Clinical Guidance

Management of Primary Paediatric Onset Nephrotic Syndrome

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Evelina London Children's Hospital (ELCH)
Primary Nephrotic Syndrome Guideline

Contents

A. Scope of guideline

This document relates to the management of Primary (Idiopathic) Nephrotic Syndrome with an onset within the paediatric age range. The aim is to provide a guideline to treatment as well as background to aid optimal clinical diagnosis and management.

Primary nephrotic syndrome is a kidney specific glomerular disease arising from injury to podocytes, the cells within the glomerular filtration barrier regulating protein filtration. This results in disruption of glomerular filtration with loss of excessive amounts of protein into the urine. Secondary nephrotic syndrome due to kidney injury resulting from systemic disease is not covered by this guideline, as management relates to treating the systemic disease in question.

Primary nephrotic syndrome is the commonest glomerular disorder of childhood. Its prevalence is between 2 –15 cases per 100,000 children in the UK, dependent on the admixture of African and South Asian populations where this is higher than European. Currently, the best prognostic marker in primary NS is steroid response and around 80% of children are steroid sensitive (SSNS). Although time to final remission cannot be reliably predicted, most SSNS patients have minimal change disease which is not associated with deterioration in kidney function and prognosis is good. 20% of patients have steroid resistance (SRNS). Focal segmental glomerulosclerosis (FSGS) is the principal diagnosis and more common in patients of West African descent in view of enrichment of predisposition alleles in the *APOL1* gene. Response to treatment is mixed and around 50% of patients with SRNS are at risk of eventual renal failure.

B. Definitions

1. Nephrotic Syndrome (NS):

- Nephrotic range proteinuria – significant urinary protein loss resulting in oedema and low serum albumin
- Low plasma albumin (< 25 g/l)
- Oedema
- Hyperlipidaemia

2. Nephrotic Relapse:

- Proteinuria measuring 3+ or greater on urine dip for 3 consecutive days
- Facial and/or peripheral oedema +/- ascites – this is how a relapse may present if urine testing has not been performed at home

3. Remission:

- Urine testing negative for protein on urine dip (i.e. complete absence of proteinuria) for 3 consecutive days

4. Frequently Relapsing:

- 2 or more relapses within 6 months of the initial response, or
- 4 or more relapses within any 12 month period

5. Steroid Dependent:

- failure to wean steroid medication as manifest by
  a) relapsing clinical course despite alternate day prednisolone or,
  b) clinical relapse within 2 weeks of stopping prednisolone

C. Classification

(i) Clinical.

Primary

- **Steroid sensitive** – initial relapse responds to 60mg/m^2 oral prednisolone within 4 weeks of treatment
- **Primary Steroid resistance** – initial relapse does not respond to 4 weeks of 60mg/m^2 oral prednisolone
- **Secondary steroid resistance** – development of steroid resistance despite previous steroid response at any time

Secondary

Systemic disease resulting in a secondary nephrotic syndrome: includes obesity (metabolic syndrome), diabetes mellitus, hypertension, post-streptococcal nephritis, Henoch-Schonlein purpura, systemic lupus erythematosus, chronic glomerulonephritis (MPGN, C3GN).

Congenital NS – presents within first 3 months after birth – >95% have a genetic cause

Early onset NS – presents between 3 months and 18 months of life – 60% have a genetic cause

(ii) Histology.

Supports clinical management and informs longer term prognosis.

Steroid sensitive nephrotic syndrome

- characteristic histology in uncomplicated steroid responsive nephrotic syndrome is minimal change: normal light microscopy, podocyte foot process fusion on EM

Steroid resistant nephrotic syndrome

- Focal segmental glomerulosclerosis (FSGS)
- Diffuse mesangial sclerosis (DMS)
- Membranous nephropathy
- Congenital nephrotic syndrome (Finnish Type)

D. Clinical Features

Typical Features	Atypical Features
Peak incidence: toddler and pre-school age group (range 2 - 5 years)	≤1yr, ≥10years
Normal BP	Elevated BP
Normal Creatinine	Elevated Creatinine
Normal complement and autoantibodies	Low C3; autoantibody positive
+/- Microscopic haematuria that resolves after the acute phase	Macroscopic Haematuria
No systemic disorder	Systemic features such as rash, joint pain/swelling
No family history of renal disease	Family history of renal disease

Children who present with *typical features*:

- >90% will be responsive to steroid treatment
- can be started on steroids without need for renal biopsy
- may require albumin if symptomatic hypovolaemia present
- will require initial admission to monitor BP, urine output and response to prednisolone
- will require monitoring and should not be discharged without a follow-up appointment

Caveats

- < 10% will have only the one initial relapse. As there are no predictive prognostic biomarkers, *all* require initial outpatient follow in view of the risk of further relapses for at least one year

- Early relapse especially within the first 4 months of diagnosis confers increased risk of steroid dependence and difficult nephrotic syndrome. Discuss these cases with the ELCH nephrotic syndrome team as may need prompt additional intervention with a steroid sparing agent.

Children with *atypical features*:

- discuss with ELCH Paediatric Nephrology ***as soon as possible*, *and before*** any treatment
- may require a renal tract ultrasound
- are likely to require renal biopsy
- are more likely to have secondary nephrotic syndrome
- are more likely to respond poorly to treatment
- may have systemic disease that requires specific treatment

E. Investigations

A diagnosis of nephrotic syndrome is established on clinical features and a urine dip. Table 1 summarises mandatory initial investigations and monitoring. Oedematous children are often difficult to bleed. As such, if there are no atypical features initial investigations may be limited to:

- FBC
- Renal and bone profile and albumin (to include sodium, potassium, urea, creatinine, calcium, phosphate, albumin and total protein)
- Varicella status
- Urine protein:creatinine ratio or albumin:creatinine ratio
- Urine sodium if suspect hypovolaemia

Secondary Investigations are:

- Measles and rubella IgG
- Liver function
- Complement: C3 and C4
- Common autoantibodies
- Renal ultrasound
- Specific investigations linked to individual presentation

Table 1: Mandatory clinical monitoring and investigations during first nephrotic relapse.

	At presentation	During hospital stay
Height	Yes	
Weight	Yes	Twice daily
Surface Area	Yes – use ideal weight for height	
BP	Yes	4 hourly
Oedema	Assessment of degree of oedema/ascites/pleural effusions	Daily +
Cardiovascular	Indicators of fluid overload: tachycardia, hypertension, respiratory distress, warm peripheries, hepatomegaly, raised JVP Indicators of hypovolaemia: tachycardia, hypertension, cool peripheries, delayed capillary refill time, oliguria	Daily +
Respiratory	If gross oedema monitor respiratory parameters +/- O_2 saturations	Continue to monitor respiratory parameters +/- O2 saturations
Fluid Balance	From outset	Input – output fluid/urine daily
Blood tests:	As listed above	Blood tests do not normally need to be repeated unless abnormal, or child is receiving diuretics. Albumin level alone does not guide treatment, so no need to repeat during initial admission.
Urine tests:	Urine dip for protein and blood Protein:creatinine ratio Sodium	Daily Weekly If hypovolaemia suspected

F. Initial Management of a first nephrotic relapse.

Initial presentation: *when to contact ELCH Paediatric Nephrology immediately for discussion +/- transfer*

Acute

1. Hypovolaemia/extreme nephrosis with fluid overload
2. Acute Renal Failure - oligoanuria +/- raised creatinine
3. Raised Blood Pressure
4. Suspected sepsis including peritonitis
5. Suspected Thrombosis

Sub-Acute

1. **Atypical Features:**

   Persistent hypertension, macroscopic hematuria, abnormal renal function, low C3/C4

2. **Need for a renal biopsy**

Primary (or secondary) steroid resistance: children who are not in remission after 28 days of treatment with prednisolone 60mg/m^2

Children presenting with nephrotic syndrome < 1 year and ≥ 10 years of age have an increased chance of an atypical nephrotic syndrome

Intial presentation: *management if uncomplicated first nephrotic relapse.*

Fortunately most cases will not present with complications. However, treatment of an uncomplicated first relapse differs from that for subsequent relapses as it is more intensive and lasts longer. The primary objective is to achieve long term nephrotic remission and minimise complications such as hypovolaemia, infection and thrombosis.

1. Steroid protocol for first nephrotic relapse

Prednisolone: doses are calculated per m^2

https://bnfc.nice.org.uk/guidance/body-surface-area-in-children-image.html

- 60mg/m^2 po daily, to a maximum daily dose of 60mg, for 28 days irrespective of whether the child goes into remission before 28 days
- then 40mg/m^2 po on alternate days for 28 days (maximum dose 40mg)
- then 30mg/m^2 po on alternate days for 14 days (maximum dose 30mg)
- then 20mg/m^2 po on alternate days for 14 days (maximum dose 20mg)
- then 10mg/m^2 po on alternate days for 14 days (maximum dose 10mg)
- then 5mg/m^2 po on alternate days for 14 days (maximum dose 5mg)
- then stop

To minimise side effects give steroids in the morning. All other medication dosing is as per ELCH formulary / Paediatric BNF.

2. Penicillin V prophylaxis

- given because of increased risk of infection
- discontinue once in remission for 3 days

3. Gastroprotection

- Ranitidine; or for ease of use (once daily dose) proton pump inhibitor of choice
- given during prednisolone treatment
- if asymptomatic, discontinue once prednisolone dose has reduced to < 5 mg alternate days

4. Fluid Restriction

- input-output monitoring of fluids and twice daily weights essential
- not always necessary if uncomplicated relapse
- consider in worsening oedema (usually manifests as an acute weight gain) or salt and water overload with a high/normal BP or BP above expected range - *discuss with Paediatric Nephrology*
- Usually < 5 years: a fluid restriction to 750 mls is sufficient
- Usually > 5 years a 1L fluid restriction is sufficient
- Do not fluid restrict nephrotic patients with clinical evidence of hypovolaemia +/- oligoanuria as this may precipitate pre-renal failure
- Increased urine output occurs when patients entering remission start off-load oedema – lift fluid restriction and monitor

5. General Advice

- parental and child education
- nephrotic diary
- salt restriction
- diet – normal

6. Vaccinations

- No live vaccines whilst immunosuppression and for <u>at least 3 to 6 months</u> subsequently
- Pneumococcal
  - recommended for all children with NS
  - routine pneumococcal vaccine may be supplemented with Pneumovax 23 for over 2 year olds
- Varicella (this is a LIVE vaccine)
  - consider in siblings of varicella negative immunosuppressed children
  - aim to administer vaccine when steroids and/or other immunosuppressive drugs have been stopped for at least 3 months
- Flu vaccination
  - injectable (inactive), not nasal spray (this is live) if on immunosuppressive therapy
  - Vaccinate patient minimum one week before siblings/class mates receive nasal
- Essential inactivated vaccines must be given but inadequate immunogenic response to vaccination may be compromised if in nephrotic relapse/taking high dose oral prednisolone
- Seek appropriate advice for other immunisations and foreign travel

Complications to look out for

1. Hypovolaemia

- a relatively common finding
- clinical assessment difficult in compensated longstanding nephrotic disease
- increased risk of thrombotic complications if left untreated

Symptoms

- Abdominal pain
- Cool peripheries
- Reduced urine output

Signs
- Capillary refill time > 2 seconds
- Toe-core temperature gap >2°C
- Poor urine output
- Hypotension (<5th centile), or paradoxically hypertension (>95th centile) can both be features of hypovolaemia
- Persistent tachycardia
- Low urinary sodium (<20mmol/L)

2. **Shock**
   - relatively uncommon in nephrotic syndrome
   - typically marked hypotension, tachycardia, very poor perfusion and lactic acidosis
   - consider usual management such as iv bolus of 10 – 20 ml/kg 4.5% albumin solution
   - avoid 0.9% saline if possible through salt load

3. **Acute renal failure**
   - Creatinine should be normal/low for age
   - Raised creatinine indicates either acute kidney injury or an atypical presentation

4. **Infections**
   - Increased risk of infection: urinary loss of immunoglobulin and immunosuppression
   - Risk high for encapsulated organisms, e.g. S. pneumoniae & H. influenza
   - Oedema increases risk of cellulitis
   - Low threshold for broad-spectrum antibiotics
   - Any infection potentiates the nephrotic relapse

5. **Spontaneous bacterial peritonitis (SBP)**
   - Bacterial infection complicating ascites
   - Any nephrotic with abdominal pain and tenderness +/- fever should be commenced on IV antibiotics (peritonitis protocol) and transferred to ELCH Paediatric Nephrology

6. **Hypertension**
   - The majority of children with uncomplicated NS have normal blood pressure.
   - If hypertension present, immediately discuss with Paediatric Nephrology prior to commencing treatment as this is an atypical feature
   - PRES (posterior reversible encephalopathy syndrome) is a risk of steroid treatment and hypertension in nephrotic syndrome

7. **Clot Formation**
   - NS is a pro-coagulant state through loss of anti-coagulant proteins
   - Children in nephrotic relapse at risk of spontaneous venous and arterial thromboses
   - Consider intravascular thrombosis as a cause of symptoms such as
     - altered behaviour or headaches/vomiting (***intracranial thrombosis***)
     - cough, chest pain and breathlessness (***pulmonary thrombo-embolism***)
     - peripheral vascular changes (***DVT or arterial ischaemia***)
     - macroscopic haematuria, palpable kidney, loin tenderness, raised creatinine, hypertension (***renal vein thrombosis***)

8. **Chickenpox exposure in non-immune patients**
    - Immunosuppressed patients testing negative for varicella IgG require prophylaxis
    - Prophylaxis recommended if prednisolone dose is equal to or exceeds
        - 2mg/kg/day for a one week
        - 1mg/kg/day for one month
        - lower doses of prednisolone if additional immunosuppression
    - Current guidance is to give prophylactic acyclovir (rather than VZIG) as follows:
        - Children < 2 years age: 10mg/kg, four times daily, days 7 to 14 after exposure
        - Children 2-17 years of age: 10mg/kg (maximum of 800mg), four times daily, days 7 to 14 after exposure
    - Patients will require acyclovir if develop chicken pox on immunosuppression
        - 1 month - 12 years: 20mg/kg (max 800mg) 4 times a day for 5 days.
        - ≥12 years: 800mg 5 times a day for 7 days.
        - Reduce dose in renal impairment

(iii) Use of 20% (salt poor) albumin in childhood nephrotic syndrome

- Use of 20% albumin is based on ***clinical features*** and ***not*** the level of plasma albumin
- Consider urine output – is this adequate?
- When 20% albumin considered, contact ELCH Paediatric Nephrology team to discuss ***before*** administering
- Give in ***daytime hours only*** and with frusemide cover as maximal expansion of the intravascular compartment may occur 2-3 hours following albumin infusion finished
- Excessive and rapid fluid shifts into the intravascular space may lead to heart failure and pulmonary oedema. Strict observations mandatory even after the end of infusion
- In very severe cases, a continuous infusion at a reduced rate with adjunct iv frusemide infusion may be required

Clinical Indications:

a) Hypovolaemia:

b) Severe oedema (without clinical features of hypovolaemia):

- causing immobility
- scrotal swelling and abdominal ascites causing discomfort
- skin breakdown

Close monitoring during 20% albumin infusion is mandatory

- Monitor oxygen saturation, pulse, blood pressure, respiratory rate every 30 minutes regularly during and for 3 hours post infusion.
- Accurate fluid balance measurement essential
- ***Beware of intravascular fluid overload due to fluid shift***:
    - increasing heart rate, BP, and respiratory rate: trend of observations crucial
    - visible JVP
    - development of oxygen requirement
- If overload develops:
    - Stop 20% albumin infusion
    - give frusemide
    - may need transfer to PICU

20% Albumin Infusion – in consultation with ELCH Paediatric Nephrology

i) Dose of 20% albumin: infuse 2.5 to 5mls/kg (0.5 to 1g/kg) over 6 hours
ii) Avoid frusemide at start of infusion as may worsen hypovolaemia

Frusemide IV is given either mid or at the end of infusion (depending on the severity of hypovolaemia), to drive diuresis:

- initial dose 0.5mg/kg – 1 mg/kg
- patients usually have normal renal function and are sensitive to frusemide
- patients who are very significantly proteinuric are relatively insensitive and may be at risk of ototoxicity if on a calcineurin inhibitor

(iv) Discharge checklist for parents

Children normally require an inpatient stay following a first presentation with nephrotic syndrome. This is to control symptoms and to educate children and parents about nephrotic syndrome. The discharge date is determined by clinical response and familiarity with the treatment protocol.

Consider contacting the specialist service for children with nephrotic syndrome at ELCH for further support and information leaflets on nephrotic syndrome via the nephrotic syndrome clinical nurse specialist on ***07342 060 351 or Beach ward if during evenings or weekends***

Before discharge, ensure carer/child:

1. Is able to dip urine daily using Albustix and record the urine test for protein
2. Has a diary to record daily urine tests (and does so every day)
3. Is able to recognise a relapse, and knows who to contact during normal hours, and out of hours
4. Is provided with advice on steroids plus a steroid card.
5. Is provided with advice regarding course of action if in contact with chicken pox or measles if child is non-immune
6. Understands advice on avoiding live vaccines
7. Is provided with adequate information about travelling - to seek advice before flying if in relapse and to take enough medication in case of relapse whilst away.
8. ***Patient must have follow up appointment scheduled before discharge.***

Further useful information for parents can be found on the Info kid website (www.infokid.org.uk)
Information for medications found on www.medicinesforchildren.org.uk
Evelina Pharmacy helpline 020714883003 and e-mail letstalkmedicines@gstt.nhs.uk

(V) Monitoring during follow-up

Daily - until in remission

1. Daily urine dip for protein – in hospital, and home
2. BP – if in hospital

3. Fluid Balance – if in hospital
4. Weight – if in hospital

Weekly

1. Monitor closely until in remission and oedema resolved on a weekly/x2 per week basis as ward attender/day case review
2. If glycosuria present, perform blood tests for plasma glucose and HbA1c with referral to endocrine team if blood levels abnormal

Subsequent Clinic Review – 2 weekly to 1 monthly depending on clinical progress

1. Urine dip for protein
2. Height
3. Weight and BMI
4. Dietetic review - where appropriate referral to obesity team
5. Psychology review if indicated
6. Community paediatric referral if indicated
7. School/nursery liaison if indicated
8. Bone age and pubertal stage where appropriate if concerns about growth
9. Ophthalmology review if indicated - if >12m continuous steroid therapy with significant cumulative steroid dose

G. Management of a subsequent nephrotic relapses

- Relapse may occur on or off steroid medication and is generally triggered by an intercurrent infection
- If child relapses, parents should telephone their GP, local hospital or specialist nephrology unit managing their child's condition for advice
- If uncomplicated, treatment with prednisolone and other supporting medications can usually be commenced at home.
- Parents should contact their local hospital immediately if the child
  - becomes unwell e.g. with abdominal pain, headache or fever
  - has worsening oedema
  - has reduced urine output
  - develops macroscopic haematuria
  - develops cool peripheries
  - develops shortness of breath

1. Prednisolone:

- 60mg/m^2 po daily, ***to a maximum daily dose of 60mg,*** until remission
- then 40mg/m^2 po on alternate days for 1 week (maximum dose 40mg)
- then 30mg/m^2 po on alternate days for 1 week (maximum dose 30mg)
- then 20mg/m^2 po on alternate days for 1 week (maximum dose 20mg)
- then 10mg/m^2 po on alternate days for 1 week (maximum dose 10mg)
- then 5mg/m^2 po on alternate days for 1 week (maximum dose 5 mg)
- then consider stopping steroids if no evidence of steroid dependence

NB. Duration of treatment is different from treatment of an initial presentation.

Supporting medication
Follow initial presentation guidelines with regard to penicillin, gasroprotection, low salt diet and symptom management.

Management of frequent nephrotic relapses or steroid dependence is tailored to the individual cand should be discussed with a Consultant Paediatric Nephrologist/Specialist Nephrotic Service at Evelina (please see Sections H and I: Management of Frequent relapses and Steroid dependence)

When to refer to Paediatric Nephrology (subsequent relapses)

- ***If proteinuria does not resolve or recurs with dose reduction contact ELCH Paediatric Nephrology as may indicate early steroid dependence and intervention with a steroid sparing agent.***
- ***If no response within 28 days to high dose oral prednisolone this is primary steroid resistance so refer to ELCH Paediatric Nephology***

H. Steroid Maintenance in frequently relapsing NS

Choice of Steroid regimen
- initially try maintenance low dose alternate-day prednisolone
- aim is to use the lowest dose of maintenance steroids that keeps the patient relapse free for at least 6 months
- selected by knowing at which dose the child relapses: use dose just above that
- dose required varies and is typically 5mg every other day, but should be no more than 0.5mg/kg alternate days to avoid side effects
- attempt to wean after 1 relapse-free year
- if > 0.5mg/kg alternate days persistently required to remain in remission and emerging steroid dependence need to consider a second line agent - **discuss with ELCH Paediatric Nephrology**

I. Management of Steroid Dependent NS

- if criteria for steroid dependence reached, early intervention with a steroid sparing agent is required to provide improved nephrotic control and avoid steroid toxicity
- renal biopsy is not generally required prior to starting a second line agent, unless patient develops secondary steroid resistance or other atypical features
- choice of second line agent should be determined in conjunction with ***advice from Paediatric Nephrology team/specialist nephrotic clinic at ELCH***
- trial of second line agent is for up to 3 months – if ineffective, escalate to next tier with further advice from specialist nephrotic syndrome service

Second line agents and treatment options

Tier 1: Mild to moderate steroid dependence
1. Mycophenolate mofetil (MMF) +/- low dose oral prednsiolone

2. Levamisole – but only useful in patients of south Asian descent +/- low dose oral prednsiolone

Tier 2: Significant steroid dependence or MMF/levamisole ineffective

1. Tacrolimus +/- low dose oral prednsiolone
2. Tacrolimus combined with low dose mycophenolate mofetil +/- low dose oral prednsiolone
3. Rituximab +/- tacrolimus/mycophenolate mofetil/low dose oral prednsiolone

Tier 3: Secondary Steroid resistance – MMF/tacrolimus/prednsiolone no longer effective

1. Rituximab +/- tacrolimus/mycophenolate mofetil/low dose oral prednsiolone or other anti-CD20 biosimilar
2. Liposorber LDL apheresis + prednisolone

Additional issues with frequently relapsing or steroid dependant disease that may require treatment

- Increased risk of infection
- Vitamin D deficiency (loss in urine)
- Hyperlipidaemia
- Hypothyroidism (loss in urine)
- Eye examination for cataracts in patients on prolonged maintenance steroid therapy >12m with significant cumulative steroid dose

The long- term treatment objective is to prevent complications such as Cushing syndrome and other steroid-related side effects such as obesity, secondary diabetes mellitus, growth retardation, bone disease and cataracts. Importantly, steroids must be used with caution in view of significant psychological, social and behavioural disturbances which may impact on a child's schooling and quality of life.

J. Indications for discussion/referral with Paedatric Nephrology at ELCH in second or subsequent nephrotic relapse

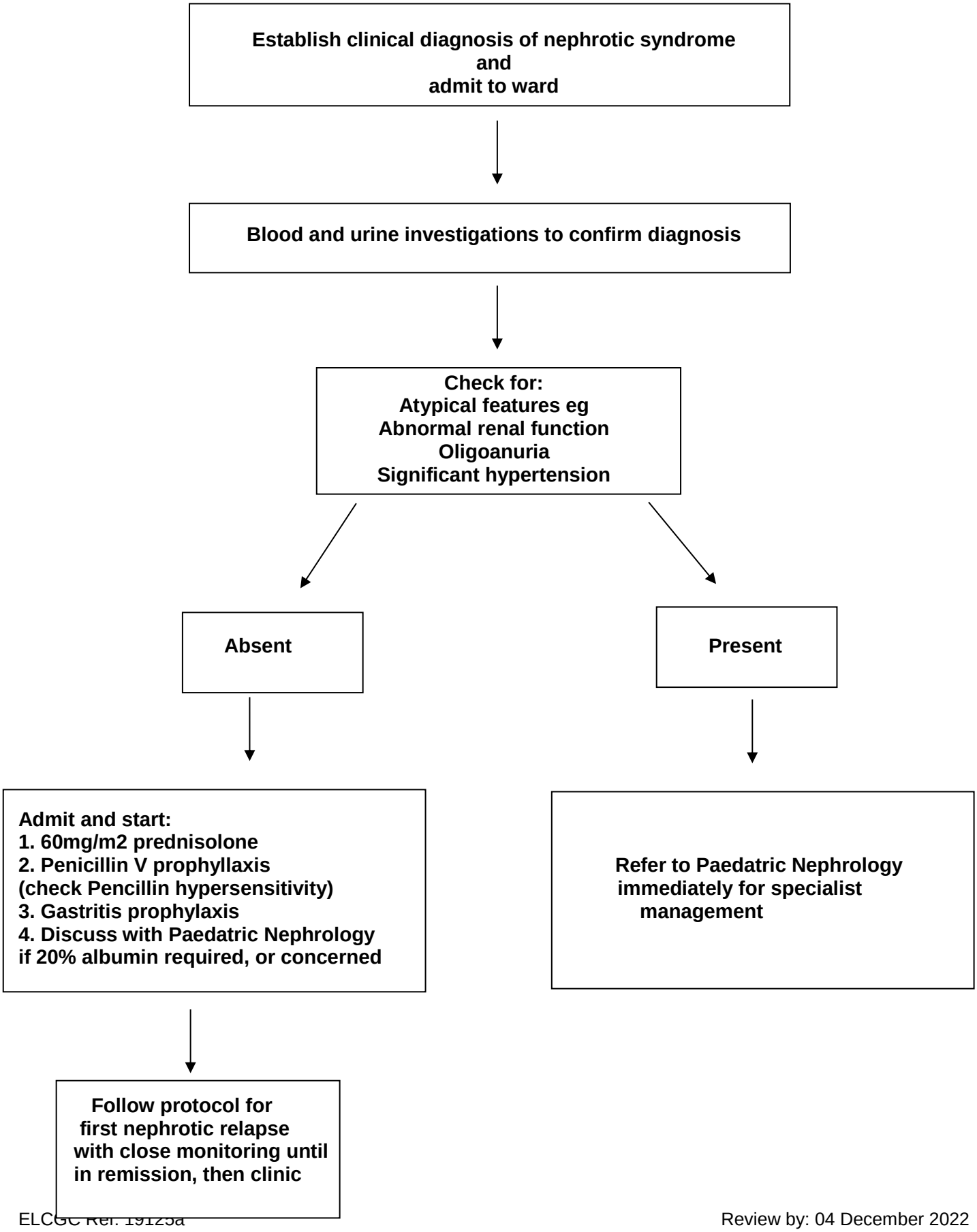
Acute Presentation

- Atypical re-presentation even if previously not
- Poor urine output
- Raised creatinine and other indicators of renal dysfunction
- Considering 20% Albumin infusion
- Unusual clinical course e.g. hypertension or macroscopic haematuria develop subsequently
- Low C3 and/or C4 or other abnormality suggesting systemic disease

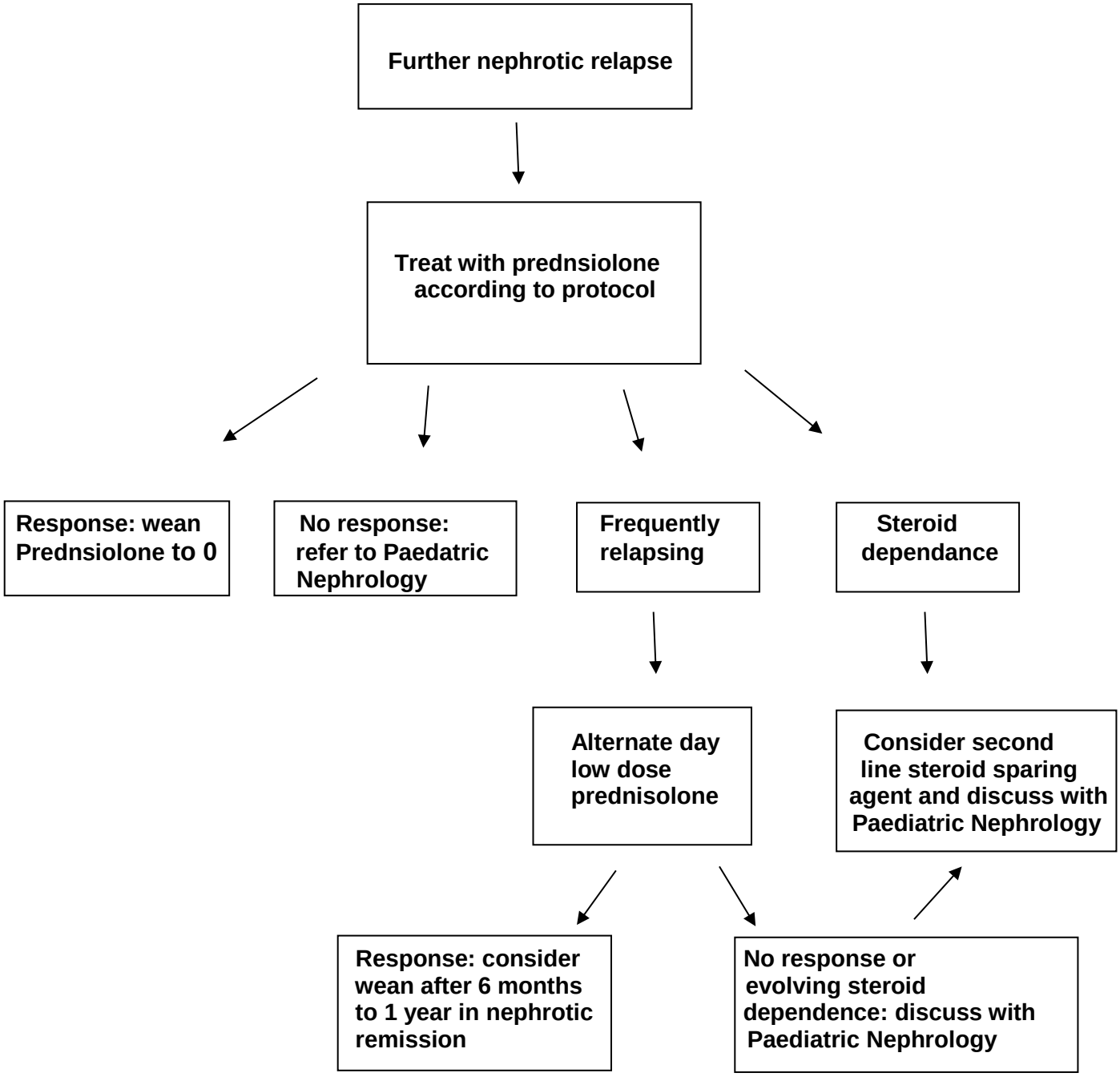
Longer Term Management Difficulties

- Steroid resistance: failure to achieve remission after 28 days of prednisolone will require renal biopsy and specialist management
- Substantive/unacceptable steroid side effects regardless of dose: will require steroid sparing agent
- Frequently relapsing or steroid dependent NS: will require steroid sparing agent
- Poor response to escalation to next tier drug – set a time limit (up to 3 months): if ineffective or pattern changes escalate treatment to next tier to avoid steroid toxicity
- Secondary steroid resistance – often resolves with addition of rituximab if SSNS (>95% chance)
- Evolution of atypical features at any point – further investigations +/- renal biopsy

Appendix 1. Management of First Presentation of Nephrotic syndrome.



Appendix 2. Management of subsequent nephrotic syndrome relapses and when to refer



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