Steroid Sensitive Nephrotic Syndrome

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Overview

• History of Nephrotic Syndrome
• Definitions and Classification of NS
• Epidemiology of NS
• Pathogenesis of NS
• Causes and Evaluation of NS
• NS-Related Complications
• Current and Potential Future Treatments for NS
History of Nephrotic Syndrome
History of Nephrotic Syndrome

- **1700-1800s** - Known that edema and proteinuria could be cured or remit spontaneously
- **1827** - Richard Bright described association between edema, proteinuria and the kidney (Bright’s Disease)
- **1905** - Friedrich von Muller separated kidney disease into “nephritis” and “nephrosis”
- **1929** - Henry Christian first used the term “nephrotic syndrome”
Clinical History of NS

• Mortality in NS
  • Prior to antibiotics: ~ 67% of children!
  • Introduction of sulfonamides (1939): ~ 42%
  • Introduction of penicillin (1944): ~ 35%
  • Introduction of steroids (1950s): ~ 9%
  • Present Day: ~3-7%
  • Most deaths now due to infection
• Clinical course more apparent after effective treatment identified
  • Not all patients responded!
Definitions and Classification of Nephrotic Syndrome
Definitions for NS

• Criteria for Diagnosis
  – Proteinuria (> 40 mg/m²/hr; protein:creatinine > 2.0; > 3.5 g/1.73 m²/24 h)
  – Hypoalbuminemia (< 2.5 g/dL)
  – Edema

• Criteria for Remission
  – Proteinuria < 4 mg/m²/hr
  – Urine albumin dipstick 0 or trace for 3 days

• Criteria for Relapse
  – Proteinuria > 40 mg/m²/hr
  – Urine albumin dipstick 2+ or greater for three days
Classification of NS

• Steroid Sensitive NS (SSNS; 40%)
  – Remission with oral steroids alone

• Frequent Relapsing NS (FRNS; 20%)
  – Remission but ≥4 relapses in any 12-month period

• Steroid Dependent NS (SDNS; 20%)
  – Relapses while still on tapering steroids
  – Relapses within 2 weeks of stopping steroids

• Steroid Resistant NS (SRNS; 20%)
  – No remission after 4-8 weeks of oral steroids
  – Controversial due to inconsistent definition!
Epidemiology of Nephrotic Syndrome
Epidemiology of NS

• Prevalence
  – Children: 16 cases/100,000 people (1 in 6000 kids)
• Annual Incidence
  – Children: 2-7 new cases/100,000 people/year
• Age-Related Correlations
  – 70-80% of pediatric patients are < 6 years old at DX
  – Increased probability of FSGS (SRNS) with increasing age
• Race-Related Correlations
  – Disease affects all races and ethnic backgrounds
  – African Americans at notably increased risk for FSGS
Pathogenesis of Nephrotic Syndrome
The Podocyte: The Key Cell Involved in NS

(Winn M P JASN, 2008)
Pathogenesis of NS

• Molecular mechanism(s) for development of nephrotic syndrome remain **unclear**

• Potential Underlying Causes
  – Soluble “factors”
  – Infectious agents
  – Genetic predisposition
  – Slit membrane dysregulation
  – Cell signaling dysregulation
  – Cytoskeletal dysregulation
  – Integrin dysregulation
Causes and Evaluation of Nephrotic Syndrome
Primary Causes of NS

• Minimal Change NS (MCNS)
• Focal Segmental Glomerulosclerosis (FSGS)
• Membranoproliferative Glomerulonephritis (MPGN)
  • Type I
  • Type II (Dense Deposit Disease)
  • Type III
• Idiopathic Membranous Nephropathy (IMN)
Secondary Causes of NS

**Systemic Diseases Associated with NS**
- Henoch-Schönlein Purpura (HSP)
- Systemic Lupus Erythematosus (SLE)
- Diabetes Mellitus
- Sarcoidosis

**Infectious Diseases Associated with NS**
- Hepatitis B (usually with IMN; rarely with MPGN)
- Hepatitis C (usually with MPGN)
- HIV (often with collapsing variant of FSGS)
Secondary Causes of NS

• **Hematologic Diseases Associated with NS**
  - Leukemia
  - Lymphoma (Hodgkin disease usually with **MCNS**)
  - Sickle Cell Anemia (usually with **FSGS**)

• **Drugs Associated with NS**
  - Non-steroidal anti-inflammatory drugs (usually **MCNS**)
  - Gold / Penacillamine / Many others!

• **Other Associations with NS**
  - Bee stings / Food allergies / Obesity / Pregnancy
Laboratory Evaluation in NS

- Serum Creatinine
  - Low (glomerular hyperfiltration)
  - Elevated (volume depletion vs. intrinsic disease)
    - MCNS: 32% of patients
    - FSGS: 41% of patients
    - MPGN: 50% of patients

- Hyponatremia
  - Typically mild
    - Due to volume overload
Laboratory Evaluation in NS

• Hypoalbuminemia
  – Due to inability of liver to make enough albumin to offset massive urinary losses
    • 400% increase in hepatic albumin mRNA synthesis
    • Overall decrease in total body albumin catabolism
    • Increased catabolism of albumin in renal tubules

• Urinary Losses of Plasma Proteins
  – Immunoglobulins / Complement components / EPO
  – Antithrombotic proteins / Transferrin / Hormone binding proteins
Pathophysiology of Edema in NS

• A state of total body **water and sodium** excess

• Pathogenesis of edema attributed to:
  – Hypoalbuminemia
  – Impaired sodium and water excretion

• **Normal State**: Close balance of forces
  – Hydrostatic – Favors transcapillary passage of fluid
  – Oncotic – Opposes transcapillary passage of fluid

• **Nephrotic State**: Imbalance of forces
  – Hypoalbuminemia \(\rightarrow\) decreased oncotic pressure
Current Treatment of Nephrotic Syndrome
Initial Treatment of NS

• Oral Glucocorticoids (GC)
  – Mainstay of therapy for NS for >50 years!
  – Initial course
    • 2 mg/kg/d (max = 60-80 mg/d) ÷ BID for 4-8 weeks
  – Clinical response
    • Children - 78% responded to 8 week course (ISKDC)
  – Variability in duration and maximal dosing create important challenges to advancing care!
    • Evidence to date challenging to interpret...
Disparity in Clinical Care in NS

Initial GC Therapy Regimen of Children with New Onset NS by 28 N. American Pediatric Nephrologists

(MacHardy, *Pediatr Nephrol*, 2009)
Alternative Treatments for FRNS and SDNS

• Daily oral GC - Mainstay of initial therapy
  – Neither target cell nor mechanism of action known
• Alternate day oral GC / IV pulse GC
• Alkylating agents (Cytoxan / chlorambucil)
• Levamisole (Europe; Not in US)
• Mycophenolate mofetil (MMF)
• Calcineurin inhibitors (cyclosporine / tacrolimus)
• Rituximab
Rituximab

- Chimeric monoclonal antibody targeted to deplete CD20+ B cells (via apoptosis)
- Many reports on idiopathic NS
  - Most in children / Few in adults
  - Few comparing to other drugs
- Use in SDNS (and FRNS) (7 studies = 210 pts)
  - To prolong remission / reduce GC side effects
  - Sustained remission in 54% (range = 36-72%)
    - 1 dose → 25-40% / 2-4 doses → >70%
- Use in SRNS Series (3 largest studies = 79 pts)
  - 27% had CR / 24% had PR / 49% had NR
  - Final Outcome = 29% in remission

(Sinha, Nat Rev Nephrol, 2013; Prytula, Pediatr Nephrol, 2010)
Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial

Kazumoto Iijima, Mayumi Sako, Kandai Naru, Rintaro Mori, Nao Tsuchida, Koichi Kamei, Kenichiro Muray, Kunihiko Aya, Koichi Nakamishi, Yoshiyuki Ohitomo, Shori Takahashi, Ryojiro Tanaka, Hiroshi Kato, Hidetoshi Nakamura, Kenji Ishikura, Shuichi Ito, Yasuo Ohashi, on behalf of the Rituximab for Childhood-onset Refractory Nephrotic Syndrome (RCONS) Study Group

- **Patients:**
  - 48 children (1-18 yr) with FRNS/SDNS

- **Treatment:**
  - Rituximab 375 mg/m² q week x 4
  - Placebo q week x 4

- **Primary Endpoint:**
  - Relapse-free period

- **Findings:**
  - Ritux (267 d) vs. Placebo (101 d) \(P<0.0001\)
  - SAE: Ritux (42%) vs. Placebo (25%; \(P=0.36\)

(iijima K et al., *Lancet*, 2014)
NS-Related Complications
NS-Related Complications

- Infection
- Acute Kidney Injury
- Thromboembolism
- Treatment-related
- Endocrine Abnormalities
- Hypertension
- Anemia
- Malnutrition
- Impaired Growth
NS-Related Complications

• Infections are the most common acute complication among pediatric NS hospitalizations in the US, but AKI is increasingly common.

(Rheault, Kerlin, Smoyer et al.; Pediatr Nephrol; 2014)
NS Complications: **Infection**

- **Clinical Presentation**
  - Abdominal pain / fever
  - Organisms: Cellulitis (*Staph*) / Peritonitis (*Pneumococcus*)

- **Risk Factors**
  - Low IgG levels
  - Impaired T lymphocyte function
  - Impaired tissue perfusion due to edema
  - Low levels of Factors B and D (↓ bacterial opsonization)
  - Immunosuppression (steroids and other drugs)
NS Complications: Acute Kidney Injury

• Clinical Presentation
  • Rising serum creatinine / Oliguria / Anuria

• Potential Causes
  • Intravascular volume depletion (transient; very common)
  • Renal interstitial edema (transient; very common)
  • Acute tubular necrosis (reversible; ± common)
  • Renal vein thrombosis (usually reversible; uncommon)
  • Acute cortical necrosis (irreversible; very uncommon)
NS Complications: Thromboembolism

• **Deep Vein Thrombosis:**
  - Poorly Functioning Catheters
  - Edematous extremity
  - Warm / painful extremity
  - Plethoric extremity

• **Pulmonary Embolism:**
  - Cough, SOB, Hemoptysis
  - Tachycardia

• **Renal Vein Thrombosis:**
  - Flank Pain
  - Macroscopic Hematuria
  - AKI (bilateral RVT)
High-Risk Clinical Groups

• Congenital NS
  – ~10% incidence of VTE
  – Less likely to remit?
  – More likely to require a central catheter?

• Secondary NS (vasculitides: SLE, HSP, DM, etc.)
  – ~17%
  – Synergistic hypercoagulable state due to inflammation?

• Membranous Nephropathy and/or class V SLE Nephritis
  – ~25% incidence of VTE
  – More physiologically similar to adult MN (~37% VTE)?

Treatment-Related Side Effects

- Corticosteroids
  - Hypertension / Cataracts
  - Bone demineralization / Growth impairment
  - Hyperlipidemia / Avascular necrosis of femoral head

- Alkylating Agents
  - Hemorrhagic cystitis (Cytox only)
  - ↑ risk for infections (Chlor > Cytox; 6.8% vs. 1.5%)
  - Seizures (Chlor > Cytox; 3.4% vs. 0%)
  - Leukopenia / Nausea / Dose-related oligospermia
  - Increased risk for malignancies
    - Lymphomas / Bladder cancer
Treatment-Related Side Effects

• Cyclosporine / Tacrolimus
  – Irreversible Interstitial Fibrosis (35-79%) (CsA)
  – Hypertension / Nausea / Vomiting
  – Headaches (CsA) / Seizure (Tacro)
  – Gingival Overgrowth / Hypertrichosis
  – Diabetes ? (Tacro, but not reported for SRNS yet)

• Mycophenolate Mofetil
  – Abd pain (25%) / Vomiting / Diarrhea / Leukopenia

• Rituximab
  – Infusion-related hypotension
  – Infusion-related fever and rigors
Potential Future Treatments for Nephrotic Syndrome
Current / Future Therapies for NS

- **Newer Available Treatments for NS**
  - Rituximab
  - ACTHar
  - Anti-TNFα Antibodies

- **Potential Future Treatments for NS**
  - PPARγ Agonists (Pioglitazone)
  - Abatacept (CTLA-4-Ig)
  - Lebrikizumab (Anti-IL-13 mAb)
  - p38 MAPK Inhibitors
Summary

• NS among most common kidney diseases in childhood
  • ~80% respond to GC / ~ 20% develop SRNS
• Mechanism still unclear but strongly related to podocyte
• NS with many primary and secondary causes:
  • Systemic diseases / Infections / Drugs / Allergic causes
• Multiple alternative treatments for FRNS and SDNS
  • Only partially effective and have significant side effects
• ~25% of NS admissions involve NS-related complication
  • Infection > AKI > Thromboembolism
  • Pneumonia now most common infection
  • >150% ↑ in AKI incidence in last decade !
• Several newer treatments becoming available
Nationwide Children’s Hospital
Clinical Cases of Nephrotic Syndrome
Clinical Case #1
Clinical Case #1

History:
• 9 year old boy with NS for 6 years
• Initially presented with SDNS
• After 4 relapses found to have MCNS 3 years ago
• On 60 mg prednisone for 8 weeks since last relapse

Exam:
• BP 147/85, Moderate pedal edema
• Moderate Cushingoid facies

Labs:
• Urine Pr/Cr 8.7, nl electrolytes, Alb 1.3, BUN 61, Cr 1.8

Impression and Plan of Care ???
NS AKI-Related Complications

- AKI is increasingly prevalent among toddlers, children, and adolescents hospitalized for NS in the US.

(Rheault, Kerlin, Smoyer et al.; *Pediatr Nephrol*; 2014)
Clinical Case #2
Clinical Case #2

– History:
  • 2 year old girl with second relapse of NS 5 months after initial diagnosis
  • Was off prednisone for 10 days prior to first relapse
  • Was on Prednisone 5 mg QOD prior to second relapse

– Exam:
  • Moderate facial and leg edema
  • Moderate ascites with moderate tenderness to palpation

– Labs:
  • Normal electrolytes, Alb 1.8, BUN 25, Cr 0.7

– Impression and Plan of Care ???
NS Infection-Related Complications

- Trends in the frequency of common infections in pediatric nephrotic syndrome (NS) hospitalizations.

(Rheault, Kerlin, Smoyer et al.; Pediatr Nephrol; 2014)
Clinical Case #3

– History:
  • 2 year old boy with edema of face after arising this AM
  • URI symptoms starting 3 days ago
  • No response to Benadryl...

– Exam:
  • Moderate facial edema
  • Moderate leg edema (L>R)

– Labs:
  • Normal electrolytes, Alb 1.6, BUN 35, Cr 0.8

– Impression and Plan of Care ???
# VTE in Childhood Nephrotic Syndrome

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- Arterial events are rare: ~0.3% of NS subjects; ~3% of TE in NS
Multifactorial Etiology of VTE

Vasculitis, Infection, Etc.

Diuretics?, Steroids?

Irritates Vessel, Infected?, Disrupts Laminar Blood Flow


Severity of Proteinuria

Compensatory Capacity, Acute Phase Response

44.8% of all NS-VTE

Time-Frames for VTE Occurrence

- Median time from NS diagnosis to VTE = 70.5 days

**Figure.** TE-free survival in A, patients with primary versus secondary NS ($P < .001$, log-rank test) and B, patients with membranous histology (MN or SLE class V) versus other diagnoses ($P < .0001$, log-rank test).