
• “when bubbles settle on the surface of the urine, it indicates a disease of the kidney and that the disease will be protracted” Hippocrates.
• Cornelus Roelans of Belgium described in 1484 a child with “whole body swelling” and treated him with warm wraps soaked with herbs.
• Theodore Zwinger of Basel in 1722 described nephrotic syndrome in children with swelling and decreased urine output.
• Coagulability of the urine, edema, and kidney disease was recognized by Richard Bright in early 1800s.
• By 1830 NS was defined as albuminuria, hypoalbuminemia, milky appearance of blood, and edema with subsequent autopsy findings of diseased kidneys.
• Virchow described “parenchymatous nephritis” with pathologic tubular involvement.
Minimal Change Disease
Etiologies of Idiopathic Nephrotic Syndrome

- T and B cell lymphocyte dysfunction
- Genetic and environmental risk factors
- Ancestry may play a role in susceptibility to INS
- Differences in genomic characteristics, allele frequencies & linkage disequilibrium.
- Identifying risk loci via genome-wide associations has provided new and useful information.
THE EFFECT OF ADRENOCORTICOTROPHIC HORMONE ON CHILDREN WITH THE NEPHROTIC SYNDROME. II. PHYSIOLOGIC OBSERVATIONS ON DISCRETE KIDNEY FUNCTIONS AND PLASMA VOLUME

BY HENRY L. BARNETT, CAROLYN W. FORMAN, HELEN McNAMARA, AND WALLACE W. MCCORORY

Unique Clinical Attributes of FSGS

- As a result of the reports of the ISKDC (1960-70's) FSGS emerged as a unique entity, distinguished from MCNS by its greater rate of steroid resistance & progression to renal failure.

Renal survival, analysed by response to IIS, is excellent in children with SRNS achieving full remission following IIS compared to patients being resistant to IIS. Ten-year ESRD-free survival rates were 94% (95% CI, 87% to 97%) in patients achieving full remission, 72% with partial remission & 43% resistant to IIS.

Agnes Trautmann et al. JASN 2017;28:3055-3065
Figure S-4: Renal survival by underlying histopathological diagnoses in 1156 performed kidney biopsy.

(A) Data by ethnicity shows frequently relapsing nephrotic syndrome at 6, 12, and 18 months from diagnosis. (B) Absolute total number of relapses by ethnicity. (C) Absolute number of relapses after treatment with cyclophosphamide. *P value ≤0.05; **P value ≤0.001.

Possible Risk Factors in NS

- 133 children in the 3 major ethnic groups were biopsied: 83 had MCD, 42 FSGS, and 8 non-specific changes.
- Ethnic differences: South Asian children had > 6 X higher incidence of NS vs Europeans or East/Southeast Asian children.
- Europeans had more relapses and steroid dependency.
- Novel genetic associations of HLA-DQA1 and PLCG2 with steroid-sensitive NS among Sri Lankan and European children (Ghadegesin et al, JASN 2015).
- Higher risk of progression from FSGS in AA with both APOL1 risk alleles.
- Susceptibility alleles in IgA nephropathy in Asians.
- Frequency of genetic variants indentified in the glucocorticoid receptor gene (*NR3C1*) & glucocorticoid induced transcript 1 gene may account for ethnic differences.

2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis

- Steroid-sensitive nephrotic syndrome (SSNS) & steroid-resistant nephrotic syndrome (SRNS) in children.
- Minimal-change disease (MCD) & idiopathic focal segmental glomerulosclerosis (FSGS) in both.
- Idiopathic membranous nephropathy (IMN).
- Idiopathic membranoproliferative glomerulonephritis (MPGN).
- GN associated with infections.
- Immunoglobulin A (IgAN) & Henoch-Schonlein purpura (hsp) nephritis.
- Renal vasculitis.
- Anti-glomerular basement membrane (anti-GBM) GN.

Idiopathic nephrotic syndrome affects 1-3 per 100,000 children <16 years of age.  
- 80% will respond to corticosteroids.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Definitions of nephrotic syndrome in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotic syndrome</td>
<td>Edema, uPCR ≥2,000 mg/g (≥200 mg/mmol), or ≥300 mg/dl or 3+ protein on urine dipstick, hypoalbuminemia ≤2.5 mg/l (≤25 g/l)</td>
</tr>
<tr>
<td>Complete remission</td>
<td>uPCR &lt;200 mg/g (&lt;20 mg/mmol) or &lt;1+ of protein on urine dipstick for 3 consecutive days</td>
</tr>
<tr>
<td>Partial remission</td>
<td>Proteinuria reduction of 50% or greater from the presenting value and absolute uPCR between 200 and 2,000 mg/g (20–200 mg/mmol)</td>
</tr>
<tr>
<td>No remission</td>
<td>Failure to reduce urine protein excretion by 50% from baseline or persistent excretion</td>
</tr>
<tr>
<td>Initial responder</td>
<td>Attainment of complete remission within initial 4 weeks of corticosteroid therapy</td>
</tr>
<tr>
<td>Initial nonresponder/steroid resistance</td>
<td>Failure to achieve complete remission after 8 weeks of corticosteroid therapy</td>
</tr>
<tr>
<td>Relapse</td>
<td>uPCR ≥2,000 mg/g (≥200 mg/mmol), or ≥300 mg/dl or 3+ protein on urine dipstick</td>
</tr>
<tr>
<td>Infrequent relapse</td>
<td>One relapse within 6 months of initial response, or one to three relapses in any 12-month period</td>
</tr>
<tr>
<td>Frequent relapse</td>
<td>Two or more relapses within 6 months of initial response, or four or more relapses in any 12-month period</td>
</tr>
<tr>
<td>Steroid dependence</td>
<td>Two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy</td>
</tr>
<tr>
<td>Late nonresponder</td>
<td>Persistent proteinuria during 4 or more weeks of corticosteroids following one or more remission</td>
</tr>
</tbody>
</table>

*uPCR* urine protein:creatinine ratio
<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Prolonged remission off therapy</td>
<td>Less effective in SD SSNS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitoring of blood count during therapy</td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td>Potential serious short- and long-term adverse effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only one course should be given</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Prolonged remission off therapy</td>
<td>Less effective in SD SSNS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitoring of blood count during therapy</td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td>Potential serious adverse effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only one course should be given</td>
</tr>
<tr>
<td>Levamisole</td>
<td>Few adverse effects</td>
<td>Continued treatment required to maintain remission</td>
</tr>
<tr>
<td></td>
<td>Generally inexpensive</td>
<td>Limited availability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not approved for SSNS in some countries</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Prolonged remissions in some children with SD SSNS</td>
<td>Continued treatment often required to maintain remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nephrotoxic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cosmetic side-effects</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Prolonged remissions in some children with SD SSNS</td>
<td>Continued treatment often required to maintain remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nephrotoxic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not approved for SSNS in some countries</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Prolonged remissions in some children with FR and SD SSNS</td>
<td>Continued treatment often required to maintain remission</td>
</tr>
<tr>
<td></td>
<td>Few adverse effects</td>
<td>Probably less effective than CNIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not approved for SSNS in some countries</td>
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</table>
Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome; Sinha et al. Kid Intl 2014.
Relapse-free survival

![Graph showing survival rates for Prednisolone (6-month group) and Placebo (3-month group). Hazard ratio 0.77 [95% CI 0.44–1.55]. Log rank P=0.15.]

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>6-Month</th>
<th>12-Month</th>
<th>18-Month</th>
<th>24-Month</th>
<th>30-Month</th>
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</thead>
<tbody>
<tr>
<td>6-Month</td>
<td>92</td>
<td>61 (31)</td>
<td>43 (18)</td>
<td>35 (4)</td>
<td>25 (6)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>3-Month</td>
<td>88</td>
<td>47 (39)</td>
<td>30 (15)</td>
<td>20 (6)</td>
<td>17 (1)</td>
<td>12 (0)</td>
</tr>
</tbody>
</table>
Survival free of frequent relapses

Time since randomization, months

Survival free of frequent relapses

Group | 6-Month | 3-Month | 0 | 6 | 12 | 18 | 24 | 30 |
<table>
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<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Month</td>
<td>92</td>
<td>81 (10)</td>
<td>56 (25)</td>
<td>47 (2)</td>
<td>35 (7)</td>
<td>22 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Month</td>
<td>88</td>
<td>62 (24)</td>
<td>49 (10)</td>
<td>36 (8)</td>
<td>30 (3)</td>
<td>18 (3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio 0.75 [95% CI 0.50–1.13]

Log rank $P=0.17$
New lessons from randomized trials in steroid-sensitive nephrotic syndrome: clear Evidence against long steroid therapy

Peter Hoyer, Kid Intl 2015
A randomized study on 3 vs 7-month prednisolone regimen for the initial episode of childhood idiopathic nephrotic syndrome at a large Saudi center; Al Talhi et al. Intl J Peds & Adol Med 2018

• Compared the standard 3 months of therapy with 60 mg/m2/day for 6 weeks followed by 40mg/m2 on alternate days for 6 weeks vs a 7 month treatment protocol with 60 mg/m2/day for 4 weeks followed by 40mg/m2 on alternate days for 8 weeks then 30mg/m2 on alternate days for 8 weeks followed by 20mg/m2 on alternate days for 8 weeks.

• Followed for 2 years; 60 subjects/group.
Supporting Evidence

• The 7 month protocol had:
  • longer time to first relapse
  • fewer relapses
  • less total steroid dose in first and second years of follow up
  • less side effects of corticosteroids
  • Evidence for longer treatment with steroids for initial presentation.
Rituximab (RTX)

• Specific B-cell depleting antibody (anti-CD20)
• One dose depletes B-cells in peripheral blood & tissues.
• Also affects T-cell subsets; binds to CD20 on B-lymphocytes.
• B-cell activating factor of the TNF family (BAFF) rises in response to rituximab.
• Potential effects on both B- & T-cell subsets may underlie any immunologic advantage.
Rituximab & the Podocyte

• May have non-immunological actions; binds sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) protein. Fornoni et al. Sci Trans Med 2011.

• Rituximab prevented podocyte SMPDL-3b downregulation, stabilized actin cytoskeleton & reduced podocyte apoptosis.

• Role in preventing recurrence of FSGS?
Rituximab for nephrotic syndrome in children; Iijima et al., Clin Exp Nephrol 2017
Mizoribine, MMF etc.

Cyclosporine

Placebo group can enter Pharmacokinetic study (RCRNS02)

Double-blind Random allocation Rituximab or placebo (375 mg/m²) weekly x4

Prednisolone treatment

Relapse of NS

Assignment at remission

Week 1 (Day 1)

Week 13 (Day 85)

Week 25 (Day 169)

Week 53 (Day 365)

Treatment failure (1) Relapse within week 13

Treatment failure (2) (3) FRNS/SDNS or SRNS within week 53
Rituximab in SDNS

• Rituximab should be considered only in children with SD SSNS who have continuing frequent relapses despite optimal combinations of prednisone & corticosteroid-sparing agents or who have serious adverse effects of therapy.

• A single open-labeled RCT with 54 subjects with SD SSNS dependent on both prednisone & CNIs found that RTX reduced rate of relapse at 3 months.

• Case series report prolonged remissions in 80% of children on RTX therapy with one-third experiencing fever, vomiting, diarrhea, skin rash, bronchospasm.

• Responders need less maintenance immunosuppression or none at all (25-83%).

• However, all patients treated in the RNRNS01 trial relapsed by 19 months after randomization.

• Need prospective studies for both MCK and FSGS using new anti-CD20 monoclonal antibodies.
Mycophenolate mofetil is inferior to tacrolimus in sustaining remission in children with idiopathic steroid-resistant nephrotic syndrome, Sinha et al. Kid Intl 2017
Relapse free-survival and survival free of treatment failure
Improving the evidence for the management of childhood Nephrotic syndrome, Crawford et al. Kid Intl. 2017

Steroid-resistant nephrotic syndrome

Calcineurin inhibitor + RAAS blockade

Resistant

Sensitive

Alternative agents

1. Calcineurin inhibitor
2. Alternative agents
3. Mycophenolate

Remission of proteinuria
A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome, Gruppen et al., the Levamisole Study Group, Kid Intl 2017
Time to 1\textsuperscript{st} relapsed was increased vs placebo & frequent relapses had better response vs steroid dependents
Efficacy and safety of mycophenolate mofetil versus levamisole in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial; Sinha et al. Kid Intl. 2019

207 Patients assessed for eligibility
58 Excluded
31 Received levamisole or MMF in past
14 High prednisolone threshold for relapses
2 Recent therapy with cyclophosphamide
7 Staying far
4 Declined consent

149 Randomized

76 Randomized to receive MMF
76 Received MMF as randomized

12 Months of follow-up
76 Follow-up for primary outcome available
12 Discontinued intervention
12 Treatment failure
  11 Occurrences of frequent relapses
  1 Significant steroid toxicity

76 Included in intent-to-treat analysis

73 Randomized to receive levamisole
73 Received levamisole as randomized

12 Months of follow-up
72 Follow-up for primary outcome available
1 Lost to follow up at 8 months
17 Discontinued intervention
15 Treatment failure
  12 Occurrences of frequent relapses
  2 Significant steroid toxicity
  1 Late steroid resistance
  2 Drug-related adverse event

73 Included in intent-to-treat analysis
1 Missing data; last outcome carried forward
Figure 2. Kaplan-Meier survival estimates. (a) Time to first relapse and (b) time to frequent relapses in patients treated with levamisole (blue line) or mycophenolate mofetil (MMF; red line). The median time to first relapse was similar for patients treated with MMF and levamisole (8.8 vs. 6.8 months; log rank $P = 0.25$). At 12 months, 15.5% of patients administered MMF and 17.7% of patients receiving levamisole showed frequent relapses ($P = 0.72$). Sinha et al. Kidney Int. 2019.
Levamisole for children with nephrotic syndrome: new evidence for the use of an "old" drug, Vivarelli et al. Kind Intl 2019
Proteinuria trend versus time for 7 patients who achieved remission with ACTH

24 Patients
7 responders (2 CR, 5PR)

Hogan J, et al. CJASN 2013;8:2072-2081
Participant flow through the ATLANTIS trial comparing ACTH with no relapse-preventing treatment with the option of crossover.

Chia-shi Wang et al. CJASN 2018;13:1859-1865
ACTH for Childhood Nephrotic Syndrome

Cohort
- 16 US sites
- 2-20 years old
- Frequently-relapsing or steroid-dependent nephrotic syndrome
- n = 31

ACTH (H.P. Acthar® gel)
- Children relapsed on ACTH treatment
- Median time-to-first relapse: 23 days

NO relapse-preventing treatment
- Children relapsed on no relapse-preventing treatment
- Median time-to-first relapse: 21 days

Conclusions
ACTH at 80 U/1.73m² twice weekly was ineffective at preventing disease relapses in pediatric nephrotic syndrome.


Chia-shi Wang et al. CJASN 2018;13:1859-1865
Effects of gluten-free, diary-free diet on childhood nephrotic syndrome and gut microbiota Uy, et. al. Peds Res ‘15

- Gluten-free & dairy-free diets may influence the composition & immune function of gut microbiota.
- Association between cow’s milk sensitivity & frequently relapsing, steroid sensitive, NS Sandberg et al. 1977.
- Elimination of specific food allergens resulted in remission.
- Gluten-free diet resulted in reduction of bacteria-induced cytokine production (TNF-a, IFN-gamma, Il-8 & 10) & total bacterial load.
- Complex relationship between diet, microbiome & immune system.
TABLE 1 Summary of the Clinical Features of the Study Patient and the Other 7 Cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (y) at Start of Gluten-Free Diet</th>
<th>Current Age (y)</th>
<th>Sex</th>
<th>NS Type (Pathology if Available)</th>
<th>Previous Immunosuppressive Therapy</th>
<th>Relapse Rate (No./Year) Prior/Post</th>
<th>Duration of Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>16</td>
<td>M</td>
<td>SD</td>
<td>Prednisone, tacrolimus, mycophenolate mofetil</td>
<td>Tacrolimus</td>
<td>4/1.5</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>12</td>
<td>M</td>
<td>SD (MCD, IgM variant)</td>
<td>Prednisone, cyclophosphamide</td>
<td>None</td>
<td>4/0</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>15</td>
<td>M</td>
<td>SD</td>
<td>Prednisone, cyclophosphamide, mycophenolate mofetil, cyclosporine, tacrolimus, galactose, rituximab</td>
<td>None while on the diet for 7 mo</td>
<td>2/0 Relapse rate rose to 3 per year when diet was stopped</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
<td>12</td>
<td>M</td>
<td>SD</td>
<td>Prednisone, cyclophosphamide</td>
<td>None</td>
<td>4/1</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>7</td>
<td>M</td>
<td>FR</td>
<td>Prednisone</td>
<td>None</td>
<td>4/1</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>26</td>
<td>F</td>
<td>SD</td>
<td>Prednisone, cyclophosphamide, methylprednisolone IV</td>
<td>None</td>
<td>3/1</td>
</tr>
<tr>
<td>7</td>
<td>7.5</td>
<td>9</td>
<td>F</td>
<td>SR (FSGS)</td>
<td>Prednisone, tacrolimus for 6 mo</td>
<td>Prednisone, low dose every other day, tacrolimus</td>
<td>Persistent</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>3.5</td>
<td>M</td>
<td>Partial response to steroids</td>
<td>Prednisone, cyclosporine</td>
<td>None</td>
<td>1/1</td>
</tr>
</tbody>
</table>

F, female; FR, frequent relapse; FSGS, focal segmental glomerulosclerosis; IgM, immunoglobulin M; IV, intravenous; M, male; MCD, minimal change disease; SR, steroid resistant; SD, steroid dependent.
Microbiome & CKD

• Progressive SRNS & CKD is associated with gut dysbiosis & gut-derived uremic toxins.
• Overgrowth of pathogenic bacteria triggers harmful inflammatory response by secreting IL-1 & 6.
• Results in systemic inflammation, worsening CKD & CVD.
• Need to fill the gaps in the microbiota, exposures, epigenetics & immune dysregulation.
Membranous Nephropathy

- Idiopathic MN accounts for 1.5% of childhood nephrotic syndrome; presents around 10 yrs of age.
- Secondary MN is seen with: SLE, hepatitis B, drugs and toxins.
- Major advancement in its pathophysiology has been the discovery of the podocyte receptor antiphospholipase A2 receptor (PLA2R) antibodies found in 70% of primary adults with MN.
- Treatment of the secondary type is specific for the etiology.
- For idiopathic, children without nephrotic syndrome are given ACEIs/ARBs and supportive therapy without immunosuppressants.
- Those with NS especially if decreased kidney function or fibrosis on biopsy, may receive alkylating agents, calcineurin inhibitors, or rituximab.
Nephrotic syndrome

PLA2R antibody

Positive → Risk assessment

High risk* → Kidney biopsy

Low risk* → No kidney biopsy
  Supportive therapy

Negative

Kidney biopsy

Risk assessment

High risk* → Supportive therapy and consider immunosuppressive therapy

Low risk* → Supportive therapy
Membranoproliferative Glomerulonephritis, C3 Glomerulopathy, and Immune-Complex-Mediated Membranoproliferative Glomerulonephritis

- MPGN is a clinically diverse group of diseases with common histologic findings and low C3 in 80-95%.

- Further characterizations is based on location of immune deposits: type 1 (subendothelial); type 2 (dense deposit disease DDD); and type 3 (subendothelial and subepithelial).

- New classification is based on whether deposits are C3G (C3 glomerulopathy) or immunoglobulin mediated (IC-MPGN).

- These account for 7.5% of nephrotic syndrome cases in children with onset in late childhood or adolescence.

- Outcome: 50% of C3 and 90% of IC-MPGN progress to ESRD with 10-20 years respectively.

- Treatment is limited; corticosteroids, MMF, and rituximab have been used along with ACEIs/ARBs with limited success.

- Recently, targeted complement pathway inhibitors are being tested in C3G.
Long-term Outcomes of Childhood Onset NS

• Life-course approach to optimizing health outcomes recognizes that exposures in childhood can affect risks for adult-onset disease.
• Retrospective chart reviews provide the only data.
• Relapses occur in adulthood 5-40%, hypertension, decreased GFR.
• Immunosuppression-related: obesity, growth failure, osteoporosis, fractures, cataracts, infertility, malignancy.
• Psychosocial: educational status, employment, martial status adversely affected.
• Higher lipid abnormalities & cardiovascular risks.
• Patient registries like cNEPTUNE and CureGN will offer opportunities to track subjects over time and when transitioned to adult care.
Frost Valley YMCA Summer Kidney Camp Program of the Ruth Carole Gottscho Foundation