Nephrotic and Nephritic syndrome

Learning objectives

- Definition of Nephrotic syndrome
- Etiopathogenesis of nephrotic syndrome
- Clinical manifestation
- Evaluation
- Management
- outcome
- Post streptococcal GMN

Introduction

- Important chronic disease in children
- 80% children show remission with steroid
- Most patients have multiple relapses

Definition

- Heavy proteinurea>3.5 gm/24 hr or >40 mg/m2/hr in children
- Hypoalbunemia <2.5 gm%
- Oedema
- Hyperlipidemia (serum cholestrol>200mg/dl)

Nephrotic range proteinurea

- Early morning protein is 3+/4+ (dipstick or boiling test)
- Spot protein/creatinine ratio >2 mg/mg or
- Urine albumin excretion >40 mg/m2 per hr (on a timed-sample).

Etiology

- **Idiopathic: 90%**
- minimal change 85%, mesangial proliferation , FSG , membranoproliferative, congenital (Finnish type)
- **Secondary: 10%**
- SLE, anaphylactoid purpura, sickle cell disease, Hodgkin lymphoma, diabetes mellitus, amyloidosis, malaria (P. malariae), intrauterine infections (syphilis, toxoplasmosis,cytomegalovirus) and other infections like HIV, parvovirus B19,hepatitis B and C virus, drugs like d-penicillamine, gold and toxins or allergies (bee sting, poison ivy, food allergy).

Pathophysiology

- Increase in permeability of glomerular BM
- T- cell dysfunction
- Mechanism of edema:
- Urine protein loss leads to hypoalbuminemia

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  decreased oncotic pressure

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  transudation of fluid
- Reduction in intravascular volume and decrease renal perfusion pressure

Pathophysiology

- **Mechanism of lipid elevation:**
- Hypoalbuminemia stimulates generalized hepatic protein synthesis including lipoprotein
- Lipid catabolism is diminished due to decrease in lipoprotein lipase

Clinical Features

clinical	Minimal change disease	Mesangial proliferation	Focal segmental glomerulosclerosis
Incidence	85%	10%	5%
Age at presentation	2-6years	2-10years	2-10years
Hypertension	10%	10-45%	35-45%
Microscopic Hematuria	10-20%	45-90%	60-80%
Response to prednisolone	95%	50-60%	20-30%
Likelihood of maintaining renal function	95%	50-60%	20-30%

Cont…

clinical	Minimal change disease	Mesangial proliferation	Focal segmental glomerulosclerosis
Light Microscopy	Normal	Increase in mesangial cells	Focal or segmental glomerular hyalinization
Immunofluoresce-nt microscopy	Normal	Negative or variable IgM and C3 deposition	Focal or segmental deposition of Igm and C3
Electron microscopy	Fusion of foot processes of podocytes	Increase in mesangial cells and matrix,small scattered electron dense deposits in mesangium	Fine granular deposits in subendothelial regions

Initial evaluation

- Detailed evaluation
- The height, weight and blood pressure should be recorded
- Regular weight record
- Physical examination is done to detect infections and underlying systemic disorder
- Infections should be treated before starting therapy with corticosteroids.

Investigations

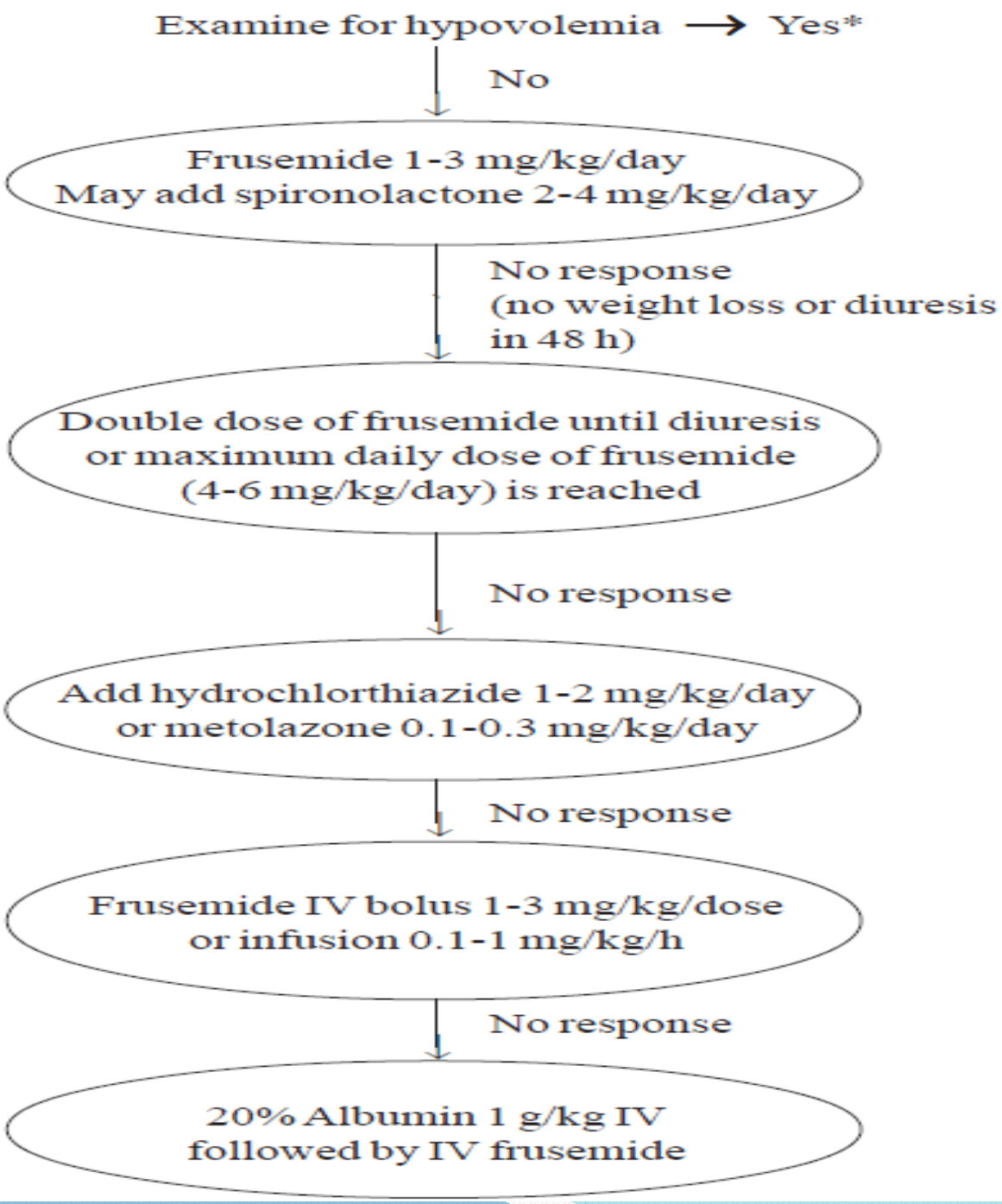
- Urinalysis
- Complete blood count
- Blood levels of Proteins, lipids, urea and creatinine and electrolytes
- ASLO and C3: gross hematuria
- Appropriate test –HbSAg, HIV and tuberculosis
- Renal biopsy

Indications for kidney biopsy

- **At Onset**
- Age of onset <1 year or >10 years
- Gross hematuria, persistent microscopic hematuria or low serum C3.
- Sustained hypertension.
- Renal failure not attributable to hypovolemia.
- Suspected secondary causes of nephrotic syndrome.
- **After Initial Treatment**
- Proteinuria persisting despite 4-weeks of daily corticosteroid therapy.
- Before treatment with cyclosporin A or tacrolimus.

Management of Nephrotic syndrome

- Relief of edema
- Hypertension
- Identify and treat infection
- Specific treatment regimen
- Complication



Definition related to nephrotic syndrome

- Remission: Urine albumin nil or trace (or proteinuria <4 mg/m2/h) for 3 consecutive early morning specimens.
- Relapse: Urine albumin 3+ or 4+ (or proteinuria >40 mg/m2/h) for 3 consecutive early morning specimens, having been in remission previously.
- Infrequent relapses: <2 relapses in 6 months of initial response or <4 relapses within any 12 months period.
- Frequent relapses: Two or more relapses in initial six months or more than three relapses in any twelve months.

Definition related to nephrotic syndrome

- Steroid dependence Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation.
- Steroid resistance Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for 4 weeks

Treatment of initial episode

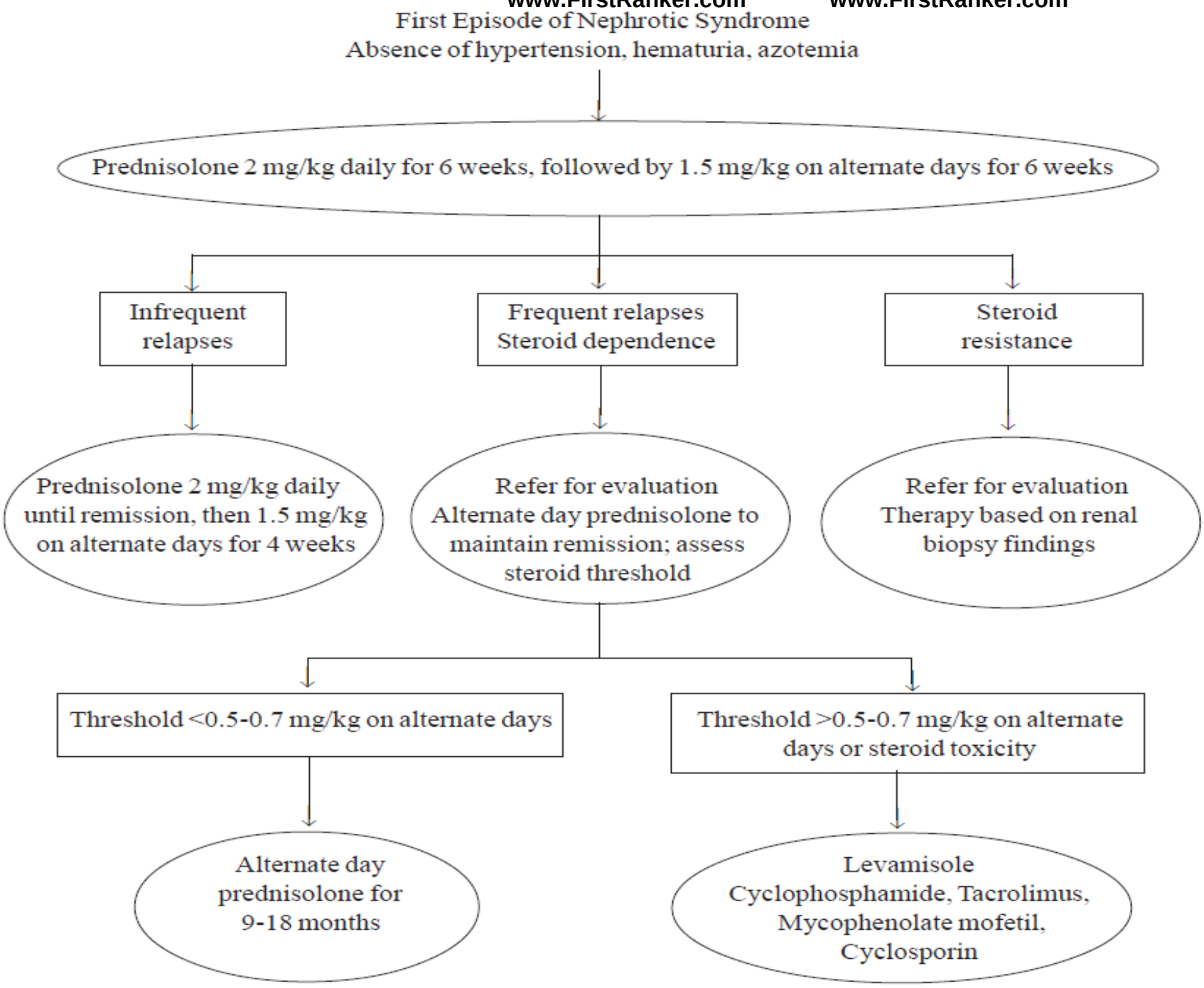
- Oral prednisolone
- 2 mg/kg/day 6weeks
- 1.5 mg/kg/EOD 6 weeks

Treatment of infrequent relapse

- Prednisolone 2 mg/kg/day till remission and then
- Prednisolone 1.5 mg/kg/day for 4 weeks

Treatment of frequent repalse or steroid dependent

- Low dose steroids with-
  - Levamisole
  - Cyclophosphamide
  - Calcineurin inhibitor : Cyclosporin,Tacrolimus
  - Mycophenolate mofetil (MMF)



Toxicity of drugs
Side effects of prednisolone

- Hirsutism
- Obesity
- Hypertension
- Behavioral problems
- Cataracts
- Striae
- Growth failure

Side effects of Levamisole

- The chief side effect of levamisole is leukopenia
- Flu-like symptoms,
- Liver toxicity
- Convulsions and skin rash are rare
- The leukocyte count should be monitored every 12-16 weeks.

Side effects of Cyclophosphamide

- Leucopenia
- Hemorrhagic cystitis
- Alopecia
- Skin rash
- Nausea

Side effects of Cyclosporin

- Hypertension
- Cosmetic symptoms
- Gum hypertrophy
- Hirsutism
- Nephrotoxicity
- hypercholesterolemia and elevated transaminases may occur
- Estimation of blood levels of creatinine is required every 2-3 months and a lipid profile annually.

Side effects of MMF

- Gastrointestinal discomfort, diarrhea and leukopenia.
- Leukocyte counts should be monitored every1-2 months
- Treatment is withheld if count falls below 4000/mm3.

Choice of agent

- Few studies comparing one study with another
- Levamisole has a modest steroid sparing effect and is a satisfactory initial choice
- Treatment with cyclophosphamide is preferred in patients showing:

I. significant steroid toxicity
II. severe relapses with episodes of hypovolemia or thrombosis, and
III. poor compliance or difficult follow up

Complications

- Infection
- Thrombosis
- Hypertension
- Hypovolumic shock
- Corticosteroid side effects
- Malnutrition

TABLE V CLINICAL FEATURES AND MANAGEMENT OF INFECTIONS*

Infection	Clinical features	Common organisms	Antibiotics, duration of treatment
Peritonitis	Abdominal pain, tenderness, distension; diarrhea, vomiting; ascitic fluid >100 leukocytes/mm^3; >50% neutrophils	*S. pneumoniae,* *S. pyogenes,* *E. coli*	Cefotaxime or ceftriaxone for 7-10 days; ampicillin and an aminoglycoside for 7-10 days
Pneumonia	Fever, cough, tachypnea, intercostal, recessions, crepitations	*S. pneumoniae,* *H. influenzae,* *S. aureus*	*Oral:* amoxicillin, co-amoxiclav, erythromycin *Parenteral:* ampicillin and aminoglycoside; or cefotaxime/ceftriaxone for 7-10 days
Cellulitis	Cutaneous erythema, induration, tenderness	*Staphylococci,* Group A streptococci, *H. influenzae*	Cloxacillin and ceftriaxone for 7-10 days Co-amoxiclav
Fungal infections	Pulmonary infiltrates, persistent fever unresponsive to antibiotics, sputum/urine showing septate hyphae	*Candida,* Aspergillus spp.	*Skin, mucosa:* fluconazole for 10 days *Systemic:* Amphotericin for 14-21 days

**Supplemental stress doses of hydrocortisone or prednisolone are usually necessary*

Outcome

- Steroid responsive - >90%
- Relapses- >70%
- Mortality – 2-5%

Patient and parents education

- Urine examination at home
- Maintain diary showing result of urine protein
- Ensure normal activity and school attendance
- Appropriate immunization

Acute glomerulophritis

- Glomerulonephritis refers to a group of glomerular diseases characterise by inflammatory changes in the glomeruli and manifesting as acute nephritic syndrome which is characterized by-
- Abrupt onset of hematuria
- Oligouria
- Edema
- Hypertension
- Subnephrotic range proteinuria
- Azotemia

Causes of Acute GMN

- Post infectious: Bacterial-Streptococcal, staphylococcal, pnemococcal, meningococcal. Bacterial endocarditis, infected ventriculoatrial shunt and prosthesis can cause acute GMN. Viral- Hepatitis B and C, mumps, HIV, varicella, infectious mononucleosis. Parasitic- malaria and toxoplasmosis
- Systemic vasculitis: HSP, SLE, PAN, Wegner's granulomatosis

Pathogenesis

Immune complex mediated disease

i. Immune complex Glomerulonephritis (70%)

- Low serum complement C3- poststreptococcal, rapidly progressive, mesangioproliferative glomerulonephritis, SLE, bacterial endocarditis, cryoglobulinemia
- Normal serum complement C3- IgA nephropathy, H-S purpura

ii. Pauci-immune glomerulonephritis (30%)

Anti-neutrophil cytoplasmic antibody positive wegener's granulomatosis, polyarteritis nodosa

iii. Anti GBM disease(<1%)

Anti-glomerular basement membrane antibody positive Good pasture syndrome.

Post streptococcal Glomerulonephritis

- Following group A beta-hemolytic streptococci
- School age children
- Boys are more frequently affected

Etiology

- Follows a pharyngeal or cutaneous infection by the nephritogenic strains of β hemolytic Group A streptococcus1 to 4 week preceding streptococcal throat/skin infection
- Strain M type 1,4 and 12 causing pharyngitis and 49,55,57 and 60 causing pyoderma
- Typical example of immune complex disease

Pathogenesis

- Immune complex deposition
- Glomeruli enlarged
- Ischemia
- Capillary wall narrowing
- Deposits of IgG and C3

Clinical feature

- Rare below 3 years of age
- Acute onset
- Latent period: Following pharyngitis- 1 to2 weeks and following cutaneous infection- 2 to 4 weeks
- Puffiness around eye and pedal edema
- Cola colored urine
- Oliguria
- Hypertension
- Atypical presentation : Convulsion, Pul edema, ARF, CHF
- Course of the disease- acute phase: 4-10 days, azotemia and hypertension:persist for 2 weeks, gross hematuria: 1-2 weeks

Laboratory investigations

- Urine : 1+/2+ protein, dysmorphic RBC's, and red cell, leukocyte or granular cast, nephrotic range poteinuria in < 5% cases
- Hemogram: Anemia, mild leucocytosis, ESR↑
- Biochemistry: C3 (normal- 77-195 mg/ dL) becomes normal in 6 to 8 weeks.
- Evidence of streptococcal infection: Throat swab culture, elevated ASO (for pharyngeal infection+ve in 80%), elevated antideoxyribonucleases-B anti-hyaluronidase antibodies (for cutaneous infection), streptozyme test
- Others- X- ray chest, ECG
- renal biopsy- to exclude other diseases in patients with-
  - ARF
  - normal C3 level
  - without evidence of preceding streptococcal infection
  - persistant gross hematuria and hypertension (>3 weeks)
  - prolonged diminished renal functions (> 2 weeks)
  - persistent low serum C3 (>8weeks)

Management

Presence of ARF and Hypertension requires hospitalisation

- Bed rest
- Diet
- Weight
- Fluid restriction
- Antibiotics
- Diuretics
- Alkalinization of urine
- Hypertension
- LVF
- ARF

Outcome and prognosis

- Overall excellent prognosis(>95% complete recovery, <1% develop RPGN))
- Symptoms resolves within 1 month
- Gross hematuria and proteinuria disappear within 2 weeks
- Microscopic hematuria may last for years
- Recurrence rare

Difference between acute nephritis and nephrotic syndrome

Acute nephritis	Nephrotic syndrome
• Characterized by hematuria, edema, hypertension, oligouria	• Characterized by heavy proteinuria, hpo albuminemia, edema,hyperlipidemia
• 90% post infective, immune complex	• 90% idiopathic
• Usually only 1 attack • Immune complex deposition	• Relapses common • Retraction of epithelial foot process
• Urine: Alb 1+/2+, hematuria, RBC cast • Blood urea/creat raised	• Urine: Selective proteinuria, No RBC • Blood urea/ creat normal

Thank you