Idiopathic nephrotic syndrome: a clinical approach

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Abstract

Children with new-onset nephrotic syndrome invariably present to general paediatrics in the first instance. Many with known nephrotic syndrome under the care of a paediatric nephrologist will present to local services with complex relapses. Using a case-based approach, this review aims to equip the general paediatrician with the skills: to assess and manage a child with a new presentation of nephrotic syndrome, to identify the complications associated with the nephrotic state, to choose the most appropriate steroid regimen and to identify those patients who should be referred to a paediatric nephrologist. We focus on the management of steroid-sensitive nephrotic syndrome (SSNS), the most common diagnosis in children presenting with nephrotic syndrome. We also discuss aspects of management of nephrotic syndrome relevant to the COVID-19 pandemic. Additionally, by the end of the article, the reader should have a basic understanding of the underlying pathophysiology of nephrotic syndrome and its resultant complications.

Keywords frequently-relapsing; nephrotic syndrome; prednisolone; relapse; steroid-dependent; steroid-sensitive; thrombosis

Introduction

Nephrotic syndrome is the most common glomerular disease of childhood. Its clinical presentation, characterized by proteinuria, hypoalbuminaemia and oedema, is thus very familiar to the general paediatrician.

There are many causes of nephrotic syndrome in children. The most clinically useful classification is by age at presentation (Figure 1).

Idiopathic nephrotic syndrome (INS) accounts for the vast majority of new presentations. The incidence of INS in the UK is around 2.3 per 100,000, increasing to 9–16 per 100,000 in children of South Asian ethnic origin. It is more common in boys, with a peak incidence between the ages of 18 months to 6 years. 90% of these children will have steroid sensitive nephrotic syndrome (SSNS - see Table 1) of whom 20% will never relapse after initial presentation and a further 30% will experience infrequent relapses. These are the clinical groups most likely to remain under the care of general paediatricians.

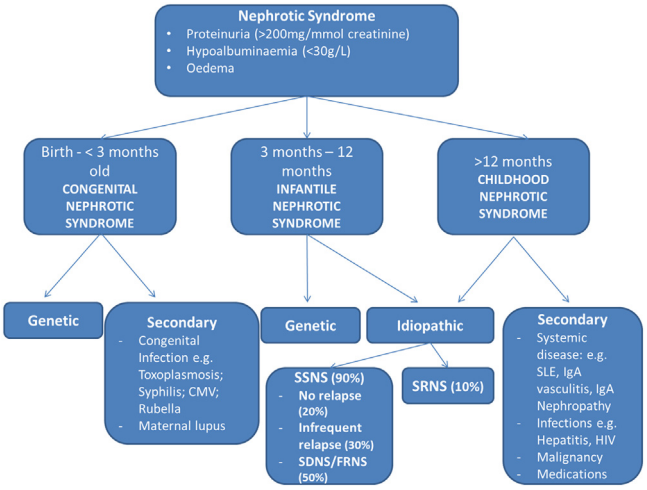


Figure 1 Classification of nephrotic syndrome by age at presentation. SSNS, steroid sensitive nephrotic syndrome; SRNS, steroid resistant nephrotic syndrome; SDNS, steroid dependent nephrotic syndrome; FRNS, frequently relapsing nephrotic syndrome; SLE, SLE, systemic lupus erythmatosis. For other definitions see Table 1.

Around 10% of children presenting with nephrotic syndrome will not respond to corticosteroids and are labelled steroid resistant nephrotic syndrome (SRNS). Underlying causes can be genetic or acquired. Nephrotic syndrome that presents under a year (labelled as congenital or infantile) is usually presumed to be steroid resistant and gene mutations that affect the structure and function of the glomerular filtration barrier comprise the commonest cause in this group. SRNS is challenging to manage, and is often associated with a poor renal outcome.

Definitions in nephrotic syndrome[1]

Relapse	≥3+ protein on dipstick testing of first morning urine sample for 3 consecutive days with or without oedema
Remission	Negative or trace protein on dipstick testing of first morning urine sample on 3 consecutive occasions
Steroid-sensitive nephrotic syndrome (SSNS)	Complete remission within 4 weeks of prednisolone at standard dose
Steroid dependent nephrotic syndrome (SDNS)	Two consecutive relapses during or within 15 days of stopping therapy with prednisolone (either during induction or consolidation phase)
Frequently relapsing nephrotic syndrome (FRNS)	≥2 relapses within 6 months of onset of disease, or ≥4 relapses in a 12 month period
Steroid-resistant nephrotic syndrome (SRNS)	Lack of complete remission after 4 weeks of prednisolone at standard dose

Table 1

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This article focuses on the more commonly encountered diagnosis of SSNS. We explore the essentials of assessment and management of the child presenting in the nephrotic state and review the clinical course of a child with SSNS using a case-based approach. We include a basic overview of the pathophysiology underlying nephrotic syndrome to aid understanding of its clinical presentation and complications.

Pathogenesis of nephrotic syndrome

Nephrotic syndrome is a glomerular disease. It arises from damage to or malfunction of the glomerular filtration barrier (GFB), resulting in leakage of albumin into the urine. The GFB consists of three distinct layers: fenestrated endothelium, the glomerular basement membrane (GBM) and specialized epithelial cells known as podocytes, which possess long foot processes whose interdigitatations form a barrier known as the slit diaphragm. The fault in the GFB can be acquired, as in secondary causes of nephrotic syndrome, or intrinsic. Many gene variants associated with nephrotic syndrome encode podocyte-related proteins.

The mechanism of damage to the GFB in steroid-sensitive nephrotic syndrome (SSNS) is poorly understood. Immune dysregulation or an unidentified circulating factor may play a role. However it arises, the most common histological finding in SSNS is minimal change disease (MCD). In MCD the histological appearance on light microscopy is normal. It is only with the more powerful electron microscopy that effacement (broadening and retraction) of podocyte foot processes may be seen.

The term MCD is often used interchangeably with SSNS. This is incorrect, since there are children with MCD who are not steroid sensitive. Moreover, there are other histological diagnoses, for example focal segmental glomerulosclerosis (FSGS), which respond to corticosteroids. Many children whose nephrotic syndrome follows a complex course can show MCD on early biopsies but FSGS later on and the relationship between these two histological findings has not been fully elucidated.

For these reasons, it is more clinically useful to define nephrotic syndrome in terms of response to treatment. Steroid-responsiveness alone determines management strategies and disease prognosis. Children with SSNS do not, therefore, undergo routine renal biopsy at diagnosis.

Pathophysiology of the nephrotic state

Traditionally, the development of the nephrotic state and its sequelae have been explained using the so-called "underfill hypothesis" (Figure 2). This asserts that loss of albumin in the urine leads to fluid leak into the tissues via reduced oncotic pressure, and that the resultant reduced intravascular volume leads to salt and fluid retention.

The opposing "overfill hypothesis" (Figure 3) postulates that it is primary sodium and fluid retention which results in oedema formation in nephrotic syndrome, as a result of activation of the epithelial sodium channel (ENaC) in the collecting duct by proteases in nephrotic urine.

Neither one of these hypotheses fully explains the clinical presentation of nephrotic syndrome. The overfill hypothesis cannot explain the nephrotic patient in hypovolaemic shock, nor is the underfill hypothesis consistent with the child who develops hypertension and pulmonary oedema on administration of albumin. In reality, either fluid state can be present and patients can rapidly move from one to the other. Both should be considered in the clinical assessment of patients with nephrotic syndrome.

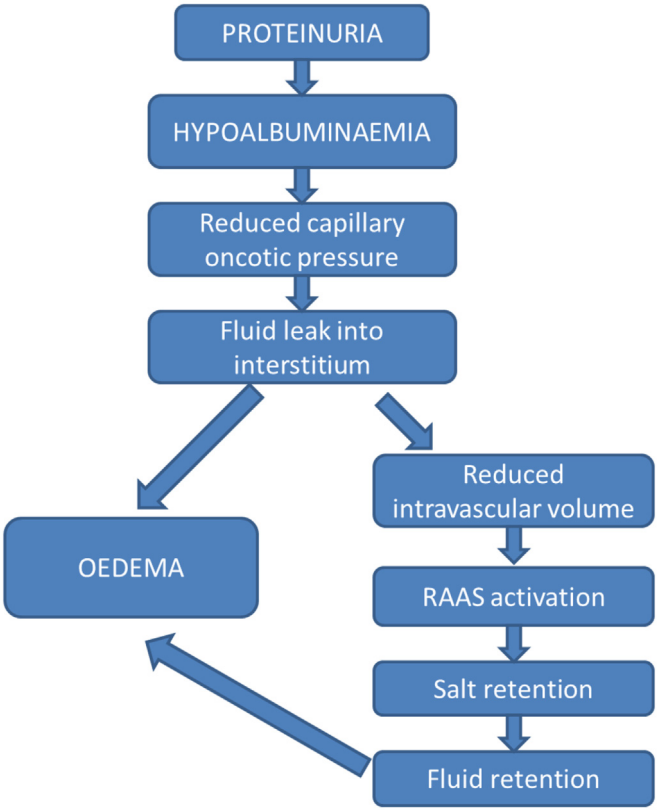


Figure 2 The underfill hypothesis of the nephrotic state. RAAS, renin angiotensin aldosterone system.

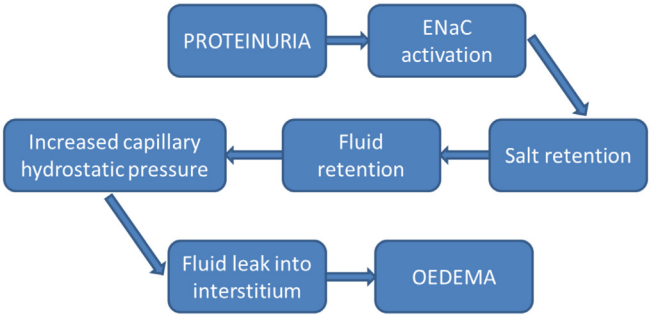


Figure 3 The overfill hypothesis. ENaC, epithelial sodium channel.

Clinical aspects of SSNS

The remainder of this review concentrates on the clinical aspects of nephrotic syndrome and to do this we take the reader through a series of case vignettes.

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Case: initial presentation

3 year-old Zain presented with a 3 day history of leg and abdominal swelling. This followed 4 weeks of eye swelling which was worse in the morning, and had not responded to antihistamines. He was otherwise well, with no history of recent illness. There was no past medical history or family history of note.

Zain was warm and well perfused, with a peripheral and central capillary refill time of <2 seconds, HR 119 and BP 107/63 (95th centile for age and height). Chest was clear, with respiratory rate 23 and saturations 97% in air. Oedema was noted up to mid-thigh and periorbitally. He had gross ascites, with a non-tender abdomen. Urine dipstick showed 4+ protein, 2+ blood.

Initial results:

Albumin, 13 g/L
Na^+, 137 mmol/L
K^+, 4.3 mmol/L
Urea, 5.5 mmol/L
Creatinine, 30 μmol/L
eGFR, >90 mL/min/1.73m^2
Varicella zoster IgG, negative (<100 IU/ml)
Urine protein:creatinine ratio, 1635 mg/mmol

Assessing a first presentation

The case is a typical presentation of INS. On first assessment, the key aims are first to identify life-threatening complications of nephrosis such as hypovolaemia, thrombosis and sepsis, and then to identify any atypical features which might suggest a diagnosis other than INS.

The essential elements of assessment are summarized in Table 2.

Atypical clinical features include age greater than 12 years, (where there is an increasing likelihood of non-MCD cause of nephrotic syndrome), or less than one year, where the diagnosis will be congenital or infantile nephrotic syndrome in the majority of cases.

Macroscopic haematuria, hypertension and renal impairment are more suggestive of a nephritic picture and a glomerulonephritis screen should be undertaken. Microscopic haematuria *can* be a feature of INS, however. Hypertension can be present in INS in the overfilled child, or, paradoxically, in the underfilled child secondary to peripheral vasoconstriction. Renal impairment can be present with a hypovolaemic state. When this occurs, elevation in urea is often more pronounced than the elevation in creatinine. Features of systemic disease such as joint pain or rash are suggestive of a secondary cause of nephrotic syndrome such as SLE. A family history of nephrotic syndrome may imply a genetic cause.

For a typical presentation, investigations can be limited to:

Urea, creatinine & electrolytes	to assess for AKI
Albumin	to document hypoalbuminaemia
Full blood count	to identify haemoconcentration associated with hypovolaemia
Varicella zoster serology	to identify non-immune children at risk of severe disease
Urine protein:creatinine ratio (early morning sample)	to confirm nephrotic range proteinuria

If atypical features are present, further investigation will likely be required. Venepuncture can be particularly challenging in the oedematous child, particularly if they are underfilled. An early discussion with a tertiary nephrology team is essential to guide further investigations and avoid repeated, traumatic attempts to take blood.

History and examination in a first presentation with nephrotic syndrome

History	Examination
Recent illnesses	Weight (including comparison with recent weight)
Reduction in urine output	Height
History of macroscopic haematuria	Volume status:
Immunisations	- Capillary refill time (Central and peripheral)
History of varicella zoster	- Peripheral perfusion
Family history of nephrotic syndrome	- HR and BP
	- JVP
	Oedema:
	- Periorbital
	- Lower limb
	- Sacral
	- Ascites
	- Scrotal/Vulval
	- Pleural effusions
	Urinalysis

Table 2

Case: early clinical course

Zain commenced oral prednisolone at 60 mg/m^2, a 750 mL fluid restriction and a low salt diet. He received prophylactic penicillin V and a 23 valent pneumococcal polysaccharide vaccine. Furosemide and spironolactone were commenced following a reduction in urine output and weight increase. Zain showed little clinical response to diuretic therapy, and developed stage 1 AKI on day 3.

Daily infusions of 20% human albumin solution were commenced to maintain urine output. Zain subsequently developed a new onset persistent occipital headache, with no associated symptoms. MRI brain was normal with no evidence of thrombosis.

Zain's urine output improved 10 days after starting steroids, and he was discharged on day 12 off diuretics, with a trace of protein on urine dip. He completed a standard course of prednisolone therapy.

Management of initial presentation

Switching off the proteinuria

Prednisolone is the mainstay of treatment. The standard treatment regimen is as follows:

- Prednisolone 60 mg/m^2 daily for 4 weeks
- Prednisolone 40 mg/m^2 alternate days for 4 weeks

Historically, there has been debate as to whether a longer tapering course of steroids might prevent future relapses. More recent large randomized controlled trials[2] have refuted this and shown no general benefit to prolonged steroid courses.

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The majority of children will enter remission within 2 weeks of daily high-dose prednisolone but it is important that the same daily dose is continued for 4 weeks. If there is no response towards 4 weeks, we would recommend discussion with paediatric nephrologists so that children can be admitted for 3 days of intravenous methylprednisolone followed by a kidney biopsy and genetic testing for non-responders.

Prevention and management of complications

Hypovolaemia: children who present in hypovolaemic shock require rapid volume expansion. 10mL/kg of 4.5% or 5% human albumin solution (HAS) is the first choice fluid, but crystalloid may be used if HAS is not readily available. Children requiring further fluid boluses require urgent discussion with a paediatric nephrologist.

Oedema

There are three stages of oedema management:

1. Gentle fluid restriction and low salt diet: Oedema can initially be managed by means of a gentle fluid restriction, accompanied by a low salt diet, which reduces thirst and thus fluid intake. Early involvement of a paediatric dietitian can be helpful for families.
2. Diuretics: Furosemide with or without spironolactone may be used to treat significant oedema if the clinician is confident that the child is euvolaemic. Diuretics can result in hypovolaemia, thus regular monitoring of fluid status, renal function and electrolytes should be performed in any child on these medications.
3. Human albumin solution (HAS): Children with persistent oedema and weight gain refractory to the above measures or with significant oedema in the presence of hypovolaemia may require IV albumin to offload fluid safely. Unless the child is shocked, this is best given as 20% HAS solution. A dose of 5 mL/kg must be given slowly, ideally over 4 hours. Furosemide is usually administered part-way through and/or at the end of the infusion, providing the child remains well-filled. Fluid status, renal function and electrolytes should be monitored regularly. HAS carries a risk of fluid overload and associated pulmonary oedema, thus infusions are most safely given in the morning and with appropriate monitoring.

Infection: urinary loss of immunoglobulins and complement puts children with nephrotic syndrome at risk of developing life-threatening infection, even before starting high-dose corticosteroids. Loss of these opsonizing factors particularly increases the risk of infection with encapsulated bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis*. There should be a high index of suspicion for infection in nephrotic children, and a low threshold for starting antibiotic treatment.

Common infections include:

- cellulitis (arising in broken, oedematous skin)
- spontaneous bacterial peritonitis (secondary to ascites)
- pneumonia

Most UK centres advocate the use of prophylactic penicillin V whilst oedema is present, although there is no strong evidence that this is beneficial. Children over the age of 2 should receive a dose of the 23 valent pneumococcal polysaccharide vaccine (PPV23) during their first episode. This should be repeated every 5 years if the child has ongoing relapses. All children with INS should be vaccinated as per the routine childhood schedule, although live vaccines should be delayed until the child is in remission off immunosuppressant therapy as per Green Book guidance.[3] In the case of the annual influenza vaccine, the inactivated IM vaccination may be required. Children in appropriate age groups should be immunized against SARS-CoV2.

Varicella vaccination should be given in those with negative varicella serology. It may also be given to non-exposed siblings. Immunosuppressed children with negative varicella serology and a significant chicken pox contact require treatment with oral aciclovir/valaciclovir from day 7 to day 14 post-exposure.

Thrombosis: urinary loss of anti-thrombotic proteins, combined with hypovolaemia and immobility results in a pro-thrombotic state. Around 3% of nephrotic children will develop thromboembolic events, with the highest risk in the 3 months after initial presentation. Most are venous in origin, arterial thrombi are rarer. Thrombosis should be considered as a cause in all children with nephrotic syndrome presenting with new symptoms. In our clinical case, for example, a new headache rightly prompted investigation for venous sinus thrombosis, one of the commonest sites of thrombosis encountered.

The risk of thrombosis is sufficiently small that prophylactic anticoagulants are not used routinely. In our clinical practice we have used short courses of low-molecular weight heparin in cases of nephrotic state associated with significant hypovolaemia, particularly if associated with immobility. A child with a history of thrombosis ought to have low-molecular weight heparin cover during relapses. TED stockings should be used in older children.

Acute kidney injury: AKI in children with SSNS most commonly arises as a result of hypovolaemia. It is usually an indication for HAS. If there is associated macroscopic haematuria, an urgent doppler ultrasound of the renal veins should be performed to assess for renal vein thrombosis.

Other aspects of care for the initial presentation

Children are usually admitted during their initial presentation. It is reassuring for parents and gives an opportunity to educate them about the disease. Useful internet signposts include InfoKID (www.infokid.org.uk) and the patient support group, Nephrotic Syndrome Trust or NeST (www.nstrust.co.uk).

At discharge, families should receive:

- a steroid warning card along with discharge medication
- a box of urinalysis sticks
- a diary to record findings
- contact numbers for advice about what to do in the event of a relapse
- a clear follow-up plan

Case: first relapse

Three months after his hospital stay, Zain developed an URTI.

Early morning urine dipsticks subsequently showed 3+ protein on 3 consecutive days, and relapse was diagnosed.

On review, he had no oedema and no signs of hypovolaemia. Zain recommenced prednisolone, entering remission after 7 days.

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Management of relapse

80% of children with SSNS will suffer at least one relapse. The standard treatment protocol is as follows:

- Prednisolone 60 mg/m^2 daily until remission (3 consecutive days of negative/trace proteinuria on dipstick)
- Prednisolone 40 mg/m^2 alternate days for 4 weeks

Clinical practice varies here as there is evidence from uncontrolled studies and small randomized controlled trials that suggests the use of half-standard dose prednisolone in relapse is equally efficacious. The 2020 Cochrane review[4] of steroid use in SSNS identified this as an important priority for future research and the question should be addressed with a formal clinical trial.

Sometimes children are treated with longer, tapering courses of prednisolone after entering remission. There is no evidence to support this. It is our practice to treat infrequent relapses with a standard course of prednisolone but to consider a slower taper in children whose disease is becoming frequently relapsing or steroid dependent.

It is good practice to review the child at their first relapse. This ensures that a relapse has been correctly identified by the family, allows for assessment for complications and permits reiteration of teaching for the family. Routine blood tests are not necessary to diagnose a relapse but should be reserved if there are other clinical concerns such as hypovolaemia. Subsequent relapses may be managed via phone/video by the clinician or specialist nurse.

Relapse secondary to upper respiratory tract infection

Relapses are frequently triggered by intercurrent infections. Evidence from relatively small clinical trials in India, Sri Lanka and the Middle East has supported the use of low-dose daily prednisolone for around one week during a URTI to prevent relapse. Whilst this practice is currently recommended by current KDIGO (Kidney Disease Improving Global Outcomes) guidelines[1], the recently published UK PREDNOS 2 study, a large, double-blind, placebo-controlled trial[5], established convincingly that there is no reduction in risk of relapse with use of low dose steroid at onset of URTI symptoms. In addition, the risk of URTIs triggering relapses was shown to be just 20% in contrast to more than 50% in earlier papers. Based on this evidence, we would not advise the routine use of daily low-dose steroids during URTIs in children with relapsing disease.

Case: relapsing disease options

Zain had a further relapse 2 months later shortly after stopping steroids, and another within 12 months of his initial presentation.

Despite treatment with levamisole and low dose steroids, he continued to relapse regularly. He showed no improvement with a course of oral cyclophosphamide, but became relapse-free on commencing tacrolimus.

Frequently relapsing and steroid dependent nephrotic syndrome

Around half of all children with SSNS will develop a frequently relapsing (FRNS) or steroid-dependent (SDNS) course. These definitions are made to guide practice as they are usually the point at which non-steroid, maintenance treatments are started to prevent relapses.

The aim of using maintenance treatments is to keep children in a disease-controlled state that minimizes relapses and steroid burden. A single relapse per year may be considered acceptable but two or more relapses per year should prompt consideration of a change of treatment.

For a child with frequently relapsing disease but no steroid dependency, the usual first choice of treatment is low-dose (15 mg/m^2 or 0.5 mg/kg) prednisolone given on alternate days. Levamisole is a good choice for FRNS, usually in combination with steroids initially, but it is less effective in steroid-dependent disease.

For SDNS, the choices of treatment include cyclophosphamide, tacrolimus, mycophenolate mofetil or rituximab. All have various clinical considerations and potential adverse effects. With the exception of rituximab, they may be used in any order. It is our practice to use cyclophosphamide first in pre-pubertal children as the 2 month course has disease-modifying effects in most children. We use tacrolimus in preference to mycophenolate, though in most European countries mycophenolate is the first-choice maintenance treatment.

In current practice, rituximab is usually reserved until other treatments have been exhausted. In England, a national commissioning policy limits rituximab use until after tacrolimus and mycophenolate have both been used.

With the exception of short course treatments (cyclophosphamide and rituximab), these treatments are usually given with expectation of continuing for at least 12 months so long as a sustained period of stable remission is obtained. Children taking maintenance treatments are monitored in out-patient clinics 3−4 monthly for growth, blood pressure and potential side-effects with regular blood tests. A renal biopsy is considered in children taking tacrolimus for more than 2 years, to assess for histological evidence of nephrotoxicity.

Long-term prognosis

Most children with relapsing SSNS will outgrow the disease in their teenage years but a significant minority will continue to experience relapses into adulthood. These young people require transition to adult renal services.

It is our practice to follow children and young people in clinic until they are relapse-free for 5 years, although they might only require an annual follow-up latterly. At the point of discharge, they need to be aware of the small risk of future relapses and it may be prudent to continue to test the urine at the time of intercurrent infection and to have an awareness of the development of even mild oedema.

Nephrotic syndrome and COVID-19

For children with nephrotic syndrome, including those who are significantly immunosuppressed, the risk of contracting COVID-19 appears to be equivalent to that of a healthy child. There is little evidence to suggest that COVID-19 infections are any more severe in children with nephrotic syndrome.

Despite this, children over the age of 12, with body mass more than 40 kg and who have received rituximab in the 12 months prior to COVID-19 infection meet the eligibility criteria for neutralizing monoclonal antibody (nMAB) treatment in the UK. Decisions to use nMABs in these children should only be made after multi-disciplinary team discussion.

COVID infection and COVID vaccination may both be associated with relapse, and it is sensible to monitor the urine for

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protein following these events. Overall, rates of relapse during the pandemic appear to be similar to pre-pandemic times, although this needs to be interpreted with caution given the decline in transmission of childhood viral illnesses during prolonged lockdowns, which might otherwise be expected to reduce relapse rates.

Conclusion

Initial evaluation of a child with INS should include assessment for life-threatening complications including hypovolaemia, thrombosis and sepsis. Most INS will respond to steroid treatment (SSNS). Any cases with atypical features or which do not respond to steroids should be discussed with at tertiary nephrology team.

50% of children with SSNS will have few or no relapses. For these children, follow-up in general paediatric clinics is very suitable. For the remainder it is a chronic disease, with frequent relapses that warrant repeated courses of high-dose steroids, and there is often a need for second-line treatments. These latter children usually find themselves under the care of paediatric nephrologists or in shared-care arrangements with local paediatricians. ◆

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Practice points

- Children presenting with nephrotic syndrome should be assessed routinely for evidence of complications such as hypovolaemia, thrombosis and infection.
- Standard steroid treatment of an initial presentation is prednisolone 60 mg/m^2 for 28 days followed by prednisolone 40 mg/m^2 on alternate days for 28 days.
- Relapse should be treated with prednisolone 60 mg/m^2 until the child enters remission, followed by 40 mg/m^2 on alternate days for 28 weeks.
- Low-dose daily prednisolone should not be routinely given to children with SSNS who have and URTI as it does not reduce the risk of relapse.
- Children with nephrotic syndrome should be followed up until relapse-free for 5 years.

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