Primary Nephrotic Syndrome

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Nephrotic syndrome is a group of symptoms including proteins in the urine (more than 50 mg/kg/day), low blood albumin levels, high cholesterol levels, and swelling.

Nephrotic syndrome is a constellation of clinical findings that is the result of massive renal losses of protein.
Nephrotic syndrome is characterized by

- **Proteinuria**: >50 mg/kg/24hr
- **Hypoalbuminemia**: <25~30g/L
- **Hyperlipidemia**: Cholesterol >5.72 mmol/L
- **Edema**: the most common symptom in NS
Secondary NS

This condition can also occur as a result of infections, use of certain drugs, cancer, genetic disorders, immune disorders, or diseases that affect multiple body systems including diabetes, HBV infections, systemic lupus erythematosus, Henoch Schonlein purpura, etc.
Congenital NS

- Finnish type of congenital nephrotic syndrome
- Diffuse Mesangial Sclerosis
- Familial FSGS
- ...

Congenital NS
## Classification of disease associated with nephrotic syndrome

<table>
<thead>
<tr>
<th>Medications:</th>
<th>Mercury, Lithium, Warfarin</th>
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</thead>
<tbody>
<tr>
<td>Allergens, venoms, immunizations:</td>
<td>bee sting</td>
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<tr>
<td>Infections:</td>
<td>Bacterial, Viral, etc.</td>
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<td>Neoplastic:</td>
<td>solid tumors, Leukemia &amp; Lymphoma</td>
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<td>Multisystem disease:</td>
<td>SLE, HSP, Goodpasture syndrome</td>
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<td>Metabolic disease:</td>
<td>Grave disease, DM,</td>
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<td>Hereditary disease:</td>
<td>Fabry disease, Nail-patella syndrome, sickle cell disease</td>
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<tr>
<td>Miscellaneous:</td>
<td>pregnancy-associated, Kimura disease, nodular panniculitis, etc.</td>
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Primary NS in children

- Minimal change disease: 80%
- FSGS: 10%
- Mesangioproliferative glomerulonephritis: 5%
- Membranous glomerulopathy
- Membranoproliferative glomerulonephritis
Heavy proteinuria---reasons and results?

- Because of the injured glomerular filtration barrier, proteinuria is the essential alteration in pathogenesis of nephrotic syndrome.

- Prolonged glomerular leakage of protein leads to hypoalbuminaemia that is associated with loss of fluid into the extracellular space, manifested as edema. Reduction in circulating volume stimulates renal retention of salt and water.
The syndrome results from a major alteration in glomerular permeability due to structural damage of the glomerular capillary wall or loss of its negative charges.
Edema may be the most common or the only clinical manifestation in some patients.
1. Hypovolemia as a consequence of reduced plasma oncotic pressure has long been considered the proximal cause of edema.
2. Enhanced tubular sodium reabsorption due to a function of multiple mediator systems like RAAS, sympathetic nervous, and vasopressor system.
Hypoalbuminemia is the major manifestation due to urinary loss and tubular epithelial reabsorption and metabolism of protein.
hyperlipidemia is one of the sentinel features of NS, the reason for this is thought to be the consequence of both increased synthesis and decreased catabolism.
When the renal biopsy is appropriate?
1. Once there are clinical features suggesting a diagnosis other than MCD.

2. If the onset of Nephrotic syndrome begins in the first year of life or after 6 years of age.

3. When there is failure to respond to a 28-day course of prednisone, particularly if there have been changes in the clinical course during this period of time.
Cardiac Output
~ 4,900mL/min

Renal Blood Flow
~ 1,200mL/min
(~ 20% of cardiac output)
Anatomy

Renal column (of Bertin)

Cortex

Major calyx

Minor calyx

Papilla

Renal column (of Bertin)

Minor calyx

Papilla
Minimal Change Glomerulonephritis
Podocyte foot process

F-actin

CD2AP

Podocin

α-actinin-4

GBM

Endothelial cell

Slit diaphragm made of nephrin molecules from two opposite foot processes

Urinary space

Direction of filtration

Capillary lumen
a much-higher-magnification electron micrograph. The urinary space and the foot processes are at the top.
only background staining in minimal nephrotic syndrome patients
Granular IgG
IgA nephropathy: IgA deposits in the mesangial area.
Focal Segmental Sclerosis
a silver-stained section with collapsing variant of FSGS
COMPLICATIONS
Infection: bacteria, virus or fungus
Electrolyte imbalance
Hypercoagulable status and Thrombosis
Acute adrenocortical insufficiency/crisis
Acute kidney injury
Growth retardation
TREATMENT
DIET CONTROL
1. water and salt
2. protein intake
3. vitamin and calcium
4. lipid
ANTIBIOTICS
Symptom control
Diuretics
Corticosteroid
Prednisone

Methylprednisolone
In Europe & America

- Prednisone 2mg/kg/D × 4~6 weeks + 1.4mg/kg/alternate-day × 4~6 weeks, then for sudden withdrawal.

In China

- Prednisone 1.5~2mg/kg/D × 6~8 weeks + Prednisone 1.5~2mg/kg/alternate-day, then tapering slowly for 4~6 months or 9~12 months.
Euphoria
(though sometimes depression or psychotic symptoms, and emotional lability)

(Benign intracranial hypertension)

Buffalo hump

(Cataracts)

Moon face, with red (plethoric) cheeks

(Hypertension)

Increased abdominal fat

(Thinning of skin)

(Avascular necrosis of femoral head)

Easy bruising

Thin arms and legs: muscle wasting

Poor wound healing

Also:

Osteoporosis
Tendency to hyperglycaemia
Negative nitrogen balance
Increased appetite
*Increased susceptibility to infection*
Obesity
According to the response to steroid

1. Steroid sensitive nephrotic syndrome
2. Frequency relapsing nephrotic syndrome
3. Steroid dependent nephrotic syndrome
4. Steroid resistant nephrotic syndrome
Cytotoxic reagents
Cyclophosphamide, CTX

- 8~12mg/kg/D×2D, 2 times per month
- 0.5~0.75g/m², 1 times per month
- Less than 150~200mg/kg/body wt
Side-effects

Many people taking cyclophosphamide do not have serious side effects. Side-effects include chemotherapy-induced nausea and vomiting (CINV), bone marrow suppression, stomach ache, diarrhea, darkening of the skin/nails, alopecia (hair loss), changes in color and texture of the hair, and lethargy. Hemorrhagic cystitis is a frequent complication, but this is prevented by adequate fluid intake and Mesna (sodium 2-mercaptoethane sulfonate). Mesna is a sulphydryl donor and binds acrolein.

Cyclophosphamide is itself carcinogenic, potentially causing transitional cell carcinoma of the bladder as a long-term complication. It can lower the body's ability to fight an infection. It can cause temporary or (rarely) permanent sterility. Although it is used to treat cancer, it may increase the risk of developing another form of cancer, sometimes months to years after treatment.

Other (serious) side effects include:

- pink/bloody urine,
- unusual decrease in the amount of urine,
- mouth sores,
- unusual tiredness or weakness,
- joint pain,
- easy bruising/bleeding,
- stopping of menstrual periods,
- infertility
- existing wounds that are slow healing.
Cyclosporine, CsA

at a dosage of 5-6mg/kg/day, either in oral solution form or capsules, in two divided doses per day.
Cyclosporin is thought to bind to the cytosolic protein cyclophilin (immunophilin) of immunocompetent lymphocytes, especially T-lymphocytes. This complex of cyclosporin and cyclophilin inhibits calcineurin, which under normal circumstances is responsible for activating the transcription of interleukin 2. It also inhibits lymphokine production and interleukin release and therefore leads to a reduced function of effector T-cells. It does not affect cytostatic activity.
potentially serious adverse drug reactions (ADRs) and adverse drug interactions. Ciclosporin interacts with a wide variety of other drugs and other substances including grapefruit juice. There have been studies into the use of grapefruit juice to increase the blood level of ciclosporin.

ADRs can include gum hyperplasia, convulsions, peptic ulcers, pancreatitis, fever, vomiting, diarrhea, confusion, breathing difficulties, numbness and tingling, pruritus, high blood pressure, potassium retention and possibly hyperkalemia, kidney and liver dysfunction (nephrotoxicity & hepatotoxicity), and obviously an increased vulnerability to opportunistic fungal and viral infections.

An alternate form of the drug, ciclosporin G (OG37-324), has been found to be much less nephrotoxic than the standard ciclosporin A. Ciclosporin G (Mol. mass 1217) differs from ciclosporin A in the amino acid 2 position, where an L-nor-valine replaces the α-aminobutyric acid.
FK506, Tacrolimus at a dosage of 100-200µg/kg/day, in capsules, in two divided doses per day.
Tacrolimus (also FK-506) is an immunosuppressive drug whose main use is after allogenic organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection. It is also used in a topical preparation in the treatment of severe atopic dermatitis (eczema), severe refractory uveitis after bone marrow transplants, and the skin condition vitiligo.
blurred vision, liver and kidney problems (it is nephrotoxic), seizures, tremors, hypertension, hypomagnesemia, diabetes mellitus, hyperkalemia, itching, insomnia, confusion, loss of appetite, hyperglycemia, weakness, depression, cramps, and neuropathy, as well as potentially increasing the severity of existing fungal or infectious conditions such as herpes zoster or polyoma viral infections.
(Mycophenolate mofetil, MMF)
at a dosage of 20-30mg/kg/day, in capsules,
in two divided doses per day.
Common adverse drug reactions (≥1% of patients) include diarrhea, nausea, vomiting, infections, leukopenia, and/or anemia. Mycophenolate sodium is also commonly associated with fatigue, headache, and/or cough. Intravenous (IV) administration of mycophenolate mofetil is also commonly associated with thrombophlebitis and thrombosis. Infrequent adverse effects (0.1–1% of patients) include esophagitis, gastritis, gastrointestinal tract hemorrhage, and/or invasive cytomegalovirus (CMV) infection.
Rituximab is a chimeric monoclonal antibody that acts by inhibiting CD20-mediated B-cell proliferation and differentiation. Four weekly Rituximab treatment, 375 mg/m² for MN, MCD, FSGS, etc.
Adverse events

Serious adverse events, which can cause death and disability, include.[18]

- Severe infusion reactions
- Cardiac arrest
- Tumor lysis syndrome, causing acute renal failure
- Infections
  - Hepatitis B reactivation
  - Other viral infections
  - Progressive multifocal leukoencephalopathy (PML)
- Immune toxicity, with depletion of B cells in 70% to 80% of lymphoma patients
- Pulmonary toxicity[17]

A small number of patients with systemic lupus erythematosus have died in the context of being treated with rituximab.[18] In some cases, reactivation of latent JC virus (a common virus that can cause progressive multifocal leukoencephalopathy) occurred in the brains of these patients. Whether rituximab caused the reactivation is unclear. There has also been at least one case of a patient with rheumatoid arthritis who developed PML in the context of treatment with rituximab.[19] JC virus reactivation (resulting in PML) in an immunosuppressed person commonly results in death or severe brain damage.

Finally, rituximab has been implicated as causing a Hepatitis E infection to become chronic (permanent) in a patient with a lymphoma. Hepatitis E infection is normally an acute (short-term) infection, suggesting the drug may have weakened the body’s immune response to the virus.[20]
ACEi and ARB
Anticoagulant therapy
low-molecular weight heparin
Treatment of hyperlipidemia
DRUGS
Selective LDL-apheresis
Prognosis
THANK YOU VERY MUCH

谢谢各位！

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thank you