Nephrotic syndrome

1- Glomerular capillaries are lined by endothelial cells, that contains "fenestrations"
2- Glomerular basement membrane (GBM) forms a continuous layer between:
   - Endothelial and mesangial cells on one side and
   - Epithelial cells on the other.
3- The membrane has 3 layers:
   1- (Central lamina densa)
   2- (Lamina rara interna, which lies between the lamina densa and the endothelial cells)
   3- (Lamina rara externa, which lies between the lamina densa and the epithelial cells)
4- Visceral epithelial cells (Podocytes) cover the capillary and project cytoplasmic "foot processes", which attach to the lamina rara externa between the foot processes "filtration slits"

- Mesangial (mesangial cells and matrix) lies between the glomerular capillaries on the endothelial cell side of the GBM and forms the medial part of the capillary wall.
- The mesangium may serve as a supporting structure for the mesangium and probably has a role in:
  1- Regulation of glomerular blood flow and filtration and
  2- Removal of macromolecules (such as immune complexes) from the glomerulus, either through a intracapillary phagocytosis or by transport through intercellular channels to the juxtaglomerular region.

Bowman's capsule, which surrounds the glomeruli, is composed of:
1- A basement membrane, which is continuous with the basement membranes of the glomerular capillaries and the proximal tubules
2- The partial epithelial cells, which are continuous with the visceral epithelial cells.

- The endothelial cell, basement membrane, and epithelial cell of the glomerular capillary wall possess strong negative ionic charges.
- These charges are a consequence of two negatively charged moieties:
  1- Protonated (heparan sulfate)  
  2- Glycoproteins containing sialic acid.

Pathophysiology:

1- Proteinuria:
   - In patients with NS, the structural changes:
     1- Damage to the GBM
     2- Thickening of the GBM
   - Certain HLA types (HLA-D, HLA-B, and HLA-A12) are associated with an increased incidence of NS.
2- In focal segmental glomerulosclerosis:
   1- A plaque factor (produced by lymphocytes) may be responsible for the increase in capillary wall permeability.
   2- Mutations in podocyte proteins (Podocin, podocin 4).

Types of Nephrotic Syndrome:

1- Primary idiopathic nephrotic syndrome (90%):
   - Minimal change nephrotic syndrome (MCNS) is the most common histologic form.
   - More than 80% of children under 7 years of age with nephrotic syndrome have MCNS.
2- Secondary nephrotic syndrome (10%):
   - May be seen with systemic lupus erythematosus, Schönlein-Henoch purpura, infections (hepatitis B, hepatitis C, malaria), Wegener and other vasculitides, allergic reactions, diabetes, amyloidosis, malignancies, congestive heart failure, constrictive pericarditis, renal vein thrombosis.
3- Congenital nephrotic syndrome:
   - The Finnish type is an autosomal recessive disorder most common presentations during the first 2 months of life.
   - Prenatal insult is supported by α1-maternal alpha-fetoprotein.

Clinical Manifestations:

1- Proteinuria:
   - In focal segmental glomerulosclerosis:
     1- Proteinuria
     2- Hematuria
     3- Renal vein thrombosis
   - Associated conditions:
     1- Allergy? Hodgkin disease, usually none
     2- Repeated or prolonged low serum levels of total complement (CH50).

Laboratory Findings:

1- Immunoglobulins:
   - HLA-B, B12 (1.5)
   - Mutations in podocin, a-actinin-4, other genes
   - HLA-DR5 (12-37)
   - Not established

Renal Pathology:

1- Light microscopy:
   - Normal
   - Focal sclerotic lesions
   - Thickened GBM, spikes
2- Immunofluorescence:
   - Negative
   - IgM, C3 in lesions
3- Electron microscopy:
   - Foot process fusion
   - Thickening of the GBM
4- Response to steroids:
   - May be slow regression
   - Not established

Pathology:

Types of proteinuria:

1- High selective proteinuria:
   - Glomerular permeability of GBM would be selectively altered by increased urinary load.
   - The common infectious complications:
     1- Anasarca: inability to open the eyes
     2- Renal failure
      3- Hemorrhage
      4- Reduced immunity

2- Hypoalbuminemia:
   - Increased urinary loss of proteins is the main cause
   - Other factors:
     1- The capacity to increase hepatic synthesis appears insufficient to compensate for the large urinary losses.
     2- Increased protein catabolism.

A- Edema:
   - Hypoalbuminemia, which causes a decrease in plasma oncotic pressure and transudation of fluid from the interstitial compartment to the interstitial space.
   - Edema is enhanced by:
     1- Causes massive generalized edema
     2- Reduced Renal perfusion pressure
     3- Activating renin-angiotensin-aldosterone system
     4- Expansion of plasma volume
     5- Loss of plasma water into the interstitial space

B- Other effects:
    1- Like albumin, the concentration of other plasma proteins are decreased:
       1- IgG and some components of complement decreased immunity
       2- Some anti-coagulant factors hypercoagulability state
       3- Vitamin D combining protein hypercalcemia
       4- Transferrin anemia

3- Hyperlipidemia:
   - Serum cholesterol, triglycerides are elevated for two reasons:
     1- Hypoalbuminemia stimulates generalized hepatic protein synthesis, including synthesis of lipoproteins.
     2- Increased urinary loss of albumin and "lipoprotein lipase" reduce plasma levels of this enzyme and lipid Catabolism is diminished.
   - Two pathologic patterns:
     1- Hypercholesterolemia alone
     2- Combined hypercholesterolemia hypertriglyceridemia
   - It plays a role in:
     1- Hyperlipidemia state
     2- Progression of glomerulosclerosis.

Summary of Primary Renal Diseases That Present as Idiopathic Nephrotic Syndrome

<table>
<thead>
<tr>
<th>FREQUENCY</th>
<th>MINIMAL CHANGE</th>
<th>FOcal SEGMENTAL</th>
<th>MEMBRANOUS</th>
<th>MEMBRANOPROLIFERATIVE</th>
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<tbody>
<tr>
<td>Type I</td>
<td>Type II</td>
<td>Nephrotic Syndrome</td>
<td>GLOMERULONEPHRITIS</td>
<td>GLOMERULONEPHRITIS</td>
</tr>
<tr>
<td>Children</td>
<td>15%</td>
<td>10%</td>
<td>&lt;5%</td>
<td>10%</td>
</tr>
<tr>
<td>Adults</td>
<td>15%</td>
<td>15%</td>
<td>50%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Clinical Manifestations:

1- Edema:
   - May be slow regression
   - Not established

Complications:

1- Infections:
   - Causes:
     1- Decreased immunity
     2- Urinary tract infections
     3- Enteric bacterial infections

2- Hypovolemia:
   - Causes:
     1- Hypoalbuminemia
     2- Plasma oncotic pressure decreases

3- Electrolyte disturbances:
   - Hyponatremia, Hypokalemia, Hypocalcemia

4- Hypercoagulability states and thrombosis:
   - Causes:
     1- Urinary loss of anti-coagulant proteins
     2- Hemostasis and hypocoagulopathy
     3- Hyperlipidemia (increased viscosity) and increased platelet aggregation

5- Acute renal failure:
   - Often precipitated by Hypovolemia
   - Reduction in the glomerular filtration rate has also been hypothesized
1. Urinalysis:
   a. Proteinuria:
      - Protein: qualitatively +++... quantitatively >0.1g/dL.
      - The ratio of urinary protein to urinary creatinine: >2
   b. Hematuria:
      - RBC may be increased in nephritic-nephrotic syndrome
      - Occasionally appears in simple nephrosis

2. Blood:
   - Hyperalbuninemia: albumin < 10g~20g/L
   - Hyperlipidemia: cholesterol > 5.7mmol/L
   - ESR > 100mm/h
   - Renal functions and serum complement 3 may be reduced → In nephritic-nephrotic syndrome,
   - Serum electrolyte determination: to evaluate hypotension, hypokalemia, hypocalcemia

Criteria of diagnosis:
1. Massive proteinuria: Urinalysis reveals >3+ or >4+. Protein excretion exceeds 100mg/kg/d.
2. Hyperalbuninemia: Serum albumin level is less than 30g/L (usually 10g~20g/L)
3. Hypercholesterolemia: the serum concentration of cholesterol is > 5.7mmol/L
4. Edema with various degrees
   - The first two items are the most necessary for diagnosis
   - The diagnosis of different clinical types of NS

Differential Diagnosis:
Primary NS should be differentiated from:
1. Secondary NS or
2. GN with nephrotic picture, such as HSP nephritis, SLE nephritis, APSGN.

Treatment:
A. General measures
1. Activity:
   - Do not restrict activity unless the patient is severely edematous or with severe hypertension or infections.
   - To prevent thrombosis, patients restricted to bed rest should change position frequently.
2. Diet:
   - The diet should provide adequate energy (calorie) intake and adequate protein (1-2 g/kg/d).
   - Sodium restriction (Low sodium or no sodium diet) is indicated for patients with edema or hypertension, but should be adjusted according to the serum levels of sodium. Long-term sodium restriction is not recommended.
   - Fluid restriction is required when the edema is severe with oliguria.
   - Replacement of vitamins and minerals.
3. Diuretic therapy:
   - Diuretic is indicated when edema is severe, esp. with ascites
   - It can be used for symptomatic relief until steroid diuresis occurs
   - Hydrochlorothiazide (HCT): 2-4mg/kg/d
   - Antisterone: may be added if HCT is not effective.
   - Salt-poor albumin at 0.5-1g/kg/iv per 1 h (when serum albumin<20g/L), followed by iv injection furosemide 1-2mg/kg/dose. Multiple use is not recommended.
   - A renal blood vessel dilator should be given (dopamine 2-4 μg/kg/min) in patients with refractory edema, combined with furosemide.
   - Hypovolemic shock or postural hypotension should be monitored during diuresis.
4. Treatment of complications
   - Anti-infection: antibiotics that cover both gram-positive and negative organisms should be given; But continuous prophylactic antibiotics are not recommended.
   - Anti-coagulation therapy: heparin, persantin, exercise of extremities, Therapy for electrolyte disturbance.

B. Specific therapy:
1. Glucocorticoid therapy
2. Cytotoxic agent therapy
3. Pulse therapy

1. Glucocorticoid therapy
- At initial diagnosis, Prednisone or Prednisolone oral therapy is the first line:
- Before starting steroid therapy, a tuberculin skin test should be done.

A. Medium-term prednisone therapy
- Commonly used in China, including 3 phases:
  1. 2mg/kg/d (maximum 60 mg/day) daily for 4 weeks
     - Remission can be achieved during this phase in most children with PNS, then entered the next phase
   - If remission isn’t achieved, continue the initial dosage, but not over 8 weeks before entered the next phase.
  2. 1.5-2mg/kg, qod (single dose, every other morning, alternate-day therapy) for another 4 weeks.
  3. Reduced by 2.5~5 mg q2-4w until stopped.
- Medium term therapy: total course is 6m
- Long term therapy: total course is 9~12m

B. Short term prednisone therapy:
- Prednisone dosage at:
  1. 2mg/kg/d (maximum 60 mg/day) daily for 4 weeks
     - Regardless of the responses, entered the next phase.
  2. 1.5mg/kg, qod for another 4 weeks, then stopped.
- The total therapy course is 8~12 weeks.
- May be associated with a higher rate of early recurrence or relapse.

NS types classified by response to steroid therapy
1. Steroid sensitive NS:
   - Complete remission is achieved within the first 8 w of the initial steroid therapy.
2. Partially steroid sensitive NS:
   - After 8w of the initial steroid therapy, edema subsides, but urinary protein is still >+++.
3. Steroid resistant NS:
   - Failure to achieve remission (urinary protein ≥+++ in spite of 8 weeks of standard prednisone therapy.
   - Steroid dependent NS: Patients who has 2~3 consecutive relapses occurring during the period of steroid taper or within 14 days of its cessation is defined as...
   - Relapse or recurrence: Patients who has urinary protein≥+ after 4w of steroid cessation or during maintenance
   - Frequent relapses or recurrences: Patients who has 2 or more relapses or recurrences within 6 months, or ≥3 within 12 months is said to have ...

Adverse effects of long term corticosteroid treatment
- Cushingoid features: obesity, round face, striae
- Increased susceptibility to infections
- Hypertension
- Osteoporosis
- Hypokalemia
- Retarded growth
- Cataracts
- Pneumocystis pneumonia
- Diabetes mellitus
- Peptic ulcer disease
- Increased susceptibility to infections
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2. Cytotoxic agent therapy:
- Cyclophosphamide, cytosporin, chlorambucil, nitrogen mustard...
- Indication:
  - Intractable NS (steroid resistance, frequent relapses or recurrences)
  - Steroid dependent NS with signs of steroid toxicity.
- The adverse effects: sexual gland damage; bone marrow depression; hemorrhagic cystitis; nausea, vomiting, gastritis; alopecia; liver damage.

3. Pulse therapy:
1. Methylprednisolone: 15~30 mg/kg/d (<1.0g/d) add 10% glucose 100~250 ml in drip, for 3 days.
   - Repeated same as above every 1~2w weeks if necessary.
2. CTX: 0.5~0.75g/m² in drip, once monthly, for 6 months if necessary.

Prognosis:
- Varies depending on the histological type
  - >90% of MNs respond to corticosteroid therapy
  - Only 30% of children never have a relapse after the initial remission
  - Approximately 50% have 1-2 relapses within 5 years
  - 20% continue to relapse 10 years after diagnosis
- Approximately 3% of patients who initially responded to steroids become steroid resistant.
- Only approximately 20% of patients with FSGS undergo remission of proteinuria
- Approximately 50% of patients with MsPGN undergo complete remission of proteinuria during steroid therapy
- MPGN has the most worse prognosis. no difference was evident in the outcome between treated and untreated patients;

Indications of renal biopsy:
- Unsuccessful therapeutic trial of steroids:
  - Steroid resistance
  - Frequent relapses or steroid dependency
  - A child >10y at onset
  - Coexistence of significant hematuria, hypertension, azotemia and depressed serum C3 at onset.
  - Secondary causes of nephrotic syndrome.

Sources:
1. Nelson
2. Lang pathophysiology
3. Sherein Shalaby lecture