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 >40mg/m^2/hour**
* **Hypoalbuminaemia (serum albumin <2.5g/dl)**
* **Hyperlipidaemia (serum cholesterol >200mg/dl or 6.5mmol/l)**
* **± oedema**

Supportive criteria

* **↑α 2 globulin**

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Archives Dis Child 1994; 70: 151-157

Definitions

Remission	**Urine protein <4 mg/m²/h or nil/trace on Albustix for 3 consecutive early morning specimens.**
Relapse	**Urine protein >40 mg/m²/h or Albustix 3+ or 4+ for 3 consecutive early morning specimens, having been in remission previously.**
Frequent relapses	**Two or more relapses within 6 months of initial response or four or more relapses in any 12 months.**
Steroid dependence	**Two consecutive relapses during corticosteroid therapy or within 14 d of its discontinuation**
Steroid resistance	**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).**
Early nonresponder	**steroid resistance during the first episode.**
Late nonresponder	**steroid resistance in a patient who had previously responded to corticosteroid therapy.**

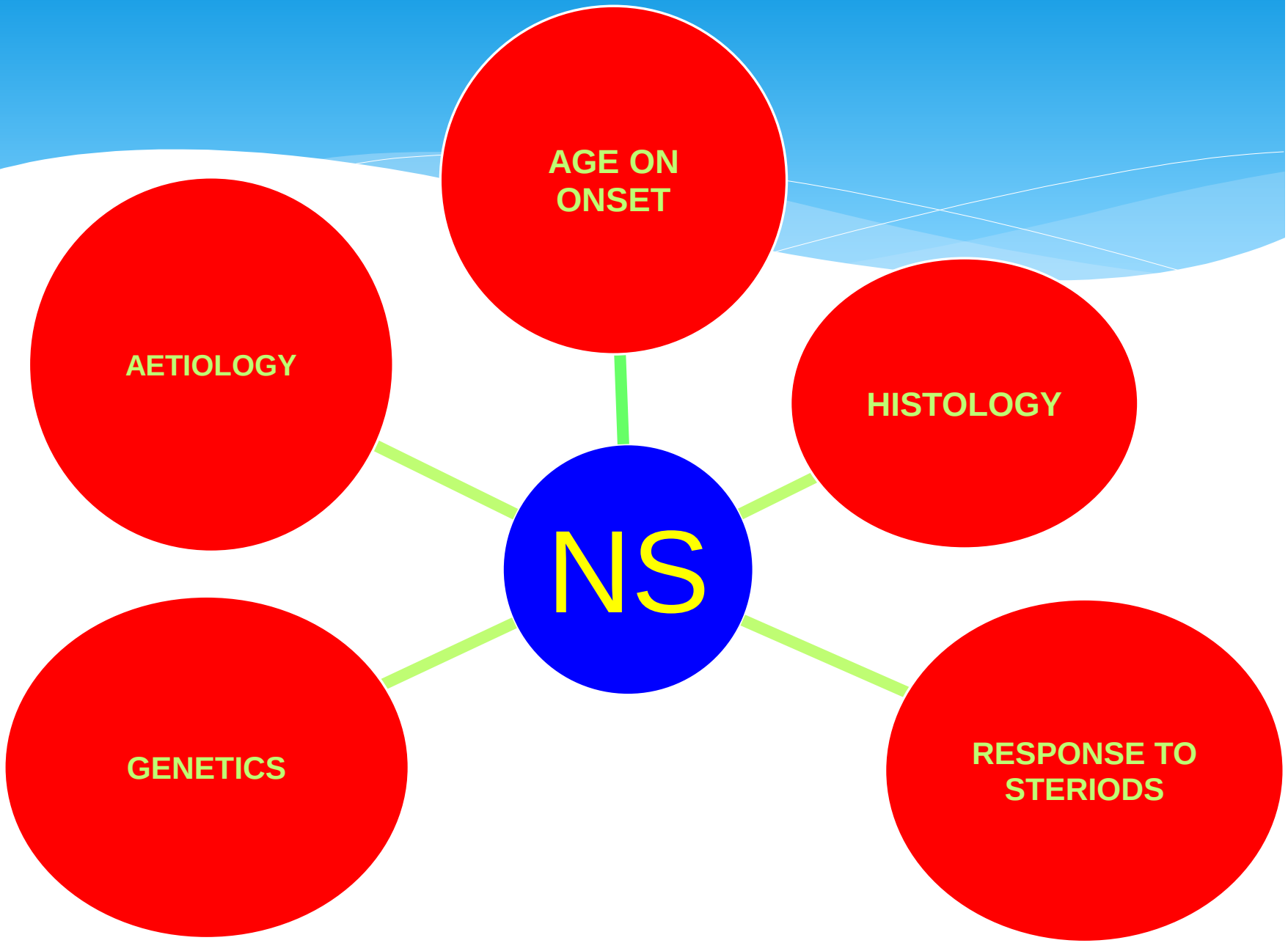
Indian Journal of Pediatrics 2012; 79(8): 1045-55.

NS IN AFRICA

1970s → Racial differences

Whites Indians	→	Pattern of disease similar to industrialised countries
Blacks	→	Distinct differences

CLASSIFICATION



PATHOPHYSIOLOGY

- 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.

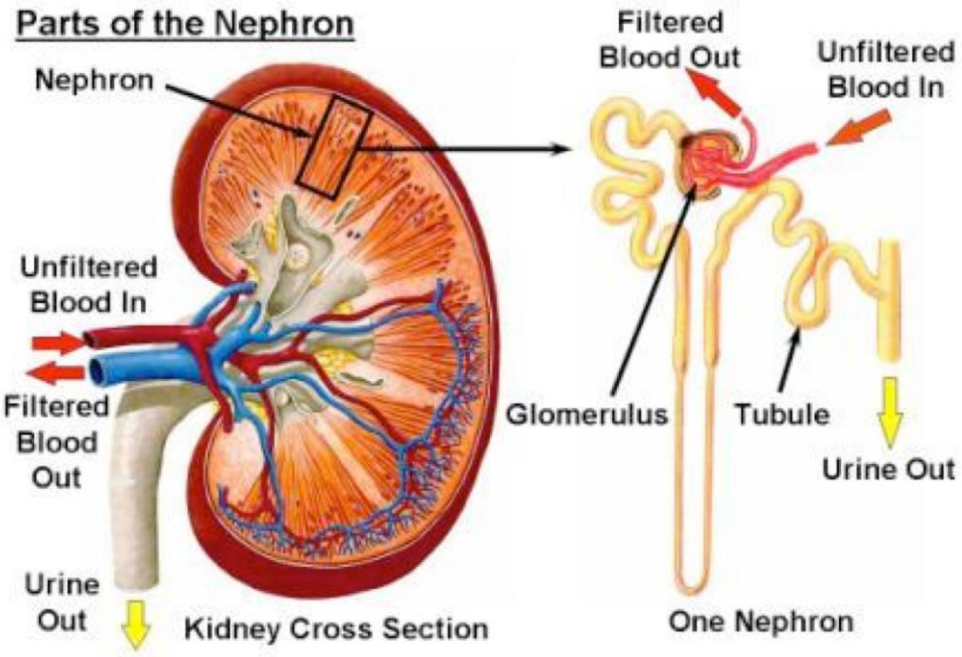
CLINICAL PRESENTATION

* 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 SENTITIVE 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
Bhimma et al Pediatr Nephrol 1997; 11(4): 429-34.

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.

J Pediatr 1981; 98(4): 561-4.
Hogg RJ et al Pediatrics 2003; 111(6 Pt 1): 1416-21.

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 prednisolone 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 4weeks.
* 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 them 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.**

Br Med J(Clin Res Ed) 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.

Intern Med 43:668-73,2004.

- **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

Clin J Am Soc Nephrol 9:1040-1048, June, 2014

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.

Hladunewich, M.A. et al.. Nephrol Dial Transplant. 2014; 29:1570-1577

Penticelli C et al Am J Kid Dis. 2006;47(2);233-240

Long-term outcome

* 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.