NEPHROTIC SYNDROME: MANAGEMENT IN CHILDHOOD

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- This document provides information on the investigation, treatment and management of nephrotic syndrome (NS) in children at initial presentation and in relapse of the condition.
- The guideline applies to children with typical idiopathic nephrotic syndrome, and may not be relevant to 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).
- The guideline is based on best available evidence including Cochrane Collaboration reviews, literature searches of PubMed, using the terms “paediatric” / “children”, “nephrotic syndrome”, and “steroid sensitive” and the recent KDIGO clinical practice guidelines for glomerulonephritis. 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.
- Appendix 2 provides a flowchart summary of management pathways

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CHANGE SUMMARY

- New Network Document

READ ACKNOWLEDGEMENT

- This document is intended for use by all health professionals (for example, doctors, nurses, dieticians and pharmacists) and is discretionary - local manager to determine which staff, if any, are to read and/or acknowledge the document..

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1 Definition and initial features of Nephrotic Syndrome

Nephrotic Syndrome is defined by the triad of:

1. Proteinuria
    i. Urine dipstick testing ≥ 300mg/dL or 3+ protein
    ii. Quantified as urine protein:creatinine ratio >200mg/mmol (0.2mg/µmol) on a first early morning urine sample or >40mg/m^2/hr on a timed sample
2. Hypoalbuminaemia
    i. serum albumin <25 g/L
3. Generalised oedema

The child with nephrotic syndrome typically presents with

- Peri-orbital swelling
- Ankle and lower limb swelling – pitting oedema
- Abdominal distension

Less commonly children may present with scrotal/vulval oedema, frank haematuria (atypical and of concern, see below) or frothy urine. The findings of fluid retention and heavy proteinuria in a child require urgent referral to a paediatrician.

Differentiating typical from atypical presentation:

	Typical	Atypical (any of these features)
Age	1-12 years	<1 year or > 10-12 years
Haematuria	Microscopic	Macroscopic*
Blood Pressure	Normal	Persistently elevated
Renal Function	Normal creatinine	Elevated Creatinine
Systemic Features	None	Symptoms +/or signs of systemic disease
Family History	None	Present

** Consider renal vein thrombosis (see section 4.4)*

For children with a typical presentation, were they to undergo a renal biopsy, histology would likely show minimal change. Children with typical features, however, are started on steroids without a biopsy. Steroid responsiveness is a better indicator of long term outcome of renal function than histology. 95% of patients with Minimal Change Nephrotic Syndrome (MCNS) achieve remission after corticosteroid therapy (1).

Early referral is appropriate in children with atypical features as they are more likely to be unresponsive to steroid treatment.

Definitions related to nephrotic syndrome:

Remission: urine protein nil or trace on dipstick (or protein:creatinine ratio <200mg/mmol or < 0.2mg/µmol) on three consecutive early morning urine specimens.

Relapse: urine protein 3+ or 4+ on early morning urine dipstick (or urine protein:creatinine ratio ≥300mg/mmol or ≥0.3mg/µmol) for 3 consecutive days after having achieved remission previously.

Frequent relapses: two or more relapses in initial 6 months or ≥ 4 relapses in any 12 months period.

Steroid dependence: relapse while on steroids or within 14 days of discontinuing steroid therapy

Steroid resistance: failure to achieve full remission within 4 weeks of commencing daily prednisone therapy (2 mg/kg or 60 mg/m^2daily)

Children with steroid resistance should be referred to a paediatric nephrologist as soon as possible.

2 Initial assessment and investigation at presentation

The initial clinical assessment of a child with Nephrotic Syndrome is directed towards making a diagnosis and detecting potential complications of nephrosis and should include:

- Height, weight, surface area
- Thorough assessment of volume status
    - Heart rate and BP
    - Perfusion: capillary refill and core-peripheral temperature gap
    - JVP and/or hepatic span
    - (Haematocrit and urinary sodium)

It is useful to document complete immunisation record and any history of chickenpox infection.

2.1 Initial Investigations

Investigations to be performed in all children

- Full Blood Count, Electrolytes, Urea and Creatinine, Liver Function Tests,
- Urinalysis and urine protein or albumin to creatinine ratio
- Hepatitis B status in children at high risk (family history, travel in endemic areas.)

Investigations to be considered in children with atypical features

- ASOT; anti-DNaseB
- C3/C4
- Renal ultrasound scan with Doppler of renal vessels

Consider screening for latent tuberculosis in children recently emigrated from areas with high prevalence of latent tuberculosis infection (2).

2.2 Indication for consultation/referral to a nephrology service

Nephrosis may be complicated by infection, hypovolaemia and thrombosis, and therefore the treating team should have a low threshold for consultation. Absolute indications for referral include:

- Any atypical features as listed above
- Suspicion of hypovolaemia (see section 4.1)
- Prior to administration of concentrated albumin (see section 3.4.1)
- Steroid Resistance

3 Management of First Presentation of Typical NS

3.1 Medications

3.1.1 Prednisolone (or prednisone)

Prednisolone should be started empirically in children presenting with features of typical NS. An **initial** course of 12 weeks is recommended. Calculation of dose according to weight or body surface area does not affect outcome (3).

2 mg/kg/day (60 mg/m^2/day) maximum 60 mg daily for 6 weeks then 1.5 mg/kg (40 mg/m^2) maximum 40mg alternate days for 6 weeks

No steroid taper is required at conclusion of this initial therapy.

This 12 week treatment regimen is recommended by the Children's Nephrotic Syndrome Consensus Conference because of maximum effect and minimisation of corticosteroid related adverse effects (4). Results of several studies from India, Europe and Japan have shown no disadvantage to cessation of therapy after 12 weeks without a taper and may limit the negative effect of prolonged courses of prednisone (5,6). A recent Cochrane update concludes that there was no significant difference in the risk for frequently relapsing NS between prednisone given for 2 or 3 months and longer durations of therapy indicating that there is no recognised benefit of increasing the duration of prednisone beyond 2 or 3 months in the initial episode of steroid sensitive nephrotic syndrome (SSNS) (7).

3.2 Ongoing Monitoring

Regular review to monitor for complications and to assess the onset of remission is needed. Parental education (see below) can take place at the same time. Depending on local resources, this may best be done as an in-patient admission.

3.2.1 During an inpatient admission

- Daily weight
- Accurate fluid balance
- Daily early morning urinalysis
- Blood pressure

The on-going assessment of children with NS includes the assessment of intravascular volume status. Children may be very oedematous, but may also have intravascular volume

depletion (See section 4.1). Hypertension may occur and should be assessed and treated as per section 4.2. Hypertension is unusual in the acute setting and if persistent should lead to reconsideration of an underlying glomerulonephritis.

3.2.2 Laboratory monitoring

Daily urinalysis (UA). Parents/carers should do this once the child has been discharged
Recheck serum electrolytes, urea and creatinine if initial creatinine is elevated and in patients requiring IV albumin and diuretics.

3.2.3 Response to treatment

A complete remission is defined as 3 or more consecutive days of trace or no protein on dipstick testing. Remission is characterised by:
Diuresis and weight reduction
Reduction in level of proteinuria on dipstick testing
Most children with nephrotic syndrome will respond to steroid treatment within 2-4 weeks. Treatment is continued for a total of 12 weeks (as per 3.1.1).

If proteinuria persists beyond the first 4 weeks of steroid treatment, children should be referred to a nephrologist for consideration of a renal biopsy.

3.3 Dietary and Fluid Management

A low salt diet is used to try to prevent exacerbation of fluid retention and oedema whilst proteinuria persists. Fluid restriction may also be helpful in limiting the increase in oedema, (generally to 2/3^{rds} maintenance although individual discretion is required). Dietary salt intake often exceeds healthy recommendations. In practice a "reduced salt diet" aims to reduce the patient's sodium intake to below the maximum recommended limits:

- 1 to 3 years 2g salt per day (0.8g sodium)
- 4 to 6 years 3g salt per day (1.2g sodium)
- 7 to 10 years 5g salt per day (2g sodium)
- 11 and over 6g salt per day (2.4g sodium)

These restrictions are lifted once the child goes into remission.

A balanced diet adequate in protein (1.5 – 2 g/kg/day) and calories is recommended. Not more than 30% calories should be derived from fats and saturated fats should be avoided.

Patients should not be advised to eat a high protein diet. Children on steroids may require weight management advice.

3.4 Oedema

Managing oedema is an integral part of supportive care. As treatment with corticosteroids usually leads to a diuresis within 2 weeks, diuretics are avoided unless significant oedema is present.

Diuretics should not be given to patients with hypovolaemia, diarrhoea or vomiting.

Patients with excessive or refractory oedema or a weight gain of 7-10% should preferably be managed in hospital with a combination of diuretics and an albumin infusion.

3.4.1 Albumin Infusion

Clinical indications for albumin include:

- Symptomatic oedema: skin compromise, cellulitis and scrotal or vulval oedema
- Symptomatic pleural effusion or ascites
- Primary peritonitis

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

Albumin (20%) is given as an infusion at a dose of 0.5g/kg to 1 g/kg over at least 4 - 6hours.

Give 1mg/kg of IV frusemide mid-infusion and repeat at the end unless a good diuretic response is in progress.

Albumin should be administered with extreme caution in patients with renal dysfunction, pneumonia or pulmonary oedema due to its potential to increase plasma volume and precipitate pulmonary oedema.

Children should be closely monitored for respiratory distress, hypertension and pulmonary oedema and where possible albumin should be administered during working hours with ECG and saturation monitoring in place.

While the infusion of albumin results in an increased urine output, the effect is transitory and repeated administration may be required.

3.5 Antibiotic prophylaxis

Although infection is the leading cause of mortality in paediatric patients with idiopathic nephrotic syndrome, there is no evidence to support the use of antibiotic prophylaxis in infection (including peritonitis) prevention. However, it may be considered in high risk groups. All patients should be immunised against pneumococcus.

3.6 Gastroprotection

The use of antacids is not usually necessary, unless the patient has upper gastrointestinal tract symptoms. However, protection against steroid induced gastric irritation may be used during steroid treatment (8).

Ranitidine 2 - 5 mg/kg twice daily (maximum 150 mg)

Omeprazole 10 mg once daily (weight 10 -20 kg)
20 mg once daily (weight > 20 kg)

3.7 Patient and Carer education

The long-term prognosis of children with steroid responsive nephrotic syndrome (SSNS) is good, with most in sustained remission with normal renal function by adolescence.

A small proportion of children, especially those with

- Early onset of nephrotic syndrome
- A frequently relapsing course requiring steroid sparing agents,

may continue to relapses beyond adolescence.

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

Carer involvement and motivation is essential in the long-term management of these patients. Carers should receive information related to the disease, its risk of complications and expected course.

The following should be highlighted:

- Home monitoring – daily urine dipstick of early morning urine should be performed during a relapse, during intercurrent infections or if there is mild peri-orbital oedema.
- This can be reduced to weekly or twice weekly during a remission.
- The detection of a relapse by detection of proteinuria prior to onset of significant oedema should be stressed.
- Patient diary – for monitoring of urine protein, intercurrent infections and medications
- Normal activity and school attendance should be ensured and the child should continue participation in sports and activities.
- Infections are an important cause of morbidity and patients should receive appropriate immunization and other measures of protection.
- Following cessation of steroids there is a risk of adrenal suppression and this should be explained to families and written information given about the potential need for steroids in the case of another acute illness or trauma.

The following are useful sources of information about Nephrotic Syndrome

- The NIH site in the US with much useful information about Nephrotic Syndrome https://www.niddk.nih.gov/health-information/health-topics/kidney-disease/nephrotic-syndrome-in-children/Pages/index.aspx
- InfoKID (UK) a partnership between RCPCH & BAPN & BKPA: http://infokid.org.uk/nephrotic-syndrome (accessed 27/2/2015)
- Royal Children's Hospital, Melbourne information booklet for families http://www.rch.org.au/uploadedFiles/Main/Content/clinicalguide/130561%20SCOTT%20Nephotic%20Syndrome%20booklet%20A5_LR.pdf (accessed 17/10/2016)
- UK National Kidney Foundation (NKF) website information: http://www.kidney.org.uk/help-and-information/ (accessed 26/2/2015)
- Rebecca has a Renal Biopsy- describes for children what a renal biopsy involves: http://www.kidney.org.uk/help-and-information/kids/kids-biopsy (accessed 12/2/2016)

4 Complications

4.1 Hypovolaemia

Oedematous patients may be intravascularly depleted. Presentation with clinical shock requires emergency intravenous volume resuscitation.

Symptoms of hypovolaemia without shock may include abdominal pain (splanchnic ischaemia / poor perfusion of the gastro-intestinal tract), dizziness, and poor urine output.

Clinical signs may include:

- cool peripheries (capillary refill time > 2 secs)
- core-peripheral temperature gap of > 2°C
- tachycardia
- paradoxical hypertension, which can precede hypotension

Hypotension is a late sign of hypovolaemia

Investigations may reveal a urinary sodium < 10 mmol/L (provided diuretics have not been administered) and a raised haematocrit.

Patients with hypovolaemia without shock, or who have refractory symptomatic oedema may benefit from a slow 20% albumin infusion. Diuretics may or may not be required and warrants discussion with a nephrologist. Symptomatic oedema includes severe swelling where there is skin compromise, cellulitis, scrotal or vulval oedema.

20% albumin should be administered during routine hours where possible. Strict monitoring of vital signs is required to detect intravascular volume overload. 20% albumin is not indicated to correct hypoalbuminaemia alone. Injudicious use can lead to either volume overload or intravascular depletion.

4.2 Hypertension

Transient hypertension occurs in a minority of patients at initial presentation. However, if persistent it may be a feature of an atypical presentation. Severe or ‘urgent’ hypertension (systolic BP >99th centile + 5mmHg) can be treated with the use of anti-hypertensive agents such as short acting nifedipine (8,9).

- Short acting nifedipine 0.25 – 0.5 mg/kg per dose. (Maximum dose 10mg) Can be repeated 4-6 hourly.

Clinical features of intravascular volume overload should be sought, and if present, treated with a diuretic. However, using diuretics in NS can precipitate Acute Kidney Injury or intravascular depletion and should be discussed with a nephrologist.

- oral frusemide 0.5-1mg/kg/dose once or twice daily, or
- IV frusemide (1mg/kg) for emergency management (8)

Persistent hypertension (systolic BP >95th centile) can be treated with longer acting agents such as amlodipine with incremental dose increases.

- Amlodipine 0.1mg/kg per day increasing in 0.1mg/kg increments every 5 days to 0.4mg/kg/day (maximum 10 mg daily) (9)

4.3 Infection

Infection remains the main cause of death in children with nephrotic syndrome. Loss of complement components and immunoglobulins whilst in the nephrotic state, may put children at an increased risk of infection, particularly with encapsulated organisms such as pneumococcus. Penicillin prophylaxis may be used in children who have not been immunised against pneumococcus.

Cellulitis should be treated promptly with antibiotics. 20% IV albumin infusion with frusemide cover should be given to reduce oedema in the presence of cellulitis.

Children on high dose steroids should receive VZIg if exposed to varicella. Primary Varicella Zoster infection should be treated with IV aciclovir or oral valaciclovir. As patients with nephrotic syndrome are immunocompromised, Herpes Zoster infection (Shingles) also requires initial IV aciclovir treatment.

4.4 Thromboembolism

Loss of proteins such as anti-thrombin III contributes to a pro-coagulant state. This can be exacerbated by hypovolaemia. Clinical features of renal vein thrombosis raising suspicion:

- Macroscopic haematuria
- Fall in haemoglobin and platelets
- Palpable, abnormally firm kidney
- Reduction in renal function
- Hypertension

Urgent Renal Doppler ultrasound and specialist referral are required if a renal vein thrombosis is suspected.

Cerebral Sinus Venous Thrombosis can also occur. A high index of suspicion is required, especially in young children with NS presenting neurological symptoms including headaches or variable conscious state and requires urgent cerebral imaging in discussion with a paediatric neurologist (10).

Treatment of overt thrombotic or embolic events requires sequential high or low molecular weight heparin and oral warfarin, in consultation with the haematology team (11,12).

5 Relapsing Nephrotic Syndrome

80% of children with steroid-sensitive nephrotic syndrome (SSNS) will relapse, and 60% of these will have five or more relapses. Predictors of fewer relapses are:

- Age older than 4 years at presentation
- Remission within 7–9 days of the start of steroid treatment in the absence of microhaematuria.

Relapse is defined by proteinuria >3+ protein for three consecutive days, and is detected by dipping the first morning urine samples.

Relapses are typically triggered by intercurrent illnesses, particularly viral upper respiratory infections. Low grade proteinuria (< 2+) may occur transiently and subside without steroid treatment as the intercurrent illness settles.

Families should be vigilant at times of intercurrent illness, and increase monitoring to daily. Instruct families to make contact using a designated contact number if

- relapse of proteinuria occurs (3 days of ≥ 3+ protein on dipstick)
- Recent trials suggest low dose steroid 'cover' (e.g. a one week course of prednisolone 0.5 mg/kg/day at the time of an intercurrent illness) may reduce risk of full relapse and therefore patients that relapse frequently may be instructed to start 0.5 mg/kg prednisolone at first sign of fever (>38°), gastroenteritis or URTI. If a patient is already on alternate day steroids then increasing frequency to daily during the infective episode may also be beneficial.

Patients can usually be managed as an outpatient with regular review while awaiting remission.

If uncertain whether there is a 'full' relapse the following can be helpful in guiding whether intervention with treatment or expectant observation is required:

- Clinical assessment (weight, BP) for fluid retention
- Quantitative urine protein: creatinine ratio on first morning urine
- Measurement of serum albumin

5.1 Management of Relapsed Nephrotic Syndrome

5.1.1 Prednisolone

Prednisolone treatment should be restarted once a relapse has been diagnosed.

2mg/kg or 60 mg/m^2 daily (maximum 60 mg) until early morning urine is trace or negative for 3 consecutive days. Then 1.5 mg/kg or 40 mg/m^2 on alternate days (maximum 40 mg) for 4 weeks then discontinued. The usual duration of treatment for a relapse is thus 5-6 weeks. Prolongation of therapy is not necessary for patients with infrequent relapses.

5.2 Monitoring and Observations

Admission is often **not** necessary with a 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.

5.2.1 Nursing

- Clinical assessment – fluid retention, complications
- Weight
- BP
- Daily first morning urine dipstick (assess proteinuria)
- Fluid balance advice

5.2.2 Laboratory

Where there is clinical uncertainty on relapse status, consider:

- First morning urine protein: creatinine or albumin: creatinine ratio
- Renal biochemistry including serum albumin

6 Management of Frequently Relapsing or Steroid Dependent Nephrotic Syndrome

Referral for discussion of second line therapy with a Paediatric Nephrologist is indicated in children with

- Frequent relapses
- Steroid dependency
- Steroid toxicity

6.1 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.

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 associated with intercurrent infections. Steroid-induced side-effects develop in a high proportion. 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.

6.2 Low Dose Alternate Day Prednisolone

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

For children controlled on low dose alternate day therapy the strategy of increasing to 0.5 mg/kg daily for about 5 days treatment during viral URTI may reduce the risk of relapse.

This approach can also be used in children with a tendency to relapse with intercurrent infection who do not require maintenance therapy to reduce the risk of relapse (7,13).

Parents can be instructed to adopt this approach.

6.3 Corticosteroid-sparing therapy

Corticosteroid-sparing agents should be given to children with frequently relapsing or steroid dependent disease who develop steroid – related adverse effects. Data is insufficient to choose among the following agents. Drug selection is based on reported efficacy, adverse effects, local availability and cost (5). A Cochrane systematic review concluded that eight week courses of cyclophosphamide or chlorambucil and prolonged courses of cyclosporin or levamisole substantially reduce the incidence of relapse in children with NS in comparison with corticosteroids alone (14). More recently mycophenolate mofetil has been used successfully and may have a more favourable side effect profile (15-17).

See Appendix for full details

- Calcineurin inhibitors include cyclosporine (initial dose of 4 to 5 mg/kg per day given in two divided doses) or tacrolimus (initial dose of 0.1 mg/kg per day given in two divided doses).
- Levamisole (dose of 2.5 mg/kg on alternate days for at least 12 months).
- MMF (initial dose of 1200 mg/m^2 per day given in two divided doses for at least 12 months).
- Alkylating agents include cyclophosphamide (dose of 2 mg/kg per day for 8 to 12 weeks [maximum cumulative dose of 168 mg/kg]) or chlorambucil (dose of 0.1 to 0.2 mg/kg per day for 8 weeks [maximum cumulative dose 11.2 mg/kg]).
- Rituximab (an anti-CD20 monoclonal) should be considered only in children who have failed combination therapy of prednisone and other corticosteroid-sparing agents and have serious adverse effects of therapy (18,19).

7 Vaccination advice

All children with NS should receive all routine childhood vaccinations, unless otherwise contraindicated. The timing of these may be interrupted if the child is treated with high dose steroids or immunosuppressant therapies. The following tables details which vaccines can be given safely (8,21):

	High dose steroids*	Low dose steroids**	Immunosuppressant †
DTaP/IPV/Hib	Yes	Yes	Yes
MenC	Yes	Yes	Yes
dTaP/IPV or DTaP/IPV	Yes	Yes	Yes
Td/IPV	Yes	Yes	Yes
Hep B	Yes	Yes	Yes
PCV/PPV	Yes	Yes	Yes
HPV	Yes	Yes	Yes
Influenza	Yes	Yes	Yes
Varicella(live)	No	Yes	No
BCG(live)°	No	Yes	No
MMR(live)	No	Yes	No

* *High dose steroid definition*
Oral prednisolone at a daily dose (or its equivalent) of 2mg/kg/day for at least one week
Or at a daily dose (or its equivalent) of 1mg/kg/day for one month

** *Low dose steroids definition*
Oral prednisolone at a daily dose of 2mg/kg/day for less than one week
Or a daily dose of 1mg/kg/day or alternate day regime for less than one month

Live vaccines should not be given until 1 month after stopping high dose steroids and changing to low dose steroids. KDIGO recommends deferring live vaccines until prednisone

dose is below either 1 mg/kg daily (20 mg/d) or 2 mg/kg on alternate days (40 mg on alternate days) (13).

†Immunosuppressive drugs

This includes patients on other types of immunosuppressive drugs (e.g. cyclosporin, cyclophosphamide, and the newer cytokine inhibitors) alone or in combination with lower doses of steroids, until at least six months after terminating such treatment.

Immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child but avoid direct exposure of the child to gastrointestinal, urinary, or respiratory secretions of vaccinated contacts for 3–6 weeks after vaccination (13).

°BCG Vaccine
This vaccine is not routinely given to children with NS. It is in this table for information only.

7.1 Pneumococcal

Most children should have received pneumococcal vaccination as part of the routine childhood immunisation schedule. Vaccination status should be confirmed. All unvaccinated children should be vaccinated and vaccination repeated every 5 years.

For a previously healthy child, currently aged >12 months, who was vaccinated according to the National Immunisation Programme schedule and received 7vPCV or 13vPVC at 2, 4 and 6 months of age, he/she should receive a further dose of 13vPCV followed 2 months later by a dose of 23vPPV. Vaccination with 23vPPV should then be repeated after 5 years if the nephrotic syndrome persists. A third dose of 23vPPV should be administered if a further 5 years has passed and the nephrotic syndrome persists. More than 3 doses of 23vPPV are not recommended (21).

Refer to The Australian Immunisation Handbook for up to date vaccination advice (21). (http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-home)

7.2 Varicella

Most children should have received varicella vaccination as part of the routine childhood immunisation schedule. Vaccination status should be confirmed. Children who have not been vaccinated, and are confirmed VZIgG negative, should receive the VZV vaccine when off all immunosuppressive therapy (22). Consider repeating Varicella status 6 - 12 monthly in the non-immune child.

Non-immune children will require VZIg if exposed to active chicken pox or shingles (13).

7.3 Seasonal Influenza and H1N1

Annual seasonal flu vaccination including H1N1 should be administered to the patient, and their household contacts (13).

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Appendix 1

STEROID SPARING THERAPY

Levamisole

Levamisole may be beneficial for children with frequent relapses (14). It is less useful if steroid dependent. Levamisole can only be given in tablet form. Tablets can be crushed. Levamisole (dose of 2.5 mg/kg on alternate days for at least 12 months). Levamisole is not registered in Australia and TGA approval would need to be sought through the Special Access Scheme (SAS). Fill out a category B form prior to initiation.

Levamisole	
Dose	2.5 mg/kg on alternate days rounded to 12.5mg doses to max. 150mg. After treatment has been established for 4 weeks steroids can be tapered. If successful, treatment can continue for up to 3 years.
Side effects rare and limited	'Idiosyncratic' neutropenia reversible on discontinuing drug. Rash ('erythema multiforme'-like) Vasculitis GI intolerance.
Monitoring	Check FBC monthly for first 3 months, at 6 months and 4-6 monthly thereafter.

Calcineurin Inhibitors – Cyclosporin or Tacrolimus

Cyclosporin is useful as a steroid sparing agent (14).

Cyclosporin	
Dose	2.5 mg/kg 12 hourly adjusted to achieve target C2 level (see below). If successful, treatment continued for at least 1 year initially, and can be continued, with careful monitoring, for 3 years or more if clinically indicated (6) before a trial off therapy if relapse free. For children less than 5 yrs. of age, three times daily dosing may be necessary. C2 level is taken two hours after morning dose.
Side effects	Hypertrichosis Gingival hyperplasia – advise vigilant dental hygiene Hypertension, Hyperkalaemia Renal dysfunction, with structural changes on long-term administration
Monitoring	C2 level checked 1 week after treatment introduction. Check C2 level 1-2 weeks after any dose changes. Therapeutic range for nephrotic syndrome is lower than for transplant patients. Aim for a 2 hour peak CsA level of 400-600 µg/L initially. Consider higher C2 levels in patients relapsing at lower levels where renal function and blood pressure remain normal. Monitor BP, UA:UC and biochemical renal function at review for features suggesting possible drug nephrotoxicity. When stable on treatment, frequency of review can reduce to 2 monthly. Renal biopsy and formal GFR if therapy to continue for more than 2 years

Tacrolimus has been used in a similar manner, in preference to cyclosporin, in children with SSNS when the cosmetic side-effects of cyclosporin are unacceptable. However, there are few data examining its efficacy (20) and no controlled trials comparing it with cyclosporin.

Tacrolimus	
Dose	0.05mg/kg 12 hourly adjusted to achieve target trough level (see below). If successful, treatment continued for at least 1 year initially. If successful, tacrolimus treatment can be continued, with careful monitoring for 3 years, or more if clinically indicated, before a trial off therapy if relapse free. Parent advised to withhold morning dose until after trough level check.
Side effects	Tremor Hyperglycaemia Hypertension Renal dysfunction, with structural changes on long-term administration Cardiomyopathy (rare)
Monitoring	12 hour trough level checked 2-3 days after treatment introduction. Check 12 hour trough 2-3 days after any dose changes. Aim for therapeutic trough levels: 4-7 microg/L. Monitor BP, UA:UC and biochemical renal function at review for features suggesting possible drug nephrotoxicity. When stable on treatment, frequency of review can reduce to 2-3 monthly. Renal biopsy and formal GFR if therapy to continue for more than 2-3 years

Mycophenolate Mofetil (MMF)

MMF has been used successfully as a second line steroid sparing agent in frequently relapsing and steroid dependent NS (15-17). Advantages include the absence of nephrotoxicity and no need for routine drug level monitoring.

MMF	
Dose	Up to 600mg/m^2/dose twice daily 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

Cyclophosphamide

For children with frequently relapsing or steroid dependent NS, cyclophosphamide can induce longer lasting remissions (8).

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

Cyclophosphamide should not be started until the child has achieved remission with corticosteroids.

A second course of cyclophosphamide should not be given, in view of potential gonadal toxicity.

Cyclophosphamide	
Dose	2.5 - 3 mg/kg/day PO 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	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; likely there is not a clinically significant increased risk compared with the general paediatric population
Monitoring	Check FBC weekly throughout treatment. Reduce dose to 50-75% if neutrophils 1.0 – 1.5x10^9/L. Stop if neutrophils <1.0x10^9/L; restart at 50-75% dose on recovery >1.5x10^9/L.

Rituximab

Rituximab is a chimeric monoclonal antibody directly linked to the depletion of CD20 B cells. Initially it was used as experimental therapy to resolve cases of difficult nephrotic syndrome when other treatment modalities failed (18, 19). Patients with difficult to control nephrotic syndrome despite use of optimal combinations of prednisone and corticosteroid-sparing agents, and/or who have serious adverse effects of therapy may be considered for this treatment. As with all the above second line therapies, patients must be referred and reviewed by a paediatric nephrologist before treatment is initiated.

APPENDIX 2: Overview of Management