SPECIAL REPORT

Consensus statement on management and audit potential for steroid responsive nephrotic syndrome

Report of a Workshop by the British Association for Paediatric Nephrology and Research Unit, Royal College of Physicians

The nephrotic syndrome is characterised by heavy proteinuria, hypoalbuminaemia, and oedema (audit point (A1); table 1; definitions table 2). It is an uncommon condition with an annual incidence in the UK of only 2–4 new cases per 100,000 children. There is racial variation in susceptibility with a reported incidence in Asian children of 9–16 per 100,000.1 2

The syndrome can be subdivided into congenital, primary (idiopathic), and secondary types. Most primary cases in children are associated with minimal histological changes in the glomeruli (minimal change nephrotic syndrome, MCNS) and respond to corticosteroid treatment.3 The correlation between MCNS and steroid responsiveness is so good that, in the absence of risk factors for other forms, an initial renal biopsy is unnecessary as minimal change histology can be assessed with confidence. However, some children with underlying diffuse mesangial proliferation or focal segmental glomerulosclerosis also respond to corticosteroids, while a few with MCNS do not.4 Such exceptions raise problems of both classification and terminology. As the histopathology in most children with primary nephrotic syndrome is not determined, it seems more appropriate that they are classified as either steroid sensitive (SSNS) or steroid resistant (SRNS). The latter group is heterogeneous, consisting of rare disorders with varying response to treatment and often a poor prognosis; they should be fully under the care of a paediatric nephrologist. However, most patients with SSNS are managed initially by general paediatricians, and subsequently on the basis of shared care with a paediatric nephrologist; they are the focus of this workshop report.

The cause of SSNS remains unknown, although the prevalence is higher in atopic families and some studies suggest an abnormality of T cell function.5 6 The albumin leak may be the consequence of loss of anionic charges in the glomerular basement membrane due to cationic proteins produced because of immune system disturbances.

Clinical features

There is a male to female ratio in SSNS of 2:1, with the condition usually starting between the ages of 2 to 6 years. There is often an antecedent history of an upper respiratory tract infection that often precipitates relapses. The children usually present with periorbital oedema, but as the condition is uncommon many children are treated for allergic conditions before its true nature is appreciated. The oedema can become generalised with ascites, pleural effusions, and diminishing urine output. There may be lethargy, irritability, poor appetite, diarrhoea, and abdominal pain which can even lead to referral

Table 1 Audit points

- Has the diagnosis of nephrotic syndrome been confirmed by quantitative analysis of proteinuria?
- Has there been a record of the height and blood pressure in the initial clinical examination and outpatient attendance?
- Were the appropriate initial investigations performed?
- Has the steroid treatment given for initial treatment and relapses as recommended?
- Has the remission and relapses been clearly documented?
- Has the patient and family kept a 'nephrotic diary'?
- Has the child on long term or frequent courses of steroids been assessed for growth and catarracts?
- Has the patient been given a steroid warning card?
- Has the patient been immunised appropriately?
- Have the parents been given adequate information including a booklet?
- Has a specialist paediatric nephrological opinion been sought at the correct time?
- Has the renal biopsy been performed and fully examined in an appropriate centre?
- Were the indications for alternative treatment documented and appropriate?
- Do the casenotes show that the risks of alternative treatment have been fully explained to the parents (and child when appropriate)?
- Does the regional paediatric centre maintain a data base of the nephrotic children referred?
- Were appropriate arrangements made for transfer to the adult unit?

Table 2 Definitions

- Nephrotic syndrome: Oedema; plasma albumin <25 g/l; proteinuria >40 mg/m²/hour or protein/creatinine ratio >200 mg/mmol

Remission: Urinary protein excretion <4 mg/hour/m² or reagent strip (Albustix)=0/trace for three consecutive days

Relapse: Urinary protein excretion >40 mg/hour/m² or Albustix = ++ or more for three consecutive days, having previously been in remission

Frequent relapses: Two or more relapses within six months of initial response or four or more relapses within any 12 month period

Steroid dependence: Two consecutive relapses occur during corticosteroid treatment or within 14 days after its cessation

Steroid resistance: Failure to achieve response in spite of four weeks' prednisolone 60 mg/day
to surgical units. Transient hypertension occurs in 10–15% of cases. Hypovolaemia may cause peripheral circulatory failure and predisposes to thrombosis.

The record of the clinical examination should include height and weight (with centiles) and blood pressure (A2).

Investigations (A3)
The following investigations are necessary at presentation:

(A) URINALYSIS AND CULTURE
There is heavy proteinuria with about 25% of patients also having transient microscopic haematuria. Gross haematuria is very rare.9

(B) EARLY MORNING URINE PROTEIN (OR ALBUMIN)/CREATININE RATIO
This shows an excellent correlation with the overnight protein excretion rate and exceeds 200 mg/mmol in nephrotic patients.9 Timed urine collections are difficult to collect in children and this ratio is preferable in clinical practice.

The proteinuria selectivity index, calculated as the ratio of the urinary clearance of IgG to albumin or transferrin, has been used to indicate steroid responsiveness, with a highly selective ratio (<0.1) characteristic of MCNS.10 The overlap between SSNS and SNS is such that the difficulty and cost of the investigation outweigh its usefulness and it no longer need be requested.

(C) BLOOD TESTS
These should be carefully planned and performed at a single venepuncture (never femoral vein because of the tendency to thrombosis) for the following analysis: (i) plasma electrolytes, albumin, and creatinine; (ii) full blood count; and (iii) hepatitis B surface antigen.

Antistreptolysin O titre, C3 and C4 components of complement, and antinuclear factor should be measured in selected cases especially when there is a mixed nephritic/ nephrotic picture.

Management
During the initial attack attention is focused on management of the oedematous state until hopefully the diuresis induced by suppression of disease activity by corticosteroids occurs.

BED REST
The child should be actively mobilised and bed rest avoided, though the child with grossly oedematous genitalia may restrict his or her activity because of discomfort.

DIETARY ADVICE
A balanced palatable diet, adequate in both energy and protein (1–2 g/kg body weight) is recommended but no systematic dietary advice is necessary in simple cases of SRNS. Previously both high and low protein diets have been advised. Animal studies have shown that although albumin synthesis is increased with protein augmentation, there is no significant effect on plasma albumin concentration or growth.11–13 Low protein diets decrease albuminuria, but there may be a risk of malnutrition.14 The whole family should receive advice about a no added salt diet which is particularly important during the initial attack. Long term prednisolone treatment impairs growth15 but stimulates appetite causing obesity and energy control may be necessary.

ANTIBIOTICS
The nephrotic child is vulnerable to infections and obvious foci should be treated. Streptococcus pneumoniae remains the most common organism producing peritonitis and sepsis, and Gram negative septicaemia is common and staphylococcal infections can cause cellulitis.16 In the oedematous child with gross ascites it is common practice to employ prophylactic oral penicillin 125 mg or 250 mg twice daily until the oedema has resolved. If peritonitis does occur, then cover for Gram negative organisms must be instigated until cultures are available.

Hypovolaemia
Rapid loss of protein may lead to hypovolaemia, particularly if accompanied by septicaemia, diarrhoea, or the injudicious use of diuretics. For reasons that are not understood a hypovolaemic crisis may be heralded by abdominal pain. The diagnosis is confirmed by evidence of peripheral circulatory failure – hypotension, cold extremities, sluggish capillary flow, and a wide central-peripheral temperature gap. There is haemoconcentration with a raised packed cell volume and avid renal tubular sodium reabsorption with a very low urine sodium concentration (<1–2 mmol/l). Hypovolaemia may cause acute tubular necrosis, be complicated by thromboses, or lead to sudden death.

A rapid infusion of plasma (purified protein fraction) 20 ml/kg or more is essential in such circumstances. Salt poor albumin infusions are expensive and can be hazardous, but may be life saving: 1 g/kg body weight as 20% solution should be given over 1–2 hours followed by a bolus of frusemide (1–2 mg/kg body weight) intravenously if oedema is severe. Albumin should be used with caution if the child is hypertensive, for if the volume status has been misjudged it may precipitate pulmonary oedema.

Diuretics and antihypertensives
While awaiting the loss of proteinuria and the subsequent diuresis produced by prednisolone (which usually takes 7–14 days in SSNS), the oedematous child should be managed with salt.
restriction and diuretics. Fluid restriction is of secondary importance but excessive fluid intake should be avoided. In the absence of hypovolaemia, careful use of diuretics such as frusemide (1–2 mg/kg/ diuretic, possibly combined with an aldosterone antagonist such as spironolactone (2 mg/kg/ body weight/day in two divided doses) can help to control the oedema. Abdominal paracentesis should only be performed if samples are required for the diagnosis of peritoneal fluid.

The child with SSNS is usually normotensive. Hypotension may indicate volume contraction. Hypertension must be very carefully evaluated. It may reflect hypervolaemia or an excessive vasconstrictive response to hypovolaemia. In the latter circumstance urine sodium concentration will be very low; in the former a raised venous pressure may be evident clinically with cardiomegaly on chest radiography and may be exacerbated by corticosteroids. If the blood pressure exceeds normal limits for age and sex then short term treatment with either atenolol (0.5–1 mg/kg body weight/day once daily) and/or nifedipine (0.25–2 mg/kg body weight/day in two doses) can be employed.

**Corticosteroids**

Prednisolone, an active metabolite of prednisone, was first used in childhood nephrotic syndrome in 1956. Both agents have been widely used since then but it remains unclear whether their mode of action is anti-inflammatory, immunosuppressive, or both. Prednisone is rapidly metabolised to prednisolone, and there is little to choose between the two preparations. Gastrointestinal absorption of both is rapid and peak plasma concentrations are reached within two hours. Soluble forms produce little gastric irritation and the expensive enteric coated formulations are usually unnecessary. Intravenous methylprednisolone, in an equivalent dose to oral prednisolone, may be useful initially in the vomiting child.

**INITIAL TREATMENT (A4)**

At present a high dose of prednisolone (60 mg/m²/day, maximum 80 mg/day) is accepted practice in most units in the UK (British Association for Paediatric Nephrology unpublished survey) for induction of remission (urine negative or with trace amounts of protein on reagent strips for three consecutive days). The steroid dosage can also be calculated on ideal body weight (equivalent dose is 2 mg/kg/day). The consensus view was that this dose of prednisolone should be continued (maximum 28 days) until remission, which would be expected in 80% of children with nephrotic syndrome, with 92% of these having minimal change histology. Eighty per cent of those patients who respond will do so within 14 days, although a further 14 days is generally needed to restore plasma albumin concentration to normal. In the event of no response by four weeks the child is regarded as steroid resistant and the advice of a paediatric nephrologist should be sought.

Once remission has been induced the dose of prednisolone is reduced to 40 mg/m²/day maximum 60 mg/day, given on alternate days for the next four weeks (table 3). Prednisolone is then stopped without tapering the dose.

This initial treatment differs from that recommended by the International Study of Kidney Diseases in Children (ISKDC) in two respects. First, alternate day rather than intermittent (three consecutive days out of seven) dosage of prednisolone is used after remission. This is because alternate day treatment controls the relapse rate more effectively than intermittent doses using the same total dose of prednisolone. The second change is that, in an attempt to reduce side effects, daily treatment is continued only until there is a response, whereas the ISKDC recommended a full four weeks of 60 mg/m²/day. However, others have shown that a dose of 30 mg/m²/day can be used for induction of remission, while at the other extreme the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) has shown a significant reduction in relapses after initial treatment of 60 mg/m²/day for six weeks followed by alternate day 40 mg/m² for six weeks. The latter regimen has a greater risk of side effects and further research in this area with long term follow up of the APN cohort is required.

**Table 3 Levels of management of SSNS**

<table>
<thead>
<tr>
<th>1. Initial episode</th>
<th>Prednisone 60 mg/m²/day (maximum 80 mg/day) until remission, followed by 40 mg/m² (maximum 60 mg/day) on alternate days for 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. First two relapses</td>
<td>Prednisone 60 mg/m²/day (maximum 80 mg/day) until remission, followed by 40 mg/m² (maximum 60 mg/day) on alternate days for 4 weeks</td>
</tr>
<tr>
<td>3. Frequent relapse</td>
<td>Maintenance prednisolone 0.1–0.5 mg/kg/alternate days for 3–6 months, then reduce</td>
</tr>
<tr>
<td>4. Relapse on prednisolone</td>
<td>Levamisole 2.5 mg/kg/alternate days for 4–12 months</td>
</tr>
<tr>
<td>5. Relapse on prednisolone</td>
<td>Steroid side effects or risk factors</td>
</tr>
<tr>
<td>6. Relapse on prednisolone</td>
<td>Cyclophosphamide 3 mg/kg/day for 8 weeks</td>
</tr>
<tr>
<td>7. Relapse on prednisolone</td>
<td>Cyclosporin 5 mg/kg/day for one year</td>
</tr>
</tbody>
</table>
| 8. Relapse post-cyclosporin | 7
A characteristic feature of SSNS is the tendency to relapse. The ISKDC originally reported a relapse rate of 60% but more recent data suggest rates of 76 to 97% and frequently relapsing rates of up to 50%. There are no predictors of the risk of subsequent relapse after the initial episode, but the number of relapses within the first six months of presentation is highly predictive of the subsequent course. Relapses generally respond much better than the initial attack and this may be related to the pharmacokinetics of prednisolone and the severe hypoproteinaemic state of many children at presentation. Proteinuria is lost after a similar treatment period on each occasion. Opinions differ on the timing of treatment in SSNS relapses as it has long been known that up to 25% spontaneously remit (about 3% per day). Treatment can usually be deferred for up to five days, but children should not be allowed to become oedematous. Prompt treatment is necessary in those children who have a past history of severe relapses, especially if complicated by hypovolaemia.

Intensification of relapse treatment has little effect on the subsequent relapse rate and the consensus view recommends the same regimen for relapses as for initial treatment, that is prednisolone 60 mg/m²/day until remission, followed by 40 mg/m² on alternate days for four weeks (table 3).

Children with a frequently relapsing or steroid dependent course, need individualised treatment and should be managed in conjunction with a paediatric nephrologist. Although there are no data on the merits of long term maintenance prednisolone versus repeated standard relapse treatment, most authorities favour the former approach. Treatment should be given for a minimum of 3–6 months as an alternate day single dose regimen rather than intermittently, although selective patients may perhaps benefit from long term daily treatment. The dose should be sufficient to maintain remission but as low as possible in order to minimise side effects. Most school age children can tolerate 0.5–0.6 mg/kg body weight on alternate days and the preschool child up to 1 mg/kg body weight on alternate days.

Parents should be taught how to test the urine for protein and to record the result together with the day’s steroid dosage in a diary.

Steroid side effects

The side effects of steroids are numerous, well recognised, and should not be taken lightly. A recent review of several large series of children given steroids for a variety of renal diseases, revealed a treatment related mortality of 5%. In order to prevent toxicity, patients on long term steroids should be seen every three months for blood pressure and growth measurement, and reviewed yearly for cataracts. Pubertal status should be assessed as appropriate and bone age should be assessed if growth is failing. The children should have a steroid warning card and receive prophylaxis for surgery, anaesthesia, or intercurrent illness for a minimum of three months after stopping steroids.

Complications

The mortality rate for SRNS is 1–4%, the main complications being infection and thrombosis. Improved surveillance and more aggressive management should reduce this figure.

Infection

S pneumoniae is an important cause of infection and many centres routinely use polyvalent pneumococcal vaccine but pneumococcal sepsis and peritonitis have been reported in immunised children. Chickenpox and measles remain the major viral threats to the immunosuppressed child. The varicella zoster immunity status could be checked as part of the routine evaluation, and many children are vulnerable. If there is exposure while taking high dose prednisolone or alkylating agents, zoster immunoglobulin should be given after discussion with the local virology laboratory. Acyclovir should be given as early as possible if the condition develops. Measles exposure necessitates checking of immunisation status with quarantine measures and gammaglobulin treatment for those at risk.

Nephrotic children should receive immunisations as normal unless they have been taking daily prednisolone for longer than one week. Under these circumstances live vaccine should be avoided until the patient has been off daily steroids for three months. Live vaccines can be given if the child is on a low dose alternate day corticosteroid regimen. Killed vaccines are best given when the child is in remission and inactivated poliomyelitis vaccine should be substituted for the live form. Live oral polio vaccine should not be given to siblings or close household contacts of children on high dose (60 mg/m²) prednisolone. Live vaccine should not be given concurrently with alkylating agents.

Thrombosis

Nephrotic patients are in a hypercoagulable state with high concentrations of fibrinogen, factor VIII: RAg and α₂-macroglobulin with a reduction in both functional and immunological antithrombin III. There is thus a tendency to arterial and venous thromboses. Aggressive investigation and treatment may be needed to prevent fatal episodes such as pulmonary thromboembolism.

Hyperlipidaemia

In those children who respond to steroids in the short term only dietary advice is required. Patients with persistent nephrotic states may need drug treatment, but the issue is not resolved.
ACUTE RENAL FAILURE

Acute renal failure occasionally occurs in SSNS. Oliguria with raised urea and creatinine concentrations suggest hypovolaemia and the need for albumin infusions. Interstitial nephritis due to drug hypersensitivity should be considered and referral to a paediatric nephrology centre is appropriate.

Information needs and psychosocial support

Parents may experience a great deal of concern and anxiety on realising that their child has a chronic illness with an uncertain aetiology and prognosis. Adequate information and often repeated explanation are essential. It should be made clear to the parents and child that MCNS is an essentially benign disorder, that progression to end stage renal failure necessitating dialysis or transplantation would not come about, and that though relapses might occur, perhaps over a period of many years, they will eventually cease, and that it is unusual for the disease to be active beyond puberty. An illustrated booklet about the condition covering aspects about the condition itself, drug treatment, renal biopsy and glossary terms is of great value* (A10).

When available a paediatric community nursing service can help support the families at home with reinforcement of information and monitoring of compliance. To be effective, information must be supplied in the appropriate language and the use of the unit social worker and interpreters may again be of great benefit.

Parents often find considerable benefit in meeting and discussing problems with other parents whose child also has nephrotic syndrome. They are often particularly concerned about the mood and behaviour changes induced by corticosteroids. A special parents’ group evening can be a useful form of support.

The general practitioner has a role in the management of intercurrent infection and of the whole family, but he/she also requires information about current management of nephrotic syndrome. Whether the family contact the paediatric unit directly or refer to the general practitioner for relapse treatment will depend upon local expertise. Particular care needs to be paid to immunisations and problems such as abdominal pain which require urgent assessment and admission.

Renal biopsy (A11)

Although minimal change is the predominant histopathological association of childhood nephrotic syndrome, other categories include focal segmental glomerulosclerosis, diffuse mesangial proliferation, mesangiocapillary glomerulonephritis, and membranous nephropathy. The pragmatic approach is that the histological category is less important than the response to corticosteroid in practice. Therefore the stages in a patient’s management when a biopsy should be considered are before treatment if the clinical features suggest a diagnosis other than MCNS or later if the child fails to respond to adequate steroid treatment. These children should be discussed with a paediatric nephrologist.

The consensus view is that the indications for renal biopsy are:

BEFORE TREATMENT

Recommended

- Onset at less than 6 months of age (congenital nephrotic syndrome types).
- Initial macroscopic haematuria (in the absence of infection) at any age.
- Persistent microscopic haematuria if associated with hypertension and/or low plasma C3, especially if female and/or adolescent.

Discretionary

- Onset between 6 and 12 months of age.
- Persistent hypertension, microscopic haematuria, or low plasma C3.
- Renal failure – persistent and not attributable to hypovolaemia.

AFTER TREATMENT

Steroid resistance

Persistence of proteinuria after four weeks’ daily prednisolone 60 mg/m² or equivalent: a biopsy should be arranged if practicable before completion of four weeks’ maintenance treatment, and is indicated whether the child is an early or late non-responder.

Frequent relapses

Biopsy is no longer advocated for SSNS when drugs such as cyclophosphamide are being considered, but may be indicated before ‘third line’ drugs such as cyclosporin.

A renal biopsy should only be performed in a major paediatric nephrology centre by a paediatric nephrologist or one in training where the through-put is sufficient to develop and maintain the technical skills of the nephrologist along with the interpretative experience of the histopathologist (A12).

Alternative treatment

INDICATIONS (A13)

There is not complete agreement about the precise stage at which alternative treatment to corticosteroids should be introduced, and the decision should be taken by a paediatric nephrologist. It is not necessary to perform a renal biopsy in this situation as the decision on alternative treatment is seldom influenced by histopathology in SSNS. Alternative treatment for SSNS should be considered in the following circumstances:

1. Relapse on prednisolone dosage >0.5 mg/kg body weight/alternate days plus one or more of the following: (a) unacceptable side effects of corticosteroid treatment; (b) high risk of toxicity – boys approaching puberty or diabetes; (c) unusually severe relapses: hypo-

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*Childhood Nephrotic Syndrome, a guide to the treatment and management, is available from the Nottingham Paediatric Renal Unit, City Hospital, Nottingham NG5 1PB.
volaemia or thrombosis; and (d) inadequate facilities for follow up or concern about compliance.

(2) Relapse on prednisolone dosage >1 mg/kg body weight/alternate days.

THERAPEUTIC OPTIONS

There are three effective drugs in addition to corticosteroids in SSNS:

(1) Alkylating agents: cyclophosphamide and chlorambucil have a powerful long lasting effect that has been clearly shown in controlled trials.32-34

(2) Levamisole, which has a weak steroid sparing effect.35

(3) Cyclosporin, which has a suppressive effect attested by many reports36 but which has only recently been confirmed by controlled trial.37

A strategy for different levels of management of SSNS is shown in table 3. In the UK the first alternative to steroids is usually cyclophosphamide, although in the rest of Europe chlorambucil is often preferred. Alkylating agents may cause bone marrow suppression, increased susceptibility to infection, hair loss, azoospermia, malignancy, and mutations – their use is a very serious decision to be balanced against the risks of continued high dose corticosteroids or an inadequately controlled nephrotic state. The case for using drugs with such potential toxicity must therefore be clearly examined in each case, explained to the parents, and documented in the casenotes (A14).

Levamisole is appropriate for relatively milder cases in whom failure to control relapses is not too serious a matter. Cyclosporin is usually reserved for cases that continue to be steroid dependent despite a course of cyclophosphamide. It is beginning to be used in preference to cyclophosphamide in children approaching puberty, especially boys who are more vulnerable to testicular damage from cyclophosphamide than at an earlier age, and in whom the disease does not have long to run. It is, however, a difficult drug to use, and requires monitoring by blood concentrations and regular measurements of glomerular filtration rate. Its use should be supervised by paediatric nephrologists.

Other treatments that have previously been mooted but have not been shown to be effective include azathioprine, vincristine, dapsone, sodium cromoglycate, pulse methylprednisolone, and hypogallic diet.

Regional paediatric nephrology centres

(A15)

Regional paediatric nephrology centres should be able to provide advice to paediatricians on a 24 hour basis, and to accept transfer of complicated patients without delay. They should have full clinical and laboratory facilities for renal biopsy and publish quality control data on number of biopsies performed, complication rate, and proportion of diagnostic failures. Nephrotic children should be managed on a basis of shared care with district paediatricians in a 'nephrotic clinic' and a register should be maintained of all nephrotic children referred to the centre.

Transfer to an adult unit (A16)

In SSNS even after a five year remission period there remains a relapse rate of approximately 15%. Many individuals are therefore still at risk into early adult life.31 Continued surveillance by an adult nephrologist is therefore important for them especially as complications can arise during pregnancy as well as for a variety of employment and social reasons. The transfer can take place at the time of school leaving. Combined adult and paediatric nephrology clinics can ensure that problems such as steroid related growth disturbances continue to be monitored. However, location of the clinic is more important with adult patients as they are less keen to travel large distances compared with children who are usually brought by their parents.

The effects of drugs such as cyclophosphamide on fertility and their teratogen potential should not be forgotten in a newly adult population.38 39 At the time of transfer the individual needs to be in full possession of the facts regarding the drugs they received in childhood and their associated risks.


Editors’ comments

We now receive consensus statements from expert panels which cannot be amended in the light of comments from the referees. These statements are not cast in stone and on this occasion our referee drew attention to the following points.

Referee’s comments and responses from
Dr Alan Watson (convenor)

Point 1. There is no clear guidance as to which patients can be handled by a general paediatrician and at what stage referral to a paediatric nephrologist should be considered.

Most children with nephrotic syndrome are admitted and treated under the care of general paediatricians. Children between the ages of 1 and 10 years are very likely to have steroid responsive minimal change disease and so prednisolone treatment is usually initiated without a renal biopsy. Children should be referred to a paediatric nephrology centre at the outset if they are less than 1 year of age or older than 12 years, as minimal change disease is less likely and the pathology will need to be defined. Patients should also be referred if the child has atypical features with a mixed nephritic/nephrotic picture associated with macroscopic haematuria, and/or renal insufficiency or hypocomplementaemia or hypertension.

If, during the course of the initial steroid treatment complications ensue such as thrombosis, peritonitis, or acute renal failure then a paediatric nephrologist’s opinion should be sought. All patients who do not respond to 28 days of daily prednisolone are classified as early steroid resistant and should be referred for consideration of renal biopsy and further management. Steroid resistance developing in subsequent prednisolone courses, steroid toxicity, and consideration of cyclophosphamide treatment also warrant discussion and possible referral to a paediatric nephrologist.

Point 2. The definition of congenital, primary, and secondary nephrotic syndromes are not clearly made. There is some confusion created between the clinical and histological categories which should be clarified.

Definitions of congenital, primary, and secondary nephrotic syndromes are beyond the remit of the paper and readers are referred to standard textbook definitions and further discussion of clinical and histological categories.¹

Point 3. The use of diuretics in an oedematous nephrotic should be expanded. It may not be wise to recommend that a general paediatrician should prescribe frusemide to a nephrotic, without prior volume expansion or discussion with a paediatric nephrologist. Attention should be drawn to the problems of spironolactone in the presence of hyperkalaeamia.

The question of diuretics in the management of the oedematous nephrotic child was discussed at some length by the expert panel. It was felt that patients could be managed safely with the doses of frusemide (1-2 mg/kg/body weight/day) and spironolactone (2 mg/kg/body weight/day) as specified so long as the children were carefully assessed for signs of hypovolaemia. Spironolactone is unlikely to result in hyperkalaeamia when combined with frusemide at this dosage and when there is no renal insufficiency. The paediatric nephrologist should be consulted if the child’s oedematous state becomes more troublesome as the combination of metolazone and frusemide might be suggested but this will require closer monitoring of the plasma electrolytes.

Point 4. Clearer guidance should be given on the dose of steroids that would allow live vaccines to be given safely.

Use of live vaccinations should be avoided until the child has been off daily steroids for at least three months but are permissible if the child is on alternate day steroids (<0.5 mg/kg/body weight/day).

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