Guidelines for the management of Nephrotic syndrome in children

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DISCLAIMER: These guidelines were produced in good faith by the author(s) in conjunction with the paediatric nephrology team at the University Hospital of Wales, Cardiff reviewing available evidence/opinion. They were designed for use by paediatric nephrologists at the University Hospital of Wales, Cardiff for children under their care. They are neither policies nor protocols but are intended to serve only as guidelines. They are not intended to replace clinical judgment or dictate care of individual patients. Responsibility and decision-making (including checking drug doses) for a specific patient lie with the physician and staff caring for that particular patient.

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May 2017

Summary
These guidelines are aimed at providing the doctors presented with a child with nephrotic syndrome with information to help identify the underlying problem and to guide management.

Introduction

Nephrotic syndrome (NS), is the commonest glomerular disorder of childhood and is characterised by heavy proteinuria (proteinuria ≥ 3+ on dipstick or protein: creatinine ratio > 200mg/mmol or > 1g/m^2/day), hypoalbuminaemia (serum albumin <25g/l) and oedema (may not develop until a few days after onset of proteinuria). The annual incidence in the UK is 2 per 100,000 children and
idiopathic nephrotic syndrome is 6 times more common in children of Asian descent living in the UK.

Classification

Primary glomerular disease

- Minimal change (80-90%)
- Focal segmental glomerulosclerosis (FSGS) (10-20%)
- MPGN
- Congenital nephrotic syndrome (presenting in 1st year of life)

Nephrotic syndrome associated with multi system disease

- HSP
- SLE

Approximately 80% of children with minimal change disease (MCD) will respond to prednisolone and this is the most important factor in terms of management and prognosis. 75-85% of these children will experience a relapse and up to 50% of these will have frequent relapses over many years. Although the typical age group for idiopathic NS is considered to be between 1-10 years, the most common age for presentation is 2 years, with 70% to 80% of cases occur in children younger than 6 years. NS is thought of as a relatively benign condition; however the mortality rate remains around 1%.

Definitions

Remission: Urine albumin nil or trace (or proteinuria <4 mg/m^2/h) for 3 consecutive early morning samples.
Relapse: Urine albumin 3+ or 4+ (or proteinuria >40 mg/m^2/h) for 3 consecutive early morning samples, having been in remission previously.
Frequent relapses: Two or more relapses in initial six months; four or more relapses in any twelve months.
Steroid dependence: Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation.
Steroid resistance: Absence of remission despite therapy with daily prednisolone for 4 weeks.

Assessment

History

Should include atopy, immunisation, common childhood infections (particularly Varicella Zoster) and family history (particularly renal disease and thrombophilia).

Examination

Should include height, weight, surface area, blood pressure, cardiovascular status and perfusion and any features of secondary NS.

Investigations

Blood	Urea and electrolytes, calcium, albumin, LFT, lipid profile, full blood count, complement - C3 and C4, Varicella titres, Selected cases - C3d, ANF, ASOT, ANCA and immunoglobulins
Urine	Dipstick for protein and glucose; Culture and microscopy for casts if gross haematuria present; Protein/albumin: creatinine ratio

Management

Treat as minimal change disease if investigations normal. The main interest is focussed on the results of complement studies. If these are abnormal then an alternative diagnosis should be considered e.g. MPGN, SLE.

Otherwise the aim is to induce remission with steroids (most patients respond within 5-14 days), which in turn promotes diuresis.

Initial episode

- Prednisolone 60 mg/m^2/day in a single morning dose for 28 days (even if proteinuria remits). Methylprednisolone 60 mg/m^2/day can be used intra-venously in the vomiting child.
- After 28 days, the dose of steroid is reduced to 40 mg/m^2 alternate days for the next 28 days and then stopped.
- A "steroid warning card" should be provided for the patient to carry.
- Ranitidine while on daily steroids.
- Reduce the risk of thrombosis by avoiding hypovolaemia and bed rest.

Oedema and ascites

- No added salt diet
- Moderate restriction of fluid intake (provided the child is not hypovolemic / in pre-renal failure). Suggested fluid intake <5 yrs = 750 mls/day, >5 yrs = 1 litre/day
- Diuretics- Not routinely recommended. Use only if severe and worsening oedema/ascites (after discussion with paediatric nephrologist), in the absence of hypovolemia (see below) - furosemide 1-2mg/kg/day in two divided doses.
- 20% Albumin (20% HAS) - Controversial and hence use after discussion with a paediatric nephrologist. Consider in those with skin breakdown / cellulitis, significant pleural effusion or troublesome genital oedema. Do not use 20% HAS in patients presenting with a nephritic picture (volume overload and hypertension) or in those with significant cardio-respiratory problems. It should be administered with caution with frequent monitoring of vital signs, particularly pulse oximetry until at least two hours after the infusion is

completed. Usual dose of 20% HAS is 2.5-5 ml/kg (0.5-1 g/kg) over 4 hrs IV with IV furosemide 1 mg/kg half way through infusion.

Hypovolemia

- Hypovolemia in an oedematous child could be easily missed. It might present with abdominal pain, hypo/hypertension, cold extremities, and prolonged capillary refill time, persistent tachycardia or prerenal failure.
- Urinary findings include osmolality >800 mOsm/kg, sodium <20 mmol/l, FE Na < 1%.
- Circulatory failure: 4.5% albumin 10-20 ml/kg over 30-60 mins IV repeated if necessary until volume status restored.
- 20% albumin 2.5 - 5ml/kg (0.5 – 1 g/kg) IV over 4 hrs with IV furosemide 1mg/kg halfway through the infusion (caution; see above) OR 4.5% albumin 5-10 ml/kg over 30-60 mins with IV furosemide 1 mg/kg at the end of the infusion.

Infection

Relapses are often triggered by infections, usually viral. In patients who are prone to relapses, a week's course of daily low dose steroids (0.5-1 mg/kg) during the infection has been shown to help prevent relapse.

It is important that patients are up to date with immunisations and aware that they **should not receive live vaccines if deemed to be immunosuppressed:**

A child who is receiving or has received in the last 3 months

(a) Prednisolone 2 mg/kg/day for > 1 week,
(b) Prednisolone 1 mg/kg/day or equivalent for 1 month i.e. 40 mg/m^2 alternate days,
(c) Lower doses of prednisolone combined with cytotoxic drugs,
(d) Long term lower dose immunosuppression e.g. prednisolone > 10 mg/m^2 alternate days.

The introduction of the nasal influenza vaccine for children has led to some children on steroids incorrectly receiving this vaccine. They should receive the killed intramuscularly administered form.

Because of the serious nature of chickenpox in immunocompromised patients, if a child is zoster IgG negative efforts should be made for them to receive chicken pox vaccine if a window of opportunity between steroid courses appears.

Chicken pox exposure within 3 months of high dose steroids or alkylating agents:

- Zoster immunoglobulin (VZIG) should be given if contact in last 10 days (ideally within 7 days). Discuss with virologist. Detailed information about the use of VZIG is available in the document *Guidance for issuing varicella-zoster immunoglobulin (VZIG)* produced by Public Health England in October 2016.
- For those seronegative contacts for whom VZIG is not indicated and/or for those for whom prophylaxis with a non-blood product is preferred, oral aciclovir at 10 mg/kg four times a day can be considered from days 7 to 14 after exposure.

For immunosuppressed patients who develop a rash the BNF recommends treatment by intravenous infusion:

Child 3 months–11 years	500 mg/m^2 every 8 hours usually for 5 days.
Child 12–17 years	10 mg/kg every 8 hours usually for 5 days.

Followed by oral aciclovir for a further 9 days.

Relapse

- Relapse within the first year is common (86%) and can occur years after the initial presentation.
- Relapse can follow immunisation or viral infection.
- Prednisolone treatment is usually delayed for at least 5 days unless the child is becoming oedematous.
- Blood tests not routinely required.
- Prescribing daily prednisolone (regular dose) instead of alternate day prednisolone for 7 days during viral infections with or without antibiotic treatment of infections can significantly reduce the risk of relapse in some children with steroid dependent nephrotic syndrome.
- Prednisolone dosage
    - Daily until remission (neg/trace for 3 days) 60 mg/m^2/day (maximum dose 80 mg)
    - Next 28 days 40 mg/m^2/alternate day (maximum 60mg)
- Subsequent therapy
    - Individualised (may/may not taper steroids)
    - At high risk of relapse (see above) - wean (10 mg/m^2/month) over 3 months
    - Frequent relapsers - taper (by 10 mg/m^2/month) over 3 months until a maintenance dose of 10-30 mg/m^2 alternate days, taking into consideration the dose in which the child is actually relapsing on. Keep on the same dose for at least 6 months before tapering or discontinuing (see below).

Steroid dependence / frequently relapsing

Consider second line of treatment in negotiation with a paediatric nephrologist if steroid side-effects are a cause for concern. Ensure that parents are given precise & adequate information on toxicity and both short & long term side effects of the drugs.

Second line therapies

Levamisole

While the primary use of levamisole world-wide is as an anti-helminthic drug, it has also been found to have immunomodulating actions and be effective in some children with SSNS. The dose used is 2.5 mg/kg taken on alternate days. The main side effect to look out for is neutropaenia and a FBC is recommended every 3 months.

Cyclophosphamide

Cyclophosphamide was developed as an oral form of the nitrogen mustard alkylating agents. It has been used for many years in SSNS where it has a steroid sparing effect. Ideally patients should be in remission before starting. It has traditionally been given orally, as an 8 week course at a dose of 3 mg/kg/day with weekly blood counts to check for neutropaenia.

Alternatively cyclophosphamide can be given intravenously at monthly intervals for 6 doses of 500 mg/m^2 each. Doses are accompanied by MESNA. The cumulative dose of cyclophosphamide is lower (120 mg/kg for a 5 year old boy on the 50th centile for height and weight as opposed to 168 mg/kg orally). There is reported to be a lower infection risk but this needs to be weighed against the necessity for siting of intravenous cannulas. An option grid is available to help discussions with families.

Information should be given about possible side effects:

- Infections
- Hair loss
- Cystitis
- Infertility
- Malignancy

An information sheet should be given to parents.

Mycophenolate mofetil (MMF)

While the amount of comparative data on the use of MMF in SSNS lags behind the more traditional second-line therapies it undoubtedly is effective and probably less toxic than cyclophosphamide and ciclosporin. The dosage recommended is 500 mg/m^2 twice daily and there is evidence that maintenance of trough levels above 2.5 µg/ml reduces relapse rate [1, 2]. Levels should be < 5 µg/ml. MMF levels indicated if concerns about compliance or response.

The dose of MMF may need to be increased if used alongside ciclosporin (600 mg/m^2 bd) and reduced if used with tacrolimus (300 mg/m^2 bd) because of the effects of these calcineurin inhibitors on MMF pharmacokinetics [3].

Calcineurin inhibitors

Ciclosporin has been shown to be effective in nephrotic syndrome and is preferred over other second-line therapies in steroid resistant disease. The dose is 1.5-2.5 mg/kg b.d. aiming for trough levels between 50 and 100 ng/ml. However because of its lipid solubility, higher levels may be needed at times of relapse because of associated hyperlipidaemia.

The evidence base for the use of tacrolimus is less established but is worth considering if side effects distinct to ciclosporin are a problem.

It is advised that a renal biopsy is performed before starting treatment because of the risk of nephrotoxicity.

Side effects include:

- Gingival hyperplasia (ensure good dental hygiene)
- Renal dysfunction (consider check biopsy)
- Myositis (check CPK especially if also taking a statin)
- Hypertrichosis (ciclosporin)
- Diabetes (tacrolimus)
- Hyperlipidaemia (ciclosporin)

Rituximab

Rituximab is a monoclonal antibody against the protein CD20, which is primarily found on the surface of B cells. It results in B cell lysis. Initially developed as a treatment for B cell malignancies, it has been used in a wide range of immune-

mediated diseases including nephrotic syndrome. It appears to be effective in steroid sensitive disease but less so in steroid resistant cases. There is a lack of controlled studies and it is difficult to know currently where it fits in the management sequence.

Suggested sequence of therapies in steroid-sensitive nephrotic syndrome with frequent relapses or steroid dependence:

Patients aged 1 – 7 years:

1. Alternate day prednisolone
2. Cyclophosphamide
3. MMF
4. Levamisole
5. Rituximab
6. Calcineurin inhibitor

Patients aged over 7 years:

1. Alternate day prednisolone
2. Levamisole
3. MMF
4. Rituximab
5. Calcineurin inhibitor
6. Cyclophosphamide

Indications for renal biopsy

A biopsy is not indicated as long as the child respond to steroids and continues to do so with each relapse.

A biopsy may be considered if:

- Aged < 12 months >10 years
- Steroid resistant
- Low serum C3
- Clinical evidence of systemic disease e.g. HSP, SLE
- Concern regarding ciclosporin nephrotoxicity
- Persistent renal impairment, persistent hypertension or family history of FSGS

References

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