Nephrotic syndrome
ASPN
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Nephrotic syndrome: what we will discuss today

- What is nephrotic syndrome
- What are the presenting features of nephrotic syndrome: symptoms/signs/lab features
- What causes it?
- Types of nephrotic syndrome
- Management
- Complications
- Prognosis
- Clinical trials in the pipeline

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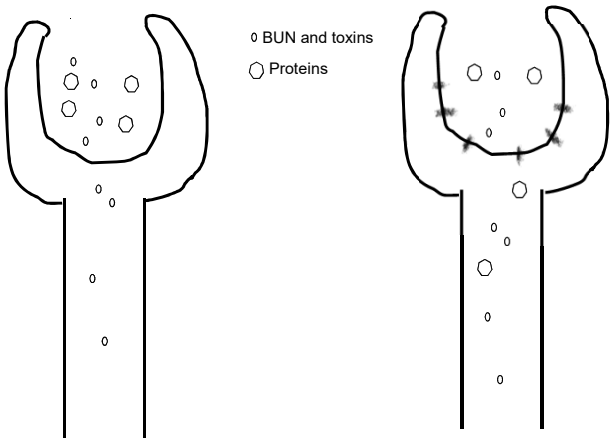
What is Nephrotic syndrome: condition where the glomerulus is leaky to protein



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Presentation: Signs/Symptoms/Laboratory manifestations

Triad:

- **Nephrotic range proteinuria**
  - Urine dipstick is 4+
  - Urine protein to creatinine ratio is >2.0, (normal is <0.2)
- **Low albumin**
- **Edema**

High cholesterol: either because of increased production by the liver or because of loss of lipoprotein lipase in the urine

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Presenting features

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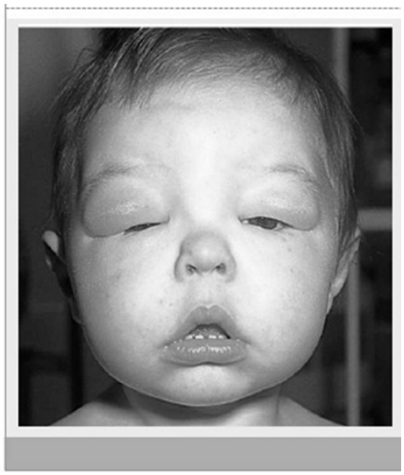
Presentation: swelling of the face



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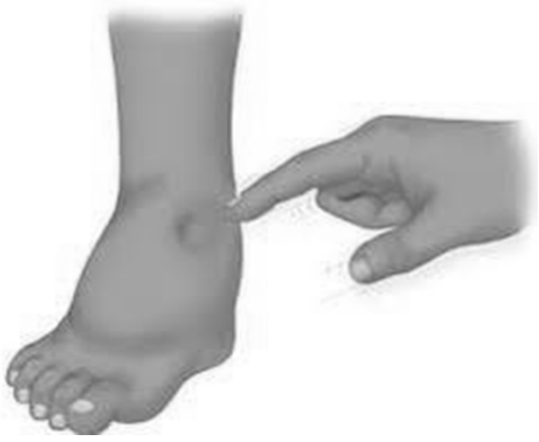
Presentation: Swelling around the ankles: Pitting edema



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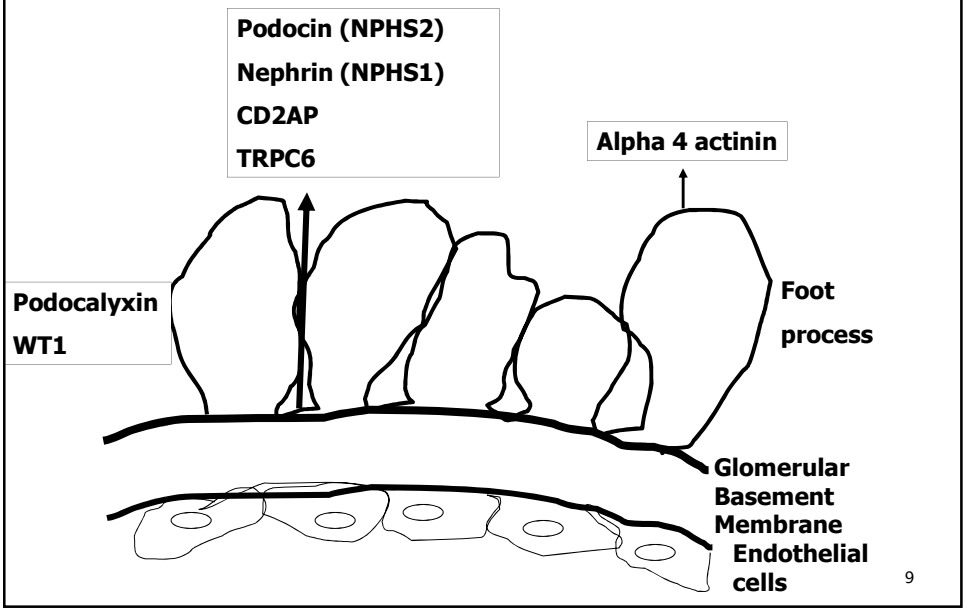
What causes it?: 1. Genetics



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What causes it? 2.Immune mediated

- Disorder of T cells, releasing cytokines leading foot process injury → foot process effacement
  - Allows glomerular permeability to albumin
- Circulating permeability factor
- Triggers:
  - Infections
  - Allergies
  - ?Vaccines

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What causes it? 3. Non immunologic due to persistent injury to the glomerulus

- Chronic interstitial nephritis
- Any condition associated with reduced nephron number including reflux nephropathy and obstructive uropathy
- Hypertension
- Alport's syndrome
- HIV
- Obesity

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Types of Nephrotic syndrome

- Primary Nephrotic Syndrome
  - Causes of Childhood Nephrotic Syndrome
  - Minimal change disease
  - Focal segmental glomerulosclerosis
  - Membranous nephropathy

Secondary Nephrotic Syndrome

- Diabetes
- Henoch-Schonlein purpura
- Hepatitis B or C
- HIV
- SLE
- Streptococcal infection

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Differential Diagnosis of Nephrotic Syndrome

Infancy:

- Congenital Nephrotic syndrome
- Diffuse Mesangial Sclerosis

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Differential Diagnosis of Nephrotic Syndrome in Children

Age (Years)	*MCD	*FSGS	Membranous	*MPGN	Other GN
1-4	95%	3%	2%	-	-
4-8	75%	15%	1%	7%	2%
8-16	52%	15%	2%	25%	6%

*MCD: Minimal Change Disease
*FSGS: Focal Segmental Glomerulosclerosis
*MPGN: Membranoproliferative Glomerulonephritis

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Minimal change disease

- Most common glomerular disorder of childhood
- Age 1-10 years (median 2-3 years)
  - Less likely minimal change if outside the age range
  - 50% nephrotic syndrome in teenagers
  - < 20% of adults with nephrotic syndrome
- Male: female = 2:1
- Majority (> 90%) respond to steroids

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Management

- Therapy (IMMUNE MODULATORS)

is based on the fact that the disease may be due to changes in immune system Initial therapy in children and in adults with minimal change disease: steroids (prednisone)

- Response to steroids determines the likelihood that a child has minimal change disease
- 90% of all cases of childhood nephrotic syndrome will respond to steroids
- 50% of this group will have frequent recurrence (RELAPSE) requiring repeated steroid use and increased risk of steroid toxicity

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Management

- Steroids PO
  - 2 mg/kg/day (60 mg/m2/day), max 60 mg/day x4-6 weeks
  - Then QOD dosing at 1.5 mg/kg/day (40 mg/m2/dose), max 40 mg. Taper over 2-3 months
  - 90% responds in 4 weeks (< 10% go into remission after 2-4 more weeks; few after 8-12 weeks)
  - Considered steroid resistant if no response by 8 weeks
- Low-sodium diet
- Protein intake 130-140% of RDA for age
- Gluten free diet

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Management

- Fluid restriction for those with Na < 125
- Low saturated fat diet
- Vitamin D supplement
  - Urinary losses of 25-OH-vitamin D and its carrier protein
- Rare to need levothyroxine supplementation due to urinary loss of iodinated proteins

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Management: Immunizations

- Pneumococcal vaccines (PCV13, PPSV23)
- Annual influenza vaccine
- Defer live vaccines until prednisone dose is < 0.5mg/kg/day
- Live vaccines contraindicated in patients taking corticosteroid-sparing immunosuppressives
- Child should avoid direct exposure to GI, urinary, or respiratory secretions of contacts who receive live vaccines, for 3-6 weeks after contact
- Give IVIG (or VZIG: Varicella IgG) if non-immune patient is exposed to varicella (close contact)

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Relapses

- Common, average 4-5x
- Urine dip with 2+ protein for 2 or more days
- Restart steroids at full dose until urine dips are trace-negative x3 consecutive days, then taper steroids

Frequently Relapsing (FR)
- 2 or more relapses within 6 months
- 4 or more relapses within 12 months

Steroid Dependent (SD)
- 2 or more consecutive relapses during tapering or within 14 days of stopping steroids

Change to steroid-sparing agent if FR or SD

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Relapses

- Partial remission
  - proteinuria 200-3500 mg/day
  - more than 50% reduction in proteinuria from baseline and < 3500 mg/day
- Non responder: less than 50% reduction in proteinuria and still >3500 mg/day

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2012 KDIGO recommendations for Frequently relapsing or Steroid Dependent Steroid Sensitive Nephrotic Syndrome

Advantages and disadvantages of corticosteroid-sparing agents as first agent for use in FR or SD SSNS

Agent	Advantages	Disadvantages
Cyclophosphamide	Prolonged remission off therapy Inexpensive	Less effective in SD SSNS Monitoring of blood count during therapy Potential serious short- and long-term adverse effects Only one course should be given
Chlorambucil	Prolonged remission off therapy Inexpensive	Less effective in SD SSNS Monitoring of blood count during therapy Potential serious adverse effects Only one course should be given Not approved for SSNS in some countries
Levamisole	Few adverse effects Generally inexpensive	Continued treatment required to maintain remission Limited availability Not approved for SSNS in some countries
Cyclosporine	Prolonged remissions in some children with SD SSNS	Continued treatment often required to maintain remission Expensive Nephrotoxic Cosmetic side-effects
Tacrolimus	Prolonged remissions in some children with SD SSNS	Continued treatment often required to maintain remission Expensive Nephrotoxic Risk of diabetes mellitus Not approved for SSNS in some countries
Mycophenolate mofetil	Prolonged remissions in some children with FR and SD SSNS Few adverse effects	Continued treatment often required to maintain remission Probably less effective than CNIs Expensive Not approved for SSNS in some countries

FR, frequently relapsing; SD, steroid-dependent; SSNS, steroid-sensitive nephrotic syndrome.

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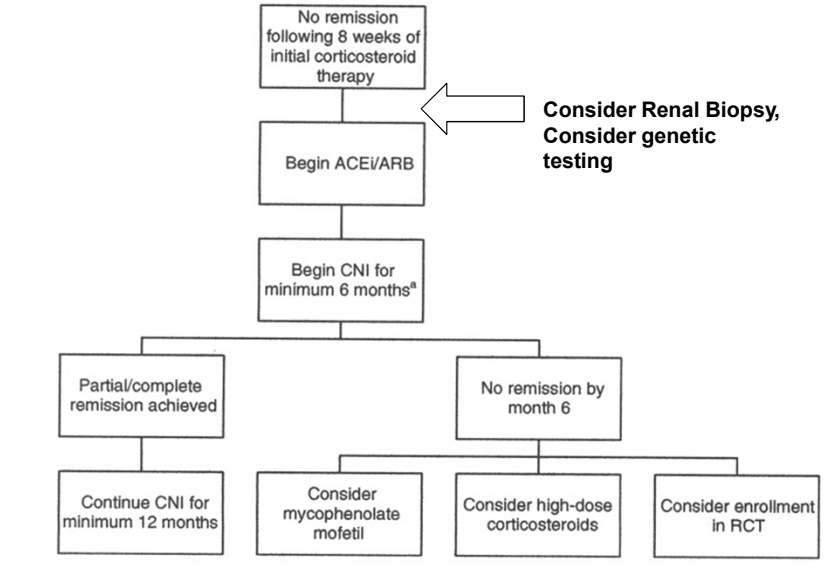
2012 KDIGO Recommendations for Steroid Resistant Nephrotic Syndrome in Children



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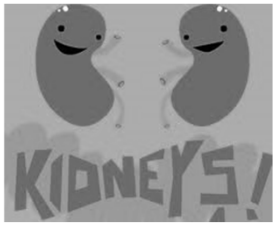
Treatment to Slow Down Kidney Damage

- Control of high blood pressure
  - ACE inhibitors (Enalapril) and ARB (Losartan, Valsartan)
- Control of excretion of protein in the
  - ACE inhibitors and ARB
- Control of high cholesterol
  - Lipid lowering agents- STATINS
- Diuretics
  - Control swelling, but risk of low blood volume



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Who is Likely to Respond to Treatment?

- Age: Children 2-10 years more likely to respond
- Histology, biopsies
  - ➢MCNS: 90% therapy responsive
  - ➢FSGS: 30% therapy responsive
  - ➢Congenital Nephrotic syndrome and most familial cases therapy unresponsive
- Race
  African American children more likely to have therapy unresponsive disease (APOL1 mutations)

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Common Complications

- Infections
- Thrombosis
- Hyperlipidemia
- Acute Renal failure
- Iron deficiency anemia
- Vitamin D deficiency
- Medication complications

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Prognosis

- Is Good if responds to steroids (regardless of how many times they relapse)
- Majority will outgrow the disease
- Those more resistant to treatment are more likely to have FSGS
  - Large proportion go on to ESRD and need renal transplant
  - High rate of recurrence in allograft with FSGS

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Focal Segmental Glomerulosclerosis

- More common in adults than children
- Suspected when children with nephrotic syndrome do not respond to steroids
- Is a biopsy diagnosis

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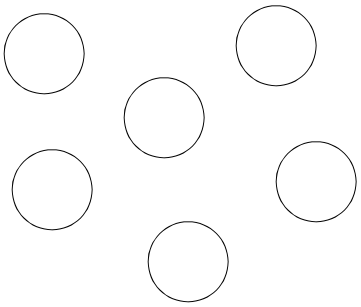
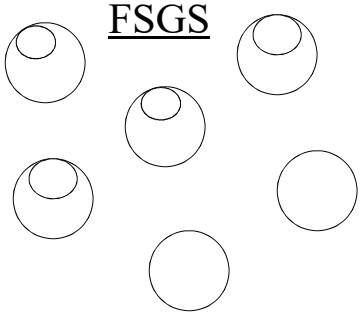
Minimal Change disease vs



- **Nil disease**

Focal segmental glomerulosclerosis

FSGS



Classic sclerotic changes in glomeruli:

Focal: <50% of total glomeruli affected

Segmental: only part of glomerulus affected

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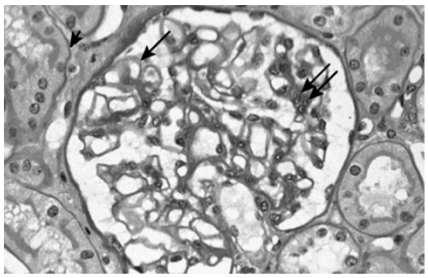
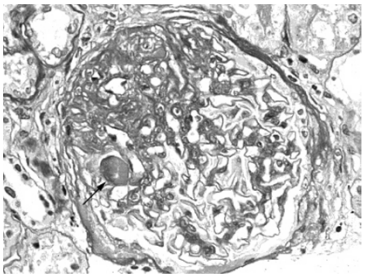
Pathology



Normal



FSGS

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Focal Segmental Glomerulosclerosis(FSGS)

Primary or Idiopathic FSGS

Secondary FSGS

- Non-nephrotic proteinuria
- Serum albumin usually normal
- Some degree of renal insufficiency
- No peripheral edema
- Represents an adaptive response to glomerular hypertrophy or hyperfiltration
  - Reduced renal mass (solitary kidney)
  - Scarring produced by previous injury (i.e. IgA nephropathy, vasculitis, lupus nephritis, ect)
- Infections
  - HIV
  - Toxins (heroin, interferon, cyclosporine, pamidronate)

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FSGS - Treatment

- Primary
  - Immunosuppressive therapy: prednisone, calcineurin inhibitors, mycophenolate mofetil, rituximab, plasmapheresis
  - Nonimmunosuppressive therapy: ACEi, lipid lowering
- Secondary
  - No immunosuppression
  - ACEi (Angiotensin converting enzyme inhibitors)

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FSGS - Prognosis

- Renal survival has been directly associated with degree of proteinuria control
- > 30% recur in transplant (primary FSGS)
  - 6% at 5 years post-trasnplant (NAPRTCS data)
  - Risk factors: childhood onset of initial disease, rapid progression to ESRD of initial disease, white race, history of recurrence in previous allograft

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Membranous nephropathy

- Very rare in children
- Suspected when children with nephrotic syndrome do not respond to steroids
- Is a biopsy diagnosis

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Membranous Nephropathy

- Histologic Lesion
  - Glomerular basement membrane thickening with little or no cellular proliferation
  - Spikes of GBM extending between immune deposits (subepithelial)

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Membranous Nephropathy

Primary MN
- Most common

Secondary MN
- Hepatitis B or C
- Autoimmune disease – class V lupus nephritis
- Malignancies (solid) – deposition of tumor Ag in the glomeruli
- Drugs (gold, penicillamine, captopril, NSAIDs)

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Membranous Nephropathy

Diagnosis

- Biopsy
- ANA, C3 (normal in idiopathic MN, low in SLE and Hep B), HepB and C
- Anti-PLA2R autoAb (serum or can stain for it on biopsy)

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Membranous Nephropathy

- Treatment
  - Immunosuppressive therapy: prednisone, cytoxan, calcineurin inhibitors
  - Nonimmunosuppressive therapy: ACEi, lipid lowering

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Membranous Nephropathy

Prognosis

- Renal survival has been directly associated with degree of proteinuria control, creatinine at presentation
- > 10-45% recur in transplant
  - Mild disease use non-immunosuppressive meds
  - Urine prot/cr > 1, use rituximab

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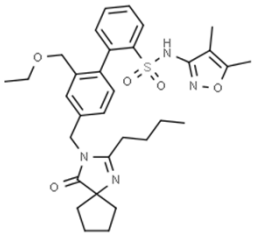
Clinical trials: Duplex study



The investigational drug (sparsentan) is a dual acting angiotensin receptor blocker and endothelin receptor antagonist. The active control is irbesartan.

- randomized, multicenter, double-blind, parallel, active-control study.
- Approximately 300 patients aged **8 to 75 years** (inclusive) will be enrolled in the study

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Clinical trials: Complexa trial

- This is a multicenter, open label, randomized study investigating two dose titration regimens of CXA-10 in subjects at least 18 years of age with primary FSGS.
- The study will be performed at approximately 25 study centers across the United States of America (USA). The recruitment period is anticipated to be up to approximately 16 months. Approximately 30 subjects will be randomized to ensure 26 subjects complete the study.

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Clinical trial: TRPC5 channel inhibitor

NEPHROLOGY

A small-molecule inhibitor of TRPC5 ion channels suppresses progressive kidney disease in animal models

Yiming Zhou,[1,2*] Philip Castonguay,[1,2*] Eriene-Heidi Sidhom,[1,2] Abbe R. Clark,[1,2] Moran Dvela-Levitt,[1,2] Sookyung Kim,[1,2] Jonas Sieber,[1,2] Nicolas Wieder,[1,2] Ji Yong Jung,[1,3] Svetlana Andreeva,[1] Jana Reichardt,[1] Frank Dubois,[1] Sigrid C. Hoffmann,[4] John M. Basgen,[5] Mónica S. Montesinos,[1,2] Astrid Weins,[1,6] Ashley C. Johnson,[7] Eric S. Lander,[2] Michael R. Garrett,[7] Corey R. Hopkins,[8] Anna Greka[1,2†]

- A First-In-Human, Phase 1/2, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of GFB-887, a TRPC5 Channel Inhibitor, in Healthy Subjects and Patients with Focal Segmental Glomerulosclerosis, Treatment-Resistant Minimal Change Disease, and Diabetic Kidney Disease

Patients >12 years of age with FSGS or treatment resistant MCD (diagnosis based either on biopsy or genetic testing)

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Nephcure Accelerating Cures Institute

GOAL: To **create a thorough database** of clinical information (Electronic Health Records) from all patients that suffer from a **primary NS condition**. The information in this database can be used to find the best standards of care and the best treatment options for patients living with these diseases. It will also speed up the development of new treatments.

NephCure Accelerating Cures Institute

WHO CAN PARTICIPATE: Any patient seen at a NACI site can consent to share their electronic health records. Currently, there are NACI sites in Ann Arbor, MI, Charlotte, NC, and Los Angeles, CA. Over the next few years, NACI will expand to include 30 sites globally.

If you are not near a NACI site, being a part of the NephCure Kidney Network is a step you can take to help reach the same goal!

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So we have discussed

- What is nephrotic syndrome
- What are the presenting features of nephrotic syndrome: symptoms/signs/lab features
- What causes it?
- Types of nephrotic syndrome
- Management
- Complications
- Prognosis
- Clinical trials in the pipeline

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Summary

- Minimal change disease accounts for most of the cases of NS in children while FSGS accounts for 10-15% of cases
- Most of the children and many adults with minimal change disease are responsive to steroid treatment
- If frequent relapses and severe side effects occur with the treatment, alternative medications are available
- Each therapy has its own risk of side-effects
- Childhood Nephrotic Syndrome often goes away during puberty
- FSGS is often unresponsive to treatment and requires kidney transplantation

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