NEPHROTIC SYNDROME: A SERIES OF UNFORTUNATE CASES

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AN APPROACH

HISTOPATHOLOGICAL DIAGNOSIS

- Minimal change
- Membranous GN
- Focal segmental GN
- C3 Glomerulonephritis (MPGN I and III)
- Dense Deposit Disease (MPGN II)
- IgA Nephropathy
  - Previous viral infection
- Crescentic GN (Rapidly Progressive GN)

CLINICAL ASSESSMENT

- Nephrotic Syndrome (presumed minimal change/FSGS in African patients)
- Nephritic Syndrome
- Mixed

INVESTIGATE AND TREAT THE PRESENTING CLINICAL PICTURE

BIOPSY TO GUIDE DEFINITIVE MANAGEMENT
CASE 1: PATIENT GLOM

- 5 year old male patient referred from district hospital
  - 4 days history of progressive body swelling

- DIFFERENTIAL CONSIDERED?
Examination: Bilateral pitting pedal oedema, soft heart sounds

- Urine dipstick: 3+ proteinuria, no haematuria
- UPCR: 0.45 mmol/l
- Albumin 19
- Cholesterol 7

CXR: small pleural effusions

WHAT TYPE OF NEPHROTIC SYNDROME IS THIS?
WHAT IS THE NEXT STEP?
THE URINE PROT:CREAT RATIO

- >0.2mmol/l = nephrotic range proteinuria
- >0.02mmol/l = abnormal proteinuria

- 0.02 – 0.2mmol/l requires workup
  - fever, systemic inflammation, heavy exercise, orthostatic

- EARLY MORNING URINE COLLECTIONS!
  - Repeat specimens; gauge response
  - Glomerular vs tubular proteinuria
INVESTIGATIONS: AETIOLOGY

- Auto-immune screen
  - Complement fractions, ANA, Anti-dsDNA Ab, proteinase 3 and myeloperoxidase antibodies
  - Consider further screening if above suggestive

- Infectious Screen
  - HIV/Hep B/Hep C/RPR/Malaria/Toxoplasmosis
INVESTIGATIONS: COMPLICATIONS

- FBC: Hb
  - Beware thrombo-embolism
  - Consider: Doppler US, CT Angio, CT Brain/MRI, antithrombin III, Protein C and S

- Iron deficiency anaemia (transferrin)

- CEU/CMP
  - ?underlying chronic kidney disease

- Infections
  - Vaccination status
  - Blood culture, peritoneal tap
  - CXR
DEFINITION: STEROID SENSITIVE NEPHROTIC SYNDROME

Following treatment with oral steroids

- URINE PCR <0.2mg/g OR 1+ PROTEINURIA IN URINE DIPSTICK FOR 3 CONSECUTIVE DAYS
WHY DO STEROIDS WORK?

- Pathogenesis
  - Disorder of T-cells; circulating permeability factor
    - Th2 response
  - Increased cytokine production
    - Eg. VEGF increases capillary permeability via Nitric oxide
  - Role of B-cells
    - Response to Ritximab (CD20 Monoclonal antibody)
  - CD80 is a T-cell co-stimulatory molecule
    - Expressed on podocytes
Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO

Rebecca M. Lombel · Debbie S. Gipson · Elisabeth M. Hodson
Chapter 3: Steroid-sensitive nephrotic syndrome in children

3.1: Treatment of the initial episode of SSNS

3.1.1: We recommend that corticosteroid therapy (prednisone or prednisolone)* be given for at least 12 weeks. (1B)

3.1.1.1: We recommend that oral prednisone be administered as a single daily dose (1B) starting at 60 mg/m²/d or 2 mg/kg/d to a maximum 60 mg/d. (ID)

3.1.1.2: We recommend that daily oral prednisone be given for 4-6 weeks (1C) followed by alternate-day medication as a single daily dose starting at 40 mg/m² or 1.5 mg/kg (maximum 40 mg on alternate days) (1D) and continued for 2-5 months with tapering of the dose. (1B)

3.2: Treatment of relapsing SSNS with corticosteroids

3.2.1: Corticosteroid therapy for children with infrequent relapses of SSNS:

3.2.1.1: We suggest that infrequent relapses of SSNS in children be treated with a single-daily dose of prednisone 60 mg/m² or 2 mg/kg (maximum of 60 mg/d) until the child has been in complete remission for at least 3 days. (2D)

3.2.1.2: We suggest that, after achieving complete remission, children be given prednisone as a single dose on alternate days (40 mg/m² per dose or 1.5 mg/kg per dose: maximum 40 mg on alternate days) for at least 4 weeks. (2C)
Steroid-sensitive nephrotic syndrome: an evidence-based update of immunosuppressive treatment in children

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8 year old male patient known to the paediatric renal service
  - DIAGNOSED with nephrotic syndrome
  - 3 relapses in the last 6 months when steroid regimen weaned

- Biopsy: MINIMAL CHANGE DISEASE
- Examination: striae on abdomen, BP >99th centile, early acanthosis nigricans

- WHAT TYPE OF NEPHROTIC SYNDROME IS THIS?
- WHAT IS THE NEXT STEP?
DEFINITIONS

FREQUENT RELAPSE: >2 episodes in 6 months or >4 episodes in 12 months

STEROID DEPENDANCE:
>2 relapses on steroid therapy, whilst weaning or within 14 days of ceasing corticosteroid therapy
3.3: Treatment of FR and SD SSNS with corticosteroid-sparing agents

3.3.1: We recommend that corticosteroid-sparing agents be prescribed for children with FR SSNS and SD SSNS, who develop steroid-related adverse effects. (1B)

3.3.2: We recommend that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for FR SSNS. (1B) We suggest that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for SD SSNS. (2C)

3.3.2.1: We suggest that cyclophosphamide (2 mg/kg/d) be given for 8–12 weeks (maximum cumulative dose 168 mg/kg). (2C)

3.3.2.2: We suggest that cyclophosphamide not be started until the child has achieved remission with corticosteroids. (2D)

3.3.2.3: We suggest that chlorambucil (0.1–0.2 mg/kg/d) may be given for 8 weeks (maximum cumulative dose 11.2 mg/kg) as an alternative to cyclophosphamide. (2C)

3.3.2.4: We suggest that second courses of alkylating agents not be given. (2D)
3.3.3: We recommend that levamisole be given as a corticosteroid-sparing agent. (1B)
3.3.3.1: We suggest that levamisole be given at a dose of 2.5 mg/kg on alternate days (2B) for at least 12 months (2C) as most children will relapse when levamisole is stopped.
3.3.4: We recommend that the calcineurin inhibitors cyclosporine or tacrolimus be given as corticosteroid-sparing agents. (1C)
3.3.4.1: We suggest that cyclosporine be administered at a dose of 4-5 mg/kg/d (starting dose) in two divided doses. (2C)
3.3.4.2: We suggest that tacrolimus 0.1 mg/kg/d (starting dose) given in two divided doses be used instead of cyclosporine when the cosmetic side-effects of cyclosporine are unacceptable. (2D)
3.3.4.3: Monitor CNI levels during therapy to limit toxicity. (Not Graded)
3.3.4.4: We suggest that CNI be given for at least 12 months, as most children will relapse when CNI are stopped. (2C)
3.3.5: We suggest that MMF be given as a corticosteroid-sparing agent. (2C)
3.3.5.1: We suggest that MMF (starting dose 1200 mg/m^2/d) be given in two divided doses for at least 12 months, as most children will relapse when MMF is stopped. (2C)
3.3.6: We suggest that rituximab be considered only in children with SD SSNS who have continuing frequent relapses despite optimal combinations of prednisone and corticosteroid-sparing agents, and/or who have serious adverse effects of therapy. (2C)
3.3.7: We suggest that mizoribine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (2C)
3.3.8: We recommend that azathioprine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (1B)
Rituximab Treatment for Relapsing Minimal Change Disease and Focal Segmental Glomerulosclerosis: A Systematic Review

Andreas Kronbichler\textsuperscript{a}  Julia Kerschbaum\textsuperscript{a}  Gema Fernandez-Fresnedo\textsuperscript{b}  Elion Hoxha\textsuperscript{c}  Christine E. Kurschat\textsuperscript{d}  Martin Busch\textsuperscript{e}  Annette Bruchfeld\textsuperscript{f}  Gert Mayer\textsuperscript{a}  Michael Rudnicki\textsuperscript{a}
CASE 3: PATIENT MEDULLA

- 9 year old female patient known to the paediatric renal service
  - DIAGNOSED with nephrotic syndrome

  - Biopsy: Focal segmental glomerulosclerosis
  - Received 9 weeks of steroids; dose as per KDIGO

  - Examination: BP>99th centile
  - Urine dipstick: 3+ proteinuria, haematuria

- WHAT TYPE OF NEPHROTIC SYNDROME IS THIS?
- WHAT IS THE NEXT STEP?
DEFINITION: STEROID RESISTANT NEPHROTIC SYNDROME

FAILURE TO ACHIEVE REMISSION WITHIN 8 WEEKS OF STEROID THERAPY
Treatment of steroid-resistant nephrotic syndrome in children: new guidelines from KDIGO

Rebecca M. Lombel · Elisabeth M. Hodson · Debbie S. Gipson
Chapter 4: Steroid-resistant nephrotic syndrome in children

4.1: Evaluation of children with SRNS

4.1.1: We suggest a minimum of 8 weeks treatment with corticosteroids to define steroid resistance. (2D)

4.1.2: The following are required to evaluate the child with SRNS (Not Graded):

- a diagnostic kidney biopsy;
- evaluation of kidney function by GFR or eGFR;
- quantitation of urine protein excretion.
4.2: Treatment recommendations for SRNS

4.2.1: We recommend using a calcineurin inhibitor (CNI) as initial therapy for children with SRNS. (1B)
   4.2.1.1: We suggest that CNI therapy be continued for a minimum of 6 months and then stopped if a partial
   or complete remission of proteinuria is not achieved. (2C)
   4.2.1.2: We suggest CNIs be continued for a minimum of 12 months when at least a partial remission is
   achieved by 6 months. (2C)
   4.2.1.3: We suggest that low-dose corticosteroid therapy be combined with CNI therapy. (2D)

4.2.2: We recommend treatment with ACE-I or ARBs for children with SRNS. (1B)

4.2.3: In children who fail to achieve remission with CNI therapy:
   4.2.3.1: We suggest that mycophenolate mofetil (2D), high-dose corticosteroids (2D), or a combination of
   these agents (2D) be considered in children who fail to achieve complete or partial remission with
   CNIs and corticosteroids.
   4.2.3.2: We suggest that cyclophosphamide not be given to children with SRNS. (2B)

4.2.4: In patients with a relapse of nephrotic syndrome after complete remission, we suggest that therapy be
restarted using any one of the following options: (2C)
   • oral corticosteroids (2D);
   • return to previous successful immunosuppressive agent (2D);
   • an alternative immunosuppressive agent to minimize potential cumulative toxicity (2D).
CASE 4: PATIENT TUBULE

- 3 month old female patient
  - 5 day history of progressive body swelling
  - Birth history – large placenta
  - Examination: Anasarca, no dysmorphism, no hepatosplenomegaly
  - Urine dipstick: 3+ proteinuria
  - UPCR: 0.35mmol/l
  - Albumin 14
  - Cholesterol 9

- WHAT TYPE OF NEPHROTIC SYNDROME IS THIS?
- WHAT IS THE NEXT STEP?
DEFINITION: CONGENITAL NEPHROTIC SYNDROME

NEPHROTIC SYNDROME DIAGNOSED WITHIN 3 MONTHS OF LIFE

CLASSIC TYPE = FINISH TYPE
**ADDITIONAL INVESTIGATIONS**

- FBC/CEU/CMP
- Thyroid function tests
- Hepatitis serology
- Auto-immune screen
- Infectious Screen

- KUB US
  - Rule out nephroblastoma if indicated

**GENETICS**
- Founder effect in SA (study at CHBH)
MANAGEMENT: ACE-I/ARB

- Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers
  - Decrease proteinuria and tubular injury
MANAGEMENT

- Vaccinate
  - Streptococcus pneumonia/Varicella
- Consider eltroxin

- ALBUMIN INFUSION WITH DIURETICS
  - Indication: congenital nephrotic, severe pleural/pericardial effusion

- Nephrectomy (Medical vs surgical)
  - Improve patient growth
- Pre-emptive dialysis and workup for transplant
CASE 5: PATIENT HENLE

- 6 year old patient with nephrotic syndrome and acute gastroenteritis
  - Sepsis/inflammation may have triggered a relapse
  - Patient oedematous

- THOROUGH CLINICAL ASSESSMENT
- STOP ACEI-I AND ARB
- STOP DIURETICS
- FLUID RESUSCITATE
  - Patients are underfilled and may require fluids
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That's all Folks!