment.

All children suitable for a second-line treatment should first be discussed with a consultant paediatric nephrologist.

An algorithm for treating FRNS/SDNS is summarised in the figure:



Key: IRNS: infrequently relapsing nephrotic syndrome; FRNS: frequently relapsing nephrotic syndrome; SDNS: steroid dependent nephrotic syndrome; PDN: prednisolone; IS: immunosuppression; CNI: calcineurin inhibitor.

Figure: algorithm for the management of SSNS (from IPNA clinical practice guideline, Trautmann et al, 2022 [1])

4.1. Tapering and long-term low-dose steroids

Children who develop early FRNS may benefit from a slowly tapered course such as the example below:

Prednisolone dose	Duration
60 mg/m^2/day	Until remission
40 mg/m^2 on alternate days	4 weeks
30 mg/m^2 on alternate days	2 weeks
20 mg/m^2 on alternate days	2 weeks
10 mg/m^2 on alternate days	2 weeks
5 mg/m^2 on alternate days	2 weeks

The initial maximal dose is 60 mg with subsequent doses in proportion. This would give a weaning duration of 12 weeks. In practice, for smaller children, this usually equates to dropping the dose by 5 mg every fortnight after the initial 4 weeks at 40 mg/m^2. For larger children, the first two reductions can be by 10 mg with later reductions by 5 mg.

In children with FRNS (but not SDNS), prednisolone may be continued long-term at low dose (approximately 5-10 mg/m^2 on alternate days or 2.5-5 mg/m^2 daily [6]) and this is the simplest form of prophylactic therapy for FRNS.

4.2. Prophylactic steroids to cover intercurrent illness

Prophylactic low-dose prednisolone should not be routinely given to children with relapsing SSNS at the time of an upper respiratory tract infection (URTI).

Although many relapses are triggered by intercurrent infections, particularly URTIs, the PREDNOS 2 trial [7] found that low-dose daily prednisolone given for 6 days at the time of an URTI did not reduce the URTI-associated relapse risk, and this finding was consistent for children taking any form of second-line treatment, or none.

The IPNA clinical practice guideline [1] undertook a small meta-analysis with previous (smaller and less robustly designed) studies that did show benefit of low-dose prednisolone and concluded that it might still be considered in children who are already taking low dose alternate day prednisolone and have a history of repeated infection-associated relapses.

4.3. Steroid-sparing second-line drugs

There are several options for steroid-sparing second-line drugs with some differences in effectiveness in different clinical situations. The benefits, dosing and side-effects of each one are discussed below. The decision on which order to treat may be made after discussion with patient and family.

The aim of second-line treatment is to achieve sustained remission (at least 12 months without relapses) or infrequently relapsing NS (no more than two relapses per year), combined within minimal drug toxicity. If the disease is suitably controlled on therapy, other than cyclophosphamide which is a defined course of treatment, it should be continued for at least one and preferably two years before stopping to see if the child has outgrown frequent relapses.

If the disease is not controlled on the choice of second-line treatment after 6-12 months, an alternative second-line treatment should be considered.

4.3.1. Levamisole

Levamisole may be more efficacious over steroids alone. The dose is 2.5 mg/kg (maximum 150 mg) on alternate days. It is available as 50 mg tablets which may be crushed. Side-effects of levamisole are rare but include leucopenia, gastro-intestinal effects, derangement of liver function and vasculitis. A full blood count, LFTs and ANCA should be monitored every 4-6 months whilst the child is taking levamisole.
Levamisole should be discontinued if there is elevation of liver enzymes. If ANCA titres are seen, a careful evaluation for vasculitis symptoms should be made. If none are seen, levamisole may be continued but with careful on-going ANCA monitoring

and a low threshold to stop if titres increase or any vasculitis symptoms develop. Parents should also be counselled to seek medical attention and request a full blood count if their child has any unusual or severe infections.

Levamisole may be best suited to children who are very frequent relapsers but not steroid-dependent. It is a well-tolerated drug and should be considered as the first-choice second-line agent in this sub-group of children with nephrotic syndrome.

Its efficacy may not become apparent for several months and it is best suited with a slow steroid taper when it is commenced. Generally it is used initially in combination with low-dose steroids initially but may subsequently be used as monotherapy. It is usually continued for at least 1-2 years. There appears to be no sustained effect once levamisole is discontinued.

4.3.2. Cyclophosphamide

This has been shown to significantly reduce the risk of relapse in FRNS [8]. The dose is 3 mg/kg once daily for 8 weeks. Dose reductions are required in renal impairment and obesity and should be discussed with pharmacist. It is available in 50 mg tablets which may not be crushed since it is a cytotoxic drug. Doses close to 75 mg may be achieved by giving 50 mg and 100 mg on alternate days. Children who are unable to take tablets will need to have cyclophosphamide suspension made by the hospital pharmacy. The suspension has a 4-week expiry and liaison with the paediatric pharmacist prior to use is necessary to ensure a continuous supply. Further information for your local pharmacist is available on the EMEESY website.

Cyclophosphamide is usually tolerated well. It may be associated with leucopenia and a weekly full blood count is necessary during throughout the 8-week course. Before commencing cyclophosphamide, there must be arrangements made:

- Who does the weekly full blood count?
- Who will chase the result?
- Who will action any changes of cyclophosphamide dose?

Dose alterations should be made as follows:

Neutrophil count ($x10^9$/l)	**Action**
>2	Continue previous dose
1.5 – 2	Reduce dose by 50%
<1.5	Stop and restart only when neutrophil count >2

If the neutrophil count remains stable for the first 4 weeks of the course, the full blood count may be checked fortnightly for the remaining 4 weeks of the course.

Cyclophosphamide may lead to hair thinning. Usually this is no more than increased hair loss on brushing but occasionally it may be more noticeable than this, particularly in older children, and rarely may result in total alopecia. Hair growth normalises after cessation of cyclophosphamide.

Cyclophosphamide may also cause bladder irritation. Mesna is not necessary with oral cyclophosphamide but children should be advised to have a good fluid intake whilst taking it.

The long-term risk of infertility for a single course of cyclophosphamide (168 mg/kg) is minimal. There is a small increased risk of malignancy following cyclophosphamide. This has been estimated as 0.2% although the follow-up periods in the studies were relatively short [9].

It is important to counsel parents/carers of all these side-effects before commencing cyclophosphamide treatment and good practice to document this in the medical notes. An information sheet on the use of cyclophosphamide in nephrotic syndrome is available on the Medicines for Children website.

In peri- and post-pubertal children consideration may be given to starting tacrolimus ahead of cyclophosphamide due to a theoretical increased risk of gonadal toxicity at this age.

4.3.3. Intravenous cyclophosphamide

Intravenous cyclophosphamide is a suitable alternative to oral cyclophosphamide where there is concern about concordance with medication for the treatment of FRNS/SDNS and is effective at a dose of 500 mg/m^2 monthly for 6 months [10].

4.3.4. Tacrolimus

Calcineurin inhibitors are effective at reducing frequency of relapses in FRNS [8]. Tacrolimus is preferred to ciclosporin due to the lack of cosmetic side-effects (gingival hyperplasia and hirsutism). Tacrolimus will usually be continued for 2 years in the first instance. Frequent tacrolimus trough levels (EDTA sample) are required when initiating tacrolimus.

Tacrolimus is available in various forms: Adoport, Modigraf (soluble granules) and Advagraf (once daily). Children should not use different brands interchangeably. If there is a need to switch from one brand to another, an early level should be performed. Current pharmacy advice is to prescribe by brand name to avoid these confusions.

Tacrolimus capsules are available in the following doses: 0.5 mg, 1 mg and 5 mg. Modigraf is a granular form available in sachets on 0.2 mg and 1 mg doses. It is given by diluting in water first and is the preferred form of tacrolimus for children unable to swallow capsules. Children as young as 5 can be trained in tablet taking. Resources developed in Newcastle are signposted from the EMEESY website.

The starting dose of tacrolimus is 0.1 mg/kg twice daily with a maximum starting dose of 5 mg bd. Doses should be adjusted to achieve an initial 12-hour trough of 5 – 8 ng/ml. Once the child is established and well-controlled on tacrolimus, on-going trough level monitoring will be required at least 3-monthly. Renal function and full blood count should also be measured 3-monthly and liver function at least 6-monthly. Trough levels for children who are well-controlled on tacrolimus should be maintained at the lowest dose that maintains a stable remission, usually 3 – 6 ng/ml.

Dose related side-effects are common in the initial period. They include headache, tremor, abdominal pain and visual disturbance. These side effects usually indicate a reduction in dose is needed. Tacrolimus may have long-term effects on renal function. Regular monitoring of renal function is required. Tacrolimus may cause reduced insulin sensitivity. Urinalysis will be regularly checked in clinic. If there is any glycosuria, a fasting blood glucose should be measured.

If children remain relapse free after 2 years on tacrolimus, it can be stopped. Weaning the dose may be more effective than an abrupt stop. If there is an early relapse, it should be recommenced following induction of remission with high-dose prednisolone. For children on tacrolimus longer than 2 years, a renal biopsy should be considered to look for evidence of nephrotoxicity (excessive glomerulosclerosis with or without arteriolar hyalinosis). Where there is significant nephrotoxicity, consideration should be given to wean in conjunction with switching to non-nephrotoxic immunosuppression such as mycophenolate or rituximab.

4.3.5. Mycophenolate mofetil

This is an antiproliferative agent in the same class, but more effective than, azathioprine.
The dose is 600 mg/m^2 bd but since it is associated with gastrointestinal upset (abdominal pain and diarrhoea) it is better tolerated if started at half-dose and increased gradually over 2 – 3 weeks.

Mycophenolate comes as either 250 mg capsules or 500 mg tablets and is available in a wide range of generic preparations that are bio-equivalent. For younger children unable to swallow tablets, it is also available as Cellcept suspension (1 g in 5 ml).

It is preferable to continue alternate-day steroids for 3-6 months after starting mycophenolate as the immunosuppressive effect is delayed.

Other side-effects of mycophenolate include anaemia, leucopenia and weight loss. Teenage girls who are sexually active should be advised to use highly effective contraception and

should be counselled to stop the drug if they are pregnant. Children who are unable to tolerate mycophenolate mofetil due to gastrointestinal side-effects may tolerate mycophenolic sodium (Myfortic®). Myfortic capsules of 360 mg are equivalent to mycophenolate mofetil 500 mg.

Monitoring for mycophenolate should include an FBC and LFTs every 3 months. Mycophenolic acid (MPA) level monitoring is not necessary if the disease is well-controlled but if relapses continue, the dose should be optimised according to levels before discontinuing. The most clinical useful level is a limited pharmacokinetic profile requiring samples at 0 minutes (before administration, C_0), 60 min (C_1), and 120 min (C_2) after administration [11]. For MMF levels that are measured in mg/L, the 120-minute area under the curve (eMPA-AUC$_{0\text{-}120}$) should be >50 mg × h/L and can be calculated using the formula:

$$\text{eMPA-AUC}_{0-120} = 8.70 + (4.63 * C_0) + (1.90 * C_1) + (1.52 * C_2).$$

Mycophenolate may be combined with tacrolimus though there is limited evidence that this is more effective than using either as monotherapy. If it is used in combination with tacrolimus, the starting dose is 300 mg/m^2 twice daily.

4.4. Rituximab

The anti-CD20 monoclonal antibody, rituximab has been shown to be effective in the treatment of nephrotic syndrome [12]. Where it has been used in FRNS/SDNS, in most cases it consolidates a remission for at least 6 months.

NHS England has published a commissioning policy for the use of Rituximab in FRNS [13]:

- It may only be given when tacrolimus and mycophenolate have been shown to be ineffective.
- Tacrolimus must be given for a minimum of 6 months; mycophenolate must be given for a minimum of 3 months
- It should be given in a paediatric centre with experience in administering Rituximab after discussion with a paediatric nephrologist
- Viral serology (hepatitis B &C, EBV, CMV, parvovirus, adenovirus and varicella) must be checked before giving

4.4.1. Dosing and administration

NHSE recommend two intravenous infusions of 750 mg/m^2 given 2 weeks apart but in subsequent literature and in our own Nottingham experience [14] we have shown that a single dose of 375 mg/m^2 can produce B-cell depletion and a relapse-free period of at least 6 months.

For children with steroid sensitive nephrotic syndrome the first course should be a single dose of 375 mg/m^2. Subsequent courses may be increased up to a total dose of 1500 mg/m^2 divided into 2 to 4 doses at 1-2 weekly intervals if there is a poor response to the initial course (maximum dose 1 g per dose).

Prior to rituximab infusion, in addition to the above viral serology, baseline CD19 and immunoglobulins should be measured. Rituximab is given at gradually increasing rates and takes several hours to give. As there is a risk of serum sickness reactions, it is given with paracetamol, steroid and anti-histamine cover. A monograph for rituximab infusion is available on the EMEESY pharmacy information page.

4.4.2. Subsequent monitoring

After rituximab is given, CD19 count should be checked at 1-2 weeks to confirm B-cell depletion. Thereafter CD19 count and immunoglobulin levels should be sent regularly (3-monthly suggested) to document the duration of B-cell repopulation.

4.4.3. Discontinuation of other immunosuppression

The evidence of the benefits or harm of combining rituximab with other immunosuppressants is not clear. Many clinicians will aim to stop other immunosuppression once B-cell depletion is confirmed and then wean steroids within months.

For children who continue to replase whilst B-cell deplete or promptly after repopulation, there is some evidence that continuing Mycophenolate or Tacrolimus may prolong the period of remission [15].

4.4.4. Repeat dosing

Most children will relapse following B-cell population, for some this can be immediate but others will not relapse until many months after B-cell repopulation. The practice of repeat doses remains a matter of debate – some re-dose after fixed-time intervals, some on B-cell repopulation and others only following subsequent relapse.

4.4.5 Long-term side-effects

Long-term effects of rituximab are not known. There have been case reports of progressive multifocal leucoencephalopathy and progressive lung fibrosis although it is not clear whether these are a result of rituximab per se or simply heavy immunosuppression.

Repeated doses of rituximab have been shown to result in persistent hypogammaglobulinaemia. On the current evidence, it appears safe to give up to four courses of rituximab before waiting to see if the child has entered a long-term remission. Immunoglobulins should be checked after each Rituximab infusion and repeated regularly (at least 6-monthly) if low. Children with persistent hypogammaglobulinaemia should be discussed with immunology before further doses are given.

5. Steroid resistant nephrotic syndrome

Children who complete 4 weeks of prednisolone 60 mg/m^2 daily without entering remission should be referred to the paediatric renal team. They will be admitted to their local hospital or Nottingham Children's Hospital for three daily pulses of methylprednisolone (600 mg/m^2). If there is some reduction in early morning proteinuria, up to two further doses may be given. If there is no response after three doses or if remission is not entered fully after 5 doses then a renal biopsy is indicated.

The NHS Genomic Medicine Service proteinuria panel test (R195) should be done. Permission to register children on RaDaR should be requested from parents if not already done.

Unless there is a strong clinical suspicion of a genetic form of nephrotic syndrome (e.g. other syndromic features, family history of SRNS or age <2 years), children should be commenced on tacrolimus (dosing as above) and their prednisolone dose reduced to 40 mg/m^2 on alternate days.
Rituximab, as two doses of 750 mg/m^2 2 weeks apart may be given if no genetic mutations are identified and there is no response to tacrolimus after 3 months [16].

Other drugs to consider for persistent nephrotic states include: ACE inhibitors and ARBs; statins; and anti-coagulation or anti-platelet agents.

6. Audit points

It is suggested that a local database be established of all new cases, contemporaneously recording drugs and relapses.

Specific points to audit from this data might include:

1. Is information and management plan documented in the notes before initial discharge?
2. Has penicillin V and immunization been given/documented?
3. Do we adhere to indications for biopsy?
4. Completion of relapse sheet in casenotes?
5. Is treatment of relapses in line with the guidelines?
6. Are children commenced on second-line treatments at appropriate times?

7. References

1. Trautmann, A. et al. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-sensitive nephrotic syndrome. Pediatric Nephrology (2022). doi:10.1007/s00467-022-05739-3.
2. Veltkamp, F. et al. Incidence and relapse of idiopathic nephrotic syndrome: Meta-analysis. Pediatrics **148**, (2021).
3. Webb, N. J. A. et al. Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation. BMJ **365**, l1800 (2019).
4. Borovitz, Y; Haskin, O; Levi S; Kas, S; Alfandary, H; Davidovits, M; Dagan, A. Lower prednisolone dosing for nephrotic syndrome relapse: a prospective, randomised study. Pediatr. Nephrol. **32**, 1647 (2017).
5. Sheikh, S. & Mishra, K. Low-dose versus conventional-dose prednisolone for nephrotic syndrome relapses : a randomized controlled non-inferiority trial. Pediatr. Nephrol. **36**, 3143–50 (2021).
6. Yadav, M., Sinha, A., Khandelwal, P., Hari, P. & Bagga, A. Efficacy of low-dose daily versus alternate-day prednisolone in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial. Pediatr. Nephrol. **34**, 829–835 (2019).
7. Christian, M. T. et al. Evaluation of Daily Low-Dose Prednisolone during Upper Respiratory Tract Infection to Prevent Relapse in Children with Relapsing Steroid-Sensitive Nephrotic Syndrome: The PREDNOS 2 Randomized Clinical Trial. JAMA Pediatr. **176**, 236–243 (2022).
8. Larkins, N. G., Liu, I. D., Willis, N. S., Craig, J. C. & Hodson, E. M. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. Cochrane Database Syst. Rev. **2020**, (2020).
9. Latta, K., von Schnakenburg, C. & Ehrich, J. H. H. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. Pediatr. Nephrol. **16**, 271–282 (2001).
10. Prasad, N., Gulati, S., Sharma, R. K., Singh, U. & Ahmed, M. Pulse cyclophosphamide therapy in steroid-dependent nephrotic syndrome. Pediatr. Nephrol. **19**, 494–498 (2004).
11. Benz, M. R. et al. Generation and Validation of a Limited Sampling Strategy to Monitor Mycophenolic Acid Exposure in Children With Nephrotic Syndrome. Ther. Drug Monit. **41**, 696–702 (2019).
12. Chan, E. et al. Use of Rituximab in Childhood Idiopathic Nephrotic Syndrome. Clin. J. Am. Soc. Nephrol. (2022) doi:10.2215/CJN.08570722.
13. NHS England. Clinical Commissioning Policy: Rituximab for the treatment of relapsing steroid sensitive nephrotic syndrome. (2015).
14. Maxted, A. P. et al. Low-dose rituximab is no less effective for nephrotic syndrome measured by 12-month outcome. Pediatr. Nephrol. **34**, 855–863

(2019).
15. Iijima, K. et al. Mycophenolate Mofetil after Rituximab for Childhood-Onset Complicated Frequently-Relapsing or Steroid-Dependent Nephrotic Syndrome. J. Am. Soc. Nephrol. **33**, 401–419 (2022).
16. NHS England. Clinical Commissioning Policy: Rituximab for the treatment of Steroid Resistant Nephrotic Syndrome in paediatric patients. (2015).

UHL Education and Training

None

Key Words

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
SOP Lead (Name and Title) A Hall – Associate Specialist	**Executive Lead** **Chief Medical Officer**
Details of Changes made during review:	