Advances in the Management of Steroid Sensitive Nephrotic Syndrome in Children

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**CASE DEFINITION**

* Heavy proteinuria defined as:
  - 3+/4+ on urinary dipsticks analysis
  - random spot urine protein: creatinine ratio $>2$ [mg/mg]
  - urine albumin excretion $>40$mg/m$^2$/hour

* Hypoalbuminaemia  (serum albumin $<2.5$g/dl)

* Hyperlipidaemia  (serum cholesterol $>200$mg/dl or $6.5$mmol/l)

* + oedema

Supportive criteria

* $\alpha 2$ globulin
<table>
<thead>
<tr>
<th>Definitions</th>
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<tbody>
<tr>
<td><strong>Remission</strong></td>
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<td>Urine protein &lt;4 mg/m²/h or nil/trace on Albustix for 3 consecutive early morning specimens.</td>
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<tr>
<td><strong>Relapse</strong></td>
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<td>Urine protein &gt;40 mg/m²/h or Albustix 3+ or 4+ for 3 consecutive early morning specimens, having been in remission previously.</td>
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<td><strong>Frequent relapses</strong></td>
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<td>Two or more relapses within 6 months of initial response or four or more relapses in any 12 months.</td>
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<td><strong>Steroid dependence</strong></td>
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<td>Two consecutive relapses during corticosteroid therapy or within 14 d of its discontinuation.</td>
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<td><strong>Steroid resistance</strong></td>
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<td>Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for 4 wk (in some institutions 3 methylprednisolone pulses are given in addition before steroid resistance is diagnosed).</td>
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<td><strong>Early nonresponder</strong></td>
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<td>Steroid resistance during the first episode.</td>
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<td><strong>Late nonresponder</strong></td>
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<td>Steroid resistance in a patient who had previously responded to corticosteroid therapy.</td>
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</tbody>
</table>
1970s

Racial differences

Whites
Indians

Pattern of disease similar to industrialised countries

Blacks

Distinct differences
CLASSIFICATION

AGE ON ONSET

AETIOLOGY

HISTOLOGY

GENETICS

RESPONSE TO STERIODS
- Loss of size selectivity and charge selectivity of the GBM.

- Immune pathogenesis – alteration in T-lymphocyte number and/or function with release of circulating factors inducing proteinuria.

- Cytokines (IL-4, IL-13, TGFβ) and kinins play a role together with the renin-angiotensin system.

- Genetic mutations in SRNS and associations with HLA class II antigens.
CLINICAL PRESENTATION

- Oedema (periorbital and pedal)
- Ascites → anasarca
- Massive proteinuria
- Haematuria (rarely macroscopic)
- Fever and infection
- Allergies and infection (URTI)
HISTOPATHOLOGICAL CLASSIFICATION

* Minimal change disease
* Focal segmental glomerulosclerosis
* Membranous nephropathy
* Proliferative glomerulonephritis
* Membranoproliferative glomerulonephritis
* Miscellaneous
STEROID SENSITIVE NEPHROTIC SYNDROME
**Introduction**

- NS is one of the most frequent glomerular diseases in children.
- Children achieving complete remission following treatment with corticosteroids are classified as having steroid sensitive NS.
- In developed countries over 80% of children have SSNS.
- Responses to steroid is tempered in developing countries in black children.
- Majority of black children have SRNS.
- >95% have minimal change disease in histopathology.
- ±5% have diffuse mesangial proliferation or FSGS.

*Gipson DS et al Pediatrics 2009 124(2): 747-57*
*Hogg RJ et al Pediatrics 2003,111,1416*
Outcome of SSNS

- Over 60% of children with SSNS have multiple relapses.
- About half of these will develop steroid dependent NS.
- These children receive multiple courses of steroids and are at high risk of developing steroid toxicity.
- The majority require steroid sparing agents to reduces the adverse effects seen with long-term use of steroids.

Common adverse effects of steroids

- Immunosuppression
- Psychosis/ mood substances
- GI perforation/ulcer
- Seizures
- Glucose intolerance
- Hirsutism
- Hypertension
- Pancreatitis
- Cataracts / glaucoma
- Myopathy
- Osteopenia / osteoporosis
- Cushings syndrome
- Impaired wound healing
- Insomnia
- Headaches
- Menstrual irregularities
- Easy bruising
- Muscle weakness
Steroid sparing agents

- Levamisole
- Cyclophosphamide
- Mycophenolate Mofetil (MMF)
- Calcineurin Inhibitors (cyclosporin and tacrolimus)
- Rituximab
- Vincristine
Management of initial episode

- Exclude secondary cause of NS
- >90% of children with MCD will respond to steroids within 8 weeks
- No need for biopsy initially if following criteria are satisfied.
  - Age >1yr and < 10yrs
  - Absences of HPT and gross haematuria
  - Normal kidney function
- Appropriate Rx of the initial episode determines long-term outcome.
- Only prednisone or prednisololone should be used as other steroid preparations not shown to be of proven benefit.
Prednisolone dosing

* 2mg/kg/day (max. 60mg in single or divided doses) x 6 weeks.
* 1.5mg (max 40mg) as single morning dose on alternate days x 6 weeks
* Tapering dose on alternate days x 2-4 months

The benefits and safety of prolonged steroid therapy, beyond 12-weeks requires further studies.

Hodson EM et al Cochrane Database System Rev 2007
Treatment of Relapse

* Exclude infection and treat appropriately.
* Use prednisone or prednisolone.
* 2mg/kg/day (single or divided doses, max 60mg) until protein is trace or nil for 3 consecutive days.
* If patient not in remission despite 2 week treatment with daily prednisone, treatment extended for 2 more weeks.
* 1.5mg/kg/day single morning dose an alternate days x 4 weeks.
* Then discontinue steroids.
Management of Steroid Dependent NS

- Biopsy not usually indicated.
- Maintenance dose of prednisolone on alternate days should not exceed 0.5mg/kg.
- Administered for 9-18 months.
- Closely monitor growth, blood pressure, feature of steroid toxicity.
- If higher doses needed then consider steroid sparing agents.

Hodson EM et al Cochrane Database System Rev 2007
Impact of IV MP with Prednisolone Alone as Initial Treatment in Adult-Onset Minimal Change Disease

- Paediatric randomised controlled study showed IV MP + prednisone achieved remission earlier than patients treated with prednisone alone.

*B r M e d J ( C l i n R e s E d) 291:1305-08, 1985*

Japanese non-randomised controlled study in adult MCD showed IV MP followed by cyclosporine achieved shorter time to remission compared with cyclosporine monotherapy and prednisolone monotherapy.


- Japanese retrospective cohort study in adults showed IV MP + Prednisolone achieved significantly earlier remission but earlier relapses.

*Nephrology (Calton) 17:263-68, 2012*

Comparison of Methylprednisolone Plus Prednisolone with Prednisolone Alone as Initial Treatment in Adult-Onset Minimal Change Disease: A Retrospective Cohort Study

ACTH – based therapy

- Was approved 50 years ago
- >3700 patients have been treated with ACTHar or ACTH 1-24.
- Best response is in idiopathic MN.
- Less well studied in other histological forms of NS.

Petricelli C et al Am J Kid Dis. 2006;47(2);233-240
Almost all patients maintain normal kidney function.

- Number of relapses is the only predictive factor of relapses occurring later in life.

- Long-term sequelae related mainly to side effects of medication.
Conclusion

- Still missing the magic bullet.
- Steroids remain the mainstay of treatment.
- Introduction of newer steroid sparing agents has improved the prognosis and minimised the long-term sequelae of steroid treatment.