Great Ormond Street Hospital for Children
NHS Foundation Trust

Clinical Guideline

Disclaimer

Clinical guidelines are best practice recommendations that are intended to assist clinical teams in the delivery of patient care at GOSH. Clinical guidelines attempt to reflect the best available research at the time of writing, but the interpretation and application of clinical guidelines remains the responsibility of the individual clinician. Caution is advised if using a GOSH clinical guideline outside of the organisation and/or beyond its review date. Printed versions of this guideline may be out of date; use of the current online version is best practice.

Care of the child with childhood onset nephrotic syndrome

Document Details	
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Guideline summary (up to 100 words):	Provides guidelines on the management childhood nephrotic syndrome, including recognition of atypical nephrotic syndrome, management of first presentation and subsequent relapses. Also includes information about non-medical management,
Key words:	'Best bet' word: **Nephrotic syndrome** 'Best bet' acronym (if applicable): NS *Please state all other relevant key words below. **All other key words:** **Childhood nephrotic syndrome** **Idiopathic nephrotic syndrome** **Steroid resistant nephrotic syndrome** **Oedema management** **Prednisolone relapse plan**
Exclusions:	Congenital nephrotic syndrome

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1 Introduction

This protocol aims to formalise a consistent treatment approach to children with nephrotic syndrome. We fully recognise that some of the recommendations in this protocol are not fully supported by evidence, simply because there is no evidence to either support or refute them. We thus fully expect that some of the recommendations will change over time. This protocol reflects the current treatment approach by the nephrotic team at GOSH and by formalising it, we aim to facilitate coordinated management of patients across primary, secondary, and tertiary care.

Please note this is a guide for management and if there are any clinical concerns then a review with or discussion with on-call nephrology team at GOSH may be required.

2 Scope

This guideline is intended to be used for the management of children presenting with suspected or proven primary, childhood onset, nephrotic syndrome

Children presenting with nephrotic syndrome but who have atypical features as listed below should be discussed with tertiary nephrology services before starting treatment. These include:

- Age of less than 1 year, more than 12 years
- Macroscopic haematuria
- Kidney impairment with a persistent rise in serum creatinine not associated with acute dehydration
- Hypertension (Above 95th percentile for age and height on more than 2 occasions)
- Insidious disease onset suggested by: long clinical history, incidental finding on tests done for other reasons, borderline low serum albumin, non-nephrotic range proteinuria
- Extrarenal features e.g. syndromic features, rash, arthritis

3 Clinical Definitions

A triad of symptoms are required for a diagnosis of nephrotic syndrome to be made:
Heavy proteinuria: urine protein to creatinine ratio above 200mg/mmol on first morning urine or 3+ (or more) on urinalysis
Oedema which is gravity dependent
Hypoalbuminemia (plasma albumin less than 30g/l)
(IPNA 2022)

Remission is defined as negative or trace proteinuria on urinalysis for 3 consecutive days
Partial remission is defined in several ways: an increase in serum albumin above 30 g/l; a decrease in urine protein/creatinine ratio by over 50% (mg/mmol) or between 20-200mg/mmol or sustained 1+ to 2+ proteinuria on urinalysis.

Relapse (for patients with known childhood nephrotic syndrome) is defined as 3 consecutive days of 3+ protein on urinalysis or 5 days of 2+ protein.

Childhood nephrotic syndrome can be classified in several ways:

Response to steroid therapy:
Steroid sensitive (SSNS)- patient enters remission after commencement of steroid treatment, usually within two weeks but can take up to 28 days.
Steroid dependent (SDNS)- patient enters remission but on at least two consecutive occasions relapses when prednisolone is weaned, or within 14 days of prednisolone treatment being stopped.
Steroid resistant (SRNS)- patient does not enter complete remission after 28 days of steroid use and after receiving 3 pulses of IV methylprednisolone. This can be primary: no response to prednisolone from the first presentation, or secondary: during treatment of a relapse.

Relapse frequency:
Infrequently relapsing- relapses occurring less than twice in a 6 month period or less than 3 times in 12 months
Frequently relapsing- relapses occurring more than twice in a 6 month period or more than three times in a year

By Age:
Congenital nephrotic syndrome- presentation within the first 3 months of life.
Infantile nephrotic syndrome- presenting after the age of 3 months but before age of 1 year.
Childhood nephrotic syndrome- presenting after the age of one, before the age of 12 (upper age limit is ill defined, see atypical features above)

Histopathology:
Kidney biopsy does not determine response to treatment in childhood nephrotic syndrome and is not routinely carried out except in certain circumstances for example atypical presentation or non-response to medication, and we would not recommend using them to describe or characterise childhood nephrotic syndrome: please see section on steroid resistance for more details.

Common histopathological findings include:
Minimal change disease (MCD) – Minimal histological changes on biopsy
Focal segmental glomerular sclerosis (FSGS)- presence of lesions affecting a portion of glomeruli on biopsy.
Other possible pathological pictures include C3 glomerulonephritis, lupus nephritis.

4 Assessment

Clinical evaluation and physical examination including:

- Presence of oedema and fluid status (see section on oedema)
- Consideration of secondary causes of nephrotic syndrome
- Extrarenal features e.g. dysmorphic features, rash, arthritis
- Anthropometry readings charted on relevant centile chart
- Vaccination status
- Family history

Routine investigations should include:

- Renal and liver function including serum albumin
- Full blood count
- Laboratory urine protein to creatinine, or urine albumin to creatinine ratio (first/early morning sample)
- Chicken pox antibody status
- Measles IgG if no history of MMR vaccination

Additional tests may be required and include:

- C3, C4
- ESR/CRP
- ANA, dsDNA
- Streptococcal antibodies
- Hepatitis C and B serology

Kidney ultrasound should be considered if reduced kidney function, macroscopic haematuria or ongoing abdominal pain.

These investigations are used to rule out an acute process like glomerulonephritis, lupus nephritis or other rarer causes of nephrotic syndrome.

5 Management

Initial prednisolone treatment

Duration	Oral prednisolone dose ($mg/m^2/day$)	Maximum daily prednisolone dose (mg)
4 weeks	**$60mg/m^2/day$**	**60**
If in remission at 4 weeks follow weaning schedule below		
4 weeks	**$40mg/ m^2/alt\ day$**	**40**
Then stop		

Prednisolone should ideally be given in the morning, and always with or soon after food. Round the dose to the nearest 5mg to enable ease of dosing for parents.

If oral prednisolone is not tolerated, (vomiting or diarrhoea, severe oedema) IV methylprednisolone can be given. IV methylprednisolone dose conversion is 4/5 of the oral prednisolone dose.

Consider switching formulation if there is difficulty with compliance, especially in young children. Prednisolone typically is available as 5mg tablets, 5mg soluble tablets and as liquid (10mg/1ml formulation).

Parental education:
Parents should be warned of the likely and possible side effects associated with prednisolone including vigilance for infection, stomach ache, increased appetite, insomnia and behavioural changes.
Parents should be shown how and when to check the urine for protein at home; and advised to keep a record. We would recommend that the urine is checked daily throughout the initial prednisolone course.
Parents should be advised to keep their child on a low salt diet whilst there is protein in the urine to help minimise oedema.
Parents should be given advice on when to seek medical attention with low tolerance for infection and possible clot formation.
If chicken pox naïve, advice should be given around contact (see section on chicken pox).

Parents can be signposted infokid.org.uk for written information about nephrotic syndrome.

Other medications

Lansoprazole or a similar proton-pump inhibitor can be used as gastro protection against ulcer formation when on high dose prednisolone. Prednisolone should always be given with food.

Follow up and monitoring of relapse

All children with active nephrotic syndrome should have regular follow up. Individual centres will have their own pathways based on their resources as to how this is managed and may include paediatrician follow up in outpatients or at home assessment with community children nurses or combination of both.

This is to monitor for their child's response to prednisolone, to support parents with monitoring of the condition and medication adherence, and to observe for complications of treatment.

If the patient does not respond to prednisolone within the first 4 weeks of treatment, please refer to steroid resistant section.

If in remission after completion of prednisolone treatment, at home daily monitoring of the urine for protein should be continued on a regular basis for at least the first 3-6 months.

6 Relapse

Most children with idiopathic NS (80% or more) will have at least one relapse. About 50% will go on to develop frequently relapsing or steroid dependent nephrotic syndrome.

A relapse is defined as 3 consecutive days of 3+ proteinuria, or 5 days of 2+ proteinuria on early morning urinalysis.
If there is 3+ proteinuria for fewer days but oedema is clinically present, then treatment should not be delayed to fulfil the above criteria.

Blood and urine tests may be useful to determine the severity of relapse but should be as clinically indicated.
If a patient is known to GOSH, please check their patient letter as they may have an individualised relapse plan.

First relapse

We would recommend that the first relapse after presentation follows a standard treatment plan with prednisolone as in the table below.

If first relapse occurs whilst on initial steroid weaning treatment still, or within 2 weeks of finishing wean, we would recommend discussion and referral to tertiary nephrology in anticipation of likely steroid dependent course of nephrotic syndrome.

Duration	Oral prednisolone dose ($mg/m^2/day$)	Maximum daily prednisolone dose (mg)
	$60mg/m^2/day$	**60**
Until 3 consecutive days negative or trace protein on early morning urinalysis then:		

4 weeks	**40mg/ m^2/alt day**	**40**
Then stop		

Hospital admission may be a requirement for management of clinically moderate to severe oedema, or if child is unwell, but most relapses, can be managed in an outpatient setting. Different hospital trusts will manage follow up in different ways including outpatient clinic settings or through community nursing monitoring.

Follow up is required to ensure remission is achieved with prednisolone treatment within a 28 day period, and to monitor for complications of nephrotic syndrome or from treatment with prednisolone.

Further relapses can be individualised to patient's likely response and treatment course.

Below is the recommended relapse treatment which can be applied for all patients presenting with a relapse. A relapse should always be assumed and treatment started if there is already the presence of clinical oedema with proteinuria.

Duration	Oral prednisolone dose ($mg/m^2/day$)	Maximum daily prednisolone dose (mg)
Until remission	$60mg/m^2/day$	60
On 3rd day of remission wean to		
1 week	$40mg/ m^2/alt\ day$	40
1 week	$30mg/ m^2/alt\ day$	30
1 week	$20mg/ m^2/alt\ day$	20
1 week	$10mg/ m^2/alt\ day$	10
If on maintenance prednisolone continue on normal dose of prednisolone otherwise stop		

IV methylprednisolone should be considered if clinically there is severe ascites, or if there is any disruption to oral absorption for example vomiting or diarrhoea. The dose of IV methylprednisolone is 4/5 of the oral dose given once per day.

Lower dose regime

If the child has clinically relapsed (e.g. 3 days of 3+ protein) and symptoms of relapse are mild, including little to no oedema, and child is otherwise well, and there have been no concerns with previous response to prednisolone during treatment for a relapse, you may want to consider using a smaller dose of prednisolone to induce remission.

We would recommend:

Duration	Oral prednisolone dose ($mg/m^2/day$)	Maximum daily prednisolone dose (mg)
Until remission	$30mg/m^2/day$	30
On 3rd day of remission wean to		
1 week	$30mg/ m^2/alt\ day$	30
1 week	$20mg/ m^2/alt\ day$	20

1 week	**10mg/ m^2/alt day**	**10**
1 week	**5mg/ m^2/alt day**	**5**
If on maintenance prednisolone continue normal dose of prednisolone otherwise stop		

If no signs of response within 7 days, or if symptoms of relapse are worsening, especially if worsening oedema then the higher dose regime of prednisolone should be started.

Viral prednisolone cover

Viral illnesses, especially upper respiratory tract infections, have been identified as triggers for relapses in some children with SSNS. Some children who experience relapses following viral illnesses may benefit from starting prednisolone at a low dose 15mg/m2/day, max dose 15mg for 6 days during active infection; or increasing their maintenance alternate day prednisolone dose to daily dose for 6 days.

However, research has shown no significant difference in rate of relapse when this is applied to the whole patient group, and should only be applied for select group where there is clear history of a correlation of illness to relapse, and discontinued if there is no clear benefit for the individual child.

7 Referral to GOSH nephrology:

Referral should be considered if:

- Resistance to steroids
- Relapses occur more than twice in 6 months
- Relapses occur whilst child is on a weaning dose of prednisolone
- There are intolerable side effects from steroid therapy
- There is concern over linear growth
- There is poor adherence to steroid therapy

Prednisolone weaning whilst waiting for a GOSH appointment:

Follow the relapse plans above but consider keeping on long term lower dose prednisolone:

For frequent relapsers, once in remission, consider keeping on the final dose in the last stage of the prednisolone weaning plan (aiming for less than 0.5mg/kg/every other day) until the clinic appointment

For steroid dependent relapsers, once in remission wean to the last successful dose of prednisolone. If this is equal to or more than 0.5mg/kg/every other day, please mark the referral as urgent

8 Strategies in frequently relapsing and/or steroid dependent nephrotic syndrome

These strategies should be carried out under the guidance of a paediatric nephrologist

Steroid sparing agents are medicines used to reduce the number of relapses a child is experiencing, and to reduce the long-term steroid exposure and associated side-effects.

They should be considered:

- In all children with frequently relapsing or steroid dependent nephrotic syndrome
- Where there are concerns over steroid side effects, especially linear growth, behaviour or adherence

Possible interventions include:

Prednisolone

- Low dose, every other day prednisolone has been used successfully to maintain remission with limited steroid side effects and should be considered as first line treatment in patients relapsing off prednisolone.
- Dose should be ideally less equivalent of 0.5mg/kg/every other day or 10mg every other day, whichever is lower.
- Regular monitoring required for steroid side effects especially linear growth, regular ophthalmology
- Live vaccines can be given when on low dose prednisolone if clinically indicated, and after 3 months of weaning off high doses of more than 1mg/kg daily.

Levamisole

- For frequently relapsing nephrotic syndrome, especially where relapses are mild, and there is a quick response to prednisolone.
- Immuno-modulating effect.
- Dose is 2.5-3 mg/kg every other day max 150mg daily.
- Available as 50mg tablets, tablet can be crushed and dissolved in sterile water.
- Therapy is usually continued for at least 1 year if successful (no further relapses). Concurrent therapy with a small dose of alternate day prednisolone may be considered.
- Requires FBC and U&E monitoring after 1 month and then every 4-6 months to check for neutropenia and renal impairment.
- Possible side effects include vasculitic type rash- medicine should be stopped and advice sought.
- Significant supply problems have occurred in more recent times which may limit use
- Live vaccines can be given when on levamisole

Cyclophosphamide

- Usually limited to children with steroid dependent nephrotic syndrome.
- Alkylating agent, immunosuppressive
- Dose: oral 3mg/kg daily dose for 8 weeks (equivalent cumulative dose over 10 or 12 weeks can also be used for ease of dosing)
- Available as tablets of 50mg formulation, suspension is 50mg/5ml. Tablets must be swallowed whole, they cannot be cut or crushed. Suspension has short shelf life.
- Requires FBC monitoring every 2 weeks for neutropenia. Dose should be halved if neutrophil count between 0.5 and 1 x 10^9 and held if neutrophils below 0.5 x 10^9, until recovery is seen. If cyclophosphamide is paused and restarted, the length of the

course should not exceed the original planned course. (e.g still stops at 8 weeks if planned for 8 weeks)
- Dose should be given in the morning with plenty of water
- Side effects include hair loss, haemorrhagic cystitis, nausea and vomiting
- Live vaccines should be avoided during treatment and for at least 3 months following completion of course

Tacrolimus (cyclosporine can be considered if diabetes or strong family history of diabetes)
- Calcineurin inhibitor; Immunosuppressive
- Used in steroid dependence or as first line treatment in steroid resistance
- Starting dose: 0.05mg/kg to 0.1mg/kg twice daily
- Dose should be titrated to achieve a trough 12 hour level of between 4 and 7 microg/L and the therapeutic levels should be measured at least 3 doses after any change in the prescription
- Available in different preparations, specific brand name should be used for prescribing as formulations are not bioequivalent.
- Adoport: 0.5mg, 0.75mg, 1mg and 2mg capsules
- Modigraf: 0.2mg, 1mg sachets of granules to be mixed with water
- Liquid suspension 1mg/1ml
- Requires monitoring: trough tacrolimus level, renal function, liver function, serum glucose, FBC at least 4 monthly once on stable dosing
- Possible side effects include tremor, immunosuppression, renal dysfunction, hypertension, glucose intolerance/diabetes
- Depending on clinical circumstances usually weaned after 1 year of remission, often to low dose or once a day dose
- Live vaccines should be avoided whilst on treatment and for 3 months following stopping of medication

Mycophenolate Mofetil (MMF)
- Immunosuppressive
- Can be used as monotherapy in frequently relapsing or SDNS, or in addition to tacrolimus in difficult to manage steroid dependence or steroid resistance.
- Dose: 600mg/m^2 in 2 divided doses. Usually started at a smaller dose and increased over a number of days to avoid possible gastric side effects
- Preparations include 250mg capsule, 500mg tablet, or 1000mg in 5ml liquid preparation
- Requires monitoring of renal function, LFTs and FBC
- Side effects include GI symptoms including nausea and vomiting, abdominal pain, diarrhoea, loss of appetite, immunosuppression, neutropenia or **leukopenia** which if ongoing may require cessation of drug
- Avoid pregnancy- age-appropriate advice should be given
- Live vaccines should be avoided whilst on treatment and for 3 months following stopping of medication

Rituximab

- CD20 Monoclonal antibody
- Use is in line with guidelines by NHS England – https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/rituximab-for-ssns-policy.pdf
- Usually given if other therapies have failed to establish control, or in the presence of intolerable side effects, or in cases of poor adherence to oral medication
- Negative hepatitis B screen (core antibody and surface antigen) required prior to treatment
- Ideally given when in remission
- Given as inpatient on nephrology ward under close monitoring
- Dose is 750mg/m^2 (max dose 1000mg) typically given as a single infusion
- This can be repeated if clinically indicated and/or there is incomplete B-cell depletion.
- Side effects include potential for severe allergic reaction/ anaphylaxis at time of infusion, and increased risk of infections, especially serious viral infections, ongoing B-cell depletion and hypogammaglobinaemia.
- Monitoring includes: CD 19 count, U&E, FBC, immunoglobulins [at 12 months following RTX]
- Vaccines should not be given for 6 months following infusion, or until b-cell count is normal.
- If **limited CD19 count suppression is viewed following rituximab, or rapid repopulation of CD19 count,** or **if rituximab causes an allergic reaction then Obinutuzumab, a humanised anti CD19** can be considered**. Initial dose is 300mg/m2, max dose 300mg.**

Combination therapy

In severe cases of steroid dependence or steroid resistance, a combination of medicines, usually tacrolimus and mycophenolate with or without rituximab are used to induce or sustain remission.

Quick reference table

Drug	Indication	Dose	Monitoring	Side effects
Low dose prednisolone	Frequently relapsing	Aim for <0.5mg/kg on alternate days max 10mg every other day	Growth Ophthalmology	Poor growth Unlikely: behavioural concerns, insomnia
Levamisole	Frequently relapsing, Mild relapses	PO 2.5- 3 mg/kg on alternate days	FBC and U&E after 1 month then every 4-6 months	Rash Neutropenia Renal impairment
Cyclophosphamide	Steroid dependent or severe steroid side effects	PO 3mg/kg for 8 weeks or 2mg/kg for 12 weeks IV- used only in exceptional circumstances	FBC every 2 weeks during course for neutrophil count	Neutropenia Hair loss Haemorrhagic cystitis
Tacrolimus (Adoport, modigraf)	Steroid dependent steroid resistant	PO 0.05 to 0.1mg/kg, aiming for trough level between 4 and 8 microg/L	Tacrolimus level U&E, FBC, glucose	Tremor Diabetes Nephrotoxicity
Mycophenolate mofetil (MMF) (cellcept/Myfortic)	Mono therapy in Frequently relapsing, steroid dependent As an adjunct to tacrolimus	PO Starting dose 600mg/m^2 in 2 divided doses (see above)	U&E, FBC, LFT	Gastric side effects including abdominal pain, loose stools, loss of appetite Neutropenia/leukopenia
Rituximab (*only given under supervision of renal consultant, on renal unit)	Steroid dependent, steroid resistant after tacrolimus and MMF	IV 750mg/m^2 (max 1000mg) 1 infusion	Hepatitis B screening pre-infusion CD19 count, FBC	Anaphylaxis- close monitoring throughout infusion Immunosuppression, risk of viral infection
Obinutuzumab (*only under supervision of renal consultant on renal unit)	Steroid dependent, steroid resistant, if poor response or allergy to rituximab	IV 300mg/m2 (max 300mg) 1 infusion Dose can be adjusted to response	Hepatitis B screening pre-infusion CD19 count, FBC	Anaphylaxis- close monitoring throughout infusion Immunosuppression, risk of viral infection

9 Steroid Resistant NS

Patients who fail to enter remission after 4 weeks of daily, high dose steroid therapy either on presentation (primary steroid resistance) or during a relapse (secondary steroid resistance) should be discussed with GOSH nephrology as soon as possible.

Consideration should be given to concordance to steroid therapy, any possible hindrance to steroid absorption (e.g. severe oedema, diarrhoea). If concerns, consider using NG tube placement or IV methylprednisolone at 4/5 of the oral prednisolone dose for 1 week and assess for response.

In proven steroid resistance (and in the absence of any atypical features as previously detailed)

Refer to GOSH nephrology for urgent outpatient appointment: "Renal Secretaries"
✉ renalsecretaries@gosh.nhs.uk

Admit and administer 3 pulses of IV methylprednisolone, dose **6**00mg/m^2 (max dose **10**00mg) over 3 consecutive days. Monitor BP and blood glucose levels
Continue oral prednisolone 60mg/m^2/day [maximum 60mg] until GOSH OPA- the aim will be to see within a week.
If current inpatient, then discuss with renal outlier registrar (Ext 1642) regarding admission to Renal Unit at GOSH for further assessment

Management at GOSH

Tacrolimus (see above for details and dosing)

- Begin prednisolone wean once tacrolimus commenced -individual plan for patient
- Monitoring of renal function, liver function, FBC and urine albumin to creatinine ratio to assess response initially monthly then reducing as indicated
- Aim for trough level between 5-8microg/l as tolerated
- Once in remission continue same dose of tacrolimus
- Depending on clinical circumstances usually weaned after 1-2 years of attaining complete remission, often to low dose or once daily regimen
- If oedematous and on diuretics, care should be taken regarding hydration status. Consider holding tacrolimus if acute diarrhoea or vomiting develops or any signs of tacrolimus toxicity.
- If no response (complete remission) after 3 to 6 months then consider combination with MMF/Rituximab

Mycophenolate Mofetil (MMF) (see above for details and dosing)

- If no response after 3 months combination therapy consider using rituximab

Rituximab

- Use is in line with guidelines by NHS England
- Negative hepatitis B screen (core antibody and surface antigen) required prior to treatment
- Given as inpatient on nephrology ward under close monitoring
- Dose is 750mg/m^2 (max dose 1000mg) repeated if clinically indicated and B-cells not depleted.

ACE/ARB inhibitor

- Lisinopril should be considered for all children with steroid resistant nephrotic syndrome with ongoing significant proteinuria
- Use with caution in presence of significant oedema and if on regular diuretics.
- Starting dose is: 0.1mg/kg once daily at night. Dose can be increased aiming for 0.5mg-1mg/kg/day as tolerated, maximum dose 40mg.
- Care should be taken to monitor BP on starting dose
- Parents should be advised to not give lisinopril if patient has acute diarrhoea or vomiting
- Renal function and electrolytes should be checked 1 week after starting, or 1 week after an increase of dose
- If Lisinopril not tolerated due to side-effects including cough, may consider conversion to an ARB- Losartan (dosing as per BNFC).

Genetics

All patients with steroid resistant NS should have a genetic screen sent to NHS laboratories for testing of genes associated with SRNS.

At GOSH, order on EPIC for "Proteinuric renal disease- by WES or large panel". A 5ml EDTA blood sample is required. Record of Discussion (ROD) and Test Order Form (TOF) needs to be completed and parents need to be consented and forms uploaded to Epic. Access to genetic testing is available to all children and young people whose families consent to do so.
If a genetic cause is found it is usually prognostic, and further therapy including ongoing management with immunosuppression should be considered/or tapered based on an individual basis by the nephrotic team at GOSH.

Consideration for renal biopsy

- Atypical features on presentation
- No response to tacrolimus therapy within 3 months

10 Oedema

Oedema is often the most complicated part of a relapse to manage, however most children with a relapse will not require any treatment or management beyond simple dietary measures.

Salt reduction is one of the most important ways of preventing oedema.

This should be advised for every patient presenting with a relapse, and should include the advice to not add salt to any food, and to avoid all highly salty foods including cheese, processed meats, takeaways, shop brought sauces, crisps etc. Usual advise would be to reduce salt to 2-3 grams per day.

A Salt awareness leaflet is available at
http://www.actiononsalt.org.uk/resources/ordering/125232.pdf
A dietitian may also be of help.

Causes of oedema in nephrotic syndrome can vary and are not fully understood; and generally can be explained by two theories:

- **Underfill:** Low serum albumin causing low oncotic pull in intravascular space, leading to fluid shift to extravascular compartment. Presents clinically as hypovolaemia with oedema; increased risk of thrombosis and AKI
- **Overfill:** Primary activation of epithelial Na channels in renal tubules leads to salt and fluid retention and overload. Presents clinically as hypervolaemia; increased risk of pulmonary oedema

For assessment of fluid status consider clinical symptoms such as abdominal pain, clinical observations, weight, peripheral and central capillary refill times, peripheral oedema, , urine output, and blood results.
It is important to remember that ongoing clinical examination is imperative as children can develop severe oedema without
All children who are inpatients with a relapse should have documented fluid balance and twice daily weights. Oral fluid intake is preferred however, if necessary because of vomiting, IV fluids should ideally be 4.5% HAS rather than crystalloids containing sodium chloride (although HAS also contains Nacl!)

Caution: Urine Sodium is not a reliable indicator of fluid state in nephrotic syndrome and should not be used to determine fluid status.

If hypovolaemia: consider use of 4.5% human albumin solution 5ml/kg bolus for intravascular expansion.

Symptomatic fluid overload: consider using a diuretics such as furosemide either orally or IV at a dose of 0.5mg/kg/dose. Care must be taken to meticulously asses**s** fluid status prior to commencing diuretics as this may lead to further intravascular depletion if not assessed properly which may in turn increase risk of thrombosis or AKI.

Oedema only needs to be managed if it is causing a clinical concern- most children with steroid sensitive nephrotic syndrome will not need any treatment for mild oedema during a relapse.

Fluid restrictions should be used with caution owing to the rapid fluid shifts that can occur and risk of acute kidney injury. Salt restriction is more important.

Caution: most remissions are preceded by diuresis, often before proteinuria has stopped and before serum albumin has recovered. If patient is at home on a fluid restriction or diuretics, families should be warned to be on the lookout for an increase in urine production, and to not give diuretics and to lift any fluid restriction if this happens.

20% Human albumin solution

Should not be given routinely and should never be used for fluid resuscitation.

Use is reserved for severe oedema, especially scrotal oedema and anasarca, unresponsive to diuretics. It should be used only under the direction of nephrology consultant at GOSH, and preferably only on a Kidney Unit or where high dependency or intensive care facilities are available. Main risk is development of pulmonary oedema.

If given in a local hospital, should only be given during daytime hours, and under close observation. Should not be given if an acute kidney injury is suspected or when there is severely reduced or no urine output. Adequate medical cover on the ward is required, and a diuretic should be pre-prescribed due to risk of pulmonary oedema.Other

Immunisations

All children should follow the childhood immunisation schedule as closely as possible. Live vaccines (MMR, BCG, nasal flu vaccine) should not be given if the child is on immunosuppressive therapy, including high dose prednisolone, within at least 6 months of rituximab infusion, or within 3 months of cyclophosphamide treatment.

All children over 2 years of age who have received the conjugate pneumococcal vaccine (PCV) need a single dose (0.5ml) of 23 valent vaccine (PPV) to provide protection against the serotypes of S. Pneumoniae not covered in the conjugate vaccine. An interval of at least 2 months is needed between the two vaccines.

For children who are naïve to chicken pox please consider varicella vaccine if a window of opportunity presents 3 months after finishing high dose prednisolone. Siblings with no history of chicken pox can also be considered to receive varicella vaccine.

Following rituximab treatment, vaccinations should be given only once B-cells have recovered (usually 6 months after infusion).

Families should be advised of the potential for relapse and inadequate immunogenic response to vaccination.

Infections
Children with nephrotic syndrome are at an increased risk of infections: during a relapse, due to loss of immunoglobulin G, and if they are on immunosuppressive medications. This includes increased risk of spontaneous bacterial peritonitis.

Prophylactic antibiotics are not recommended during a relapse, regardless of fluid status but there should be a low threshold for treatment if infection is suspected.

All parents should be advised to seek medical attention if their child has a fever or they are not well during a relapse, or if they are on high dose prednisolone or other immunosuppressive treatment.

Chicken pox
Varicella immunity status should be checked on presentation. If not immune, all parents should be given advice about what to do in case of exposure when on high dose prednisolone, or on immunosuppressive medication, or within 3 months of stopping medication.

“Guidelines on post exposure prophylaxis for varicella and shingles” should be followed for suspected contacts (available via the gov.uk website).

Children presenting with suspected chicken pox, who are in relapse or on immunosuppressive will require treatment with appropriate anti-viral medication. Local guidelines should be followed.

Thrombosis

Thrombosis is a known risk in children with NS. Routine prophylaxis is not recommended and instead a low threshold for suspecting thrombosis is advised.
Typical red flag for consideration of thrombosis include: persistent headaches, chest pain, abdominal pain, unilateral leg pain, hard swelling independent of generalised oedema, new

onset macroscopic haematuria. Low threshold for imaging is required to rule out and treat an acute thrombus in time.

Hyperlipidaemia

Hyperlipidaemia is a well-known finding in nephrotic syndrome, however there is no adequate evidence of the effect of this long term, or for the use of statins as part of management.

Ophthalmology

Children on long-term steroids should have an annual eye check up with a referral to the paediatric ophthalmologists for any concerns.

Bone health and vitamin D

Calcium supplementation should only be considered if there is insufficient dietary calcium intake.
Vitamin D levels should be monitored annually aiming for levels above 50ng/ml. Correction should be as per BNFC or local guidelines.

Routine vitamin D levels should not be measured during a relapse, and ideally should be done at least 3 months after a relapse.

11 Information Needs & Psychosocial Support

- Adequate information and often repeated explanation are essential especially on diagnosis, and with the introduction of prednisolone treatment.
- Families should be directed to Infokid website for more information (https://infokid.org.uk/)
- Liaison with school or nursery staff may be beneficial, especially with behavioural difficulties associated with prednisolone use
- Referral to a social worker and psychologist should be considered for children and families having particular difficulties

12 References

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13 Document control

Document Control	
Hosting Clinical Directorate:	Body, bones and mind
Clinical specialty/specialties to be published under:	Nephrology
Version Information	
New guideline ☐ Scheduled review ☐ Amended due to updates ☒	
Version number:	3
Previous title (if applicable):	N/A
Last version number (if applicable):	2.0
Last approval date (if applicable):	N/A
Major amendments made (if applicable):	As per clinical guideline committee review
Consultation	
Individuals/groups/teams consulted on the guideline development/updates:	Nephrology MDT
Local Ratification Process	
Committees that have ratified the guidelines prior to presentation at Clinical Guidelines Committee:	GOSH 13/06/2025
Legal Team sign off (if applicable):	
Does the guideline include information about consent?	No
If yes, has the Legal Team reviewed the guideline and signed it off?	N/A
Drugs and Therapeutics Committee sign off (if applicable):	
Does the guideline include information about drugs or therapeutic agents?	Yes
If yes, and the specialist pharmacist has confirmed that DTC approval is required, has this been done?	No, preciously approved at DTC 2024
Nutrition Steering Committee sign off (if applicable):	

Does the guideline include information about nutrition or feeds or nutrition-related products?	No
If yes, has the NSC approved the described nutrition or feeds or nutrition-related product guidance?	NA
Medicines and Therapeutics Oversight Assurance Committee sign off (if applicable):	
Does the guideline include information about use of a medical device or medical equipment that is to be used innovatively / is not what the manufacturer has intended as its use?	No
If yes, has the MTOAC approved the described innovative use of medical devices/equipment?	N/A
Clinical Guidelines Committee approval:	
Date Approved by Guideline Committee:	**June 2025**
Guideline Expiry Date:	**June 2028**