# NOTES
# NEPHROTIC SYNDROME

## GENERALLY, WHAT IS IT?

### PATHOLOGY & CAUSES

- Collection of diseases caused by inflammation, damage to glomeruli of kidney; glomeruli become more permeable, allow proteins from blood into urine → proteinuria

#### Proteinuria

- Hallmark of nephrotic syndromes
  - Loss of protein (mostly albumin) → hypoalbuminemia; lowers oncotic pressure in blood → water moves out of vessels into interstitium → edema
  - ↓ proteins → ↑ lipids → hyperlipidemia; ↑ lipids filtered in glomeruli → lipiduria; fatty casts, foamy urine

### CAUSES

- Immune-mediated, metabolic, hemodynamic disturbances
- *Primary:* kidney lesion
  - Minimal change disease, focal segmental glomerulosclerosis, membranous glomerulonephritis, membranoproliferative glomerulonephritis
- *Secondary:* systemic disease
  - Diabetic nephropathy, lupus nephritis

### COMPLICATIONS

- *Loss of proteins (e.g. anticoagulants, iron-carrying proteins):* thromboembolism, renal vein thrombosis, microcytic hypochromic anemia, infections, hypocalcaemia

### SIGNS & SYMPTOMS

- Proteinuria, hypoalbuminemia, edema, hyperlipidemia, lipiduria, hypercoagulability

### DIAGNOSIS

#### LAB RESULTS

- Protein/blood in urine
- *Decreased glomerular filtration rate:* estimated from serum creatinine clearance

#### Kidney biopsy

- Changes under light/electron microscope, immunofluorescence
- *Blood test:* albumin, cholesterol levels

### TREATMENT

#### MEDICATIONS

- Edema
  - Diuretics (furosemide), medical nutrition therapy
- Blood pressure control
  - Angiotensin converting enzyme (ACE) inhibitors
- Hyperlipidemia
  - Reduce cholesterol, saturated fat intake
- Hypercoagulability
  - Heparin
- Infections
  - Antibacterial drugs
- Immunosuppressants
  - Cyclophosphamide, prednisone

**MNEMONIC: Protein LEAC**
**Nephrotic syndrome findings**
**Protein**uria
**L**ipid up
**E**dema
**A**lbumin down
**C**holesterol up

# DIABETIC NEPHROPATHY

osms.it/diabetic-nephropathy

## PATHOLOGY & CAUSES

- Kidney damage caused by Type I, Type II diabetes

### CAUSES

**Excess glucose in blood**

- Overrides renal threshold for glucose (160–180mg/dl) → glycosuria
- Non-enzymatic glycation of proteins → basement membranes thicken → hyaline arteriosclerosis
- Hyaline arteriosclerosis, arteriole dilatation increases pressure in glomerulus → increased glomerular filtration rate (first stage)
- Thickening of basement membrane → glomerulus expands, filtration slits widen → increased permeability
- High-pressure state → supportive mesangial cells secrete more structural matrix → Kimmelstiel–Wilson nodules
- Damage glomeruli → decreased glomerular filtration rate (second stage)

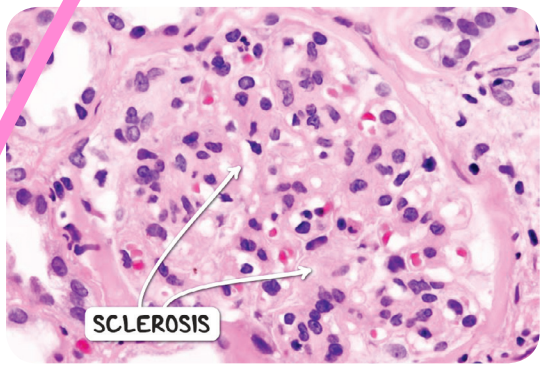


**Figure 118.1** Histological appearance of the glomeruli in a case of diabetic nephropathy. There is diffuse sclerosis of the glomerulus.

### RISK FACTORS

- Family history, poor control of diabetes, duration of diabetes (more common if developed at younger age); poor control of hypertension; obesity

## SIGNS & SYMPTOMS

- Mostly asymptomatic

## DIAGNOSIS

### LAB RESULTS

- Microalbuminuria (30–300mg/day), macroalbuminuria (> 300mg/day)

## TREATMENT

### MEDICATIONS

- Control hyperglycemia
- *ACE inhibitors/angiotensin receptor blockers:* reduce constriction of efferent arteriole → lower pressure in glomerulus

# FOCAL SEGMENTAL GLOMERULOSCLEROSIS

osms.it/focal-segmental

## PATHOLOGY & CAUSES

- Histologic finding of glomerular damage, not distinct disease.
- Affects parts (segmental) of some (focal) glomeruli of nephron; damage, scarring → proteinuria
- Foot processes of podocytes damaged → plasma proteins, lipids permeate glomerular filter
- Proteins, lipids trapped → build up inside glomeruli → hyalinosis (hyaline/glassy view on histology) → scar tissue (glomerulosclerosis)

### CAUSE

- *Primary:* unknown
- *Secondary:* result of underlying cause
  - Sickle cell disease, HIV, renal hyperfiltration (e.g. unilateral renal agenesis), heroin abuse
- *Genetic forms:* FSGS 1–6

### RISK FACTORS

- More common in black people of African descent/people of Latin American descent
- Morbid obesity
- Chronic kidney disease (congenital malformation)

### COMPLICATIONS

- *End-stage renal failure:* inconsistent response with treatment; adults—more involved segments of kidney's glomeruli → kidney failure

## SIGNS & SYMPTOMS

- Proteinuria, hypoalbuminemia, edema, hyperlipidemia, lipiduria, hypercoagulability

## DIAGNOSIS

### LAB RESULTS

- Protein in urine > 3.5g/L

**Kidney biopsy: most definitive**

- *Light microscopy:* segmental sclerosis, hyalinosis of glomeruli
- *Electron microscope:* effacement of foot processes of podocytes
- *Immunofluorescence:* nonspecific focal deposits of IgM, complement proteins not always seen (sometimes trapped in hyalinosis)

## TREATMENT

### MEDICATIONS

- Blood pressure reduction
  - ACE inhibitors
- Edema
  - Diuretics
- Prednisone/calcineurin inhibitors
  - Depend on nephrotic-range proteinuria, likelihood of reversibility

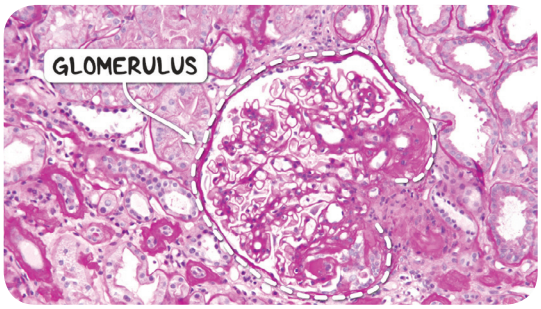


**Figure 118.2** Histological appearance of focal segmental glomerulosclerosis. There is sclerosis and hyalinosis of only one part of the glomerulus, in this case the hilar part. The more distal part is normal.

# LUPUS NEPHRITIS

osms.it/lupus-nephritis

## PATHOLOGY & CAUSES

- Inflammation of kidney due to systemic lupus erythematosus.
- Focal (nephrons in one area)/diffuse (all nephrons in both kidneys)
- *Caused by antinuclear antibodies (anti-dsDNA):* bind to nuclear antigens, form antigen-antibody complexes
- Antigen-antibody complexes deposit in capillary walls, basement membrane, Bowman's space → initiate inflammatory response → Type III hypersensitivity reaction

## TYPES

### Class I

- Minimal mesangial glomerulonephritis

### Class II

- Mesangial proliferative glomerulonephritis

### Class III

- Focal glomerulonephritis

### Class IV

- Diffuse proliferative nephritis

### Class V

- Membranous glomerulonephritis

### Class VI

- Advanced sclerosing lupus nephritis

## COMPLICATIONS

- Renal vein thrombosis, pulmonary embolism, rapidly progressive glomerulonephritis

## SIGNS & SYMPTOMS

- Nephrotic, nephritic syndrome
- *Nephritic syndrome:* hematuria, hypertension, edema, proteinuria, oliguria

## DIAGNOSIS

### LAB RESULTS

**Kidney biopsy**

- Microscopic presentation depends on class of lupus nephritis

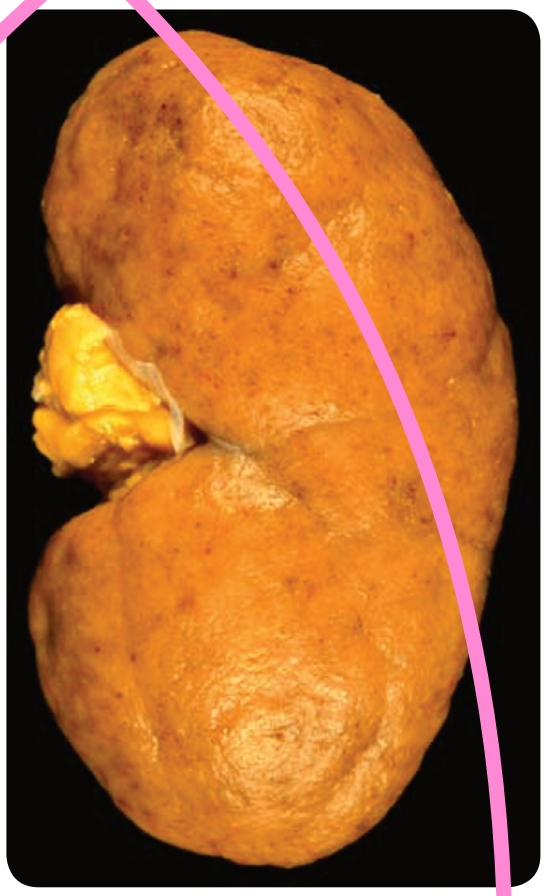

**Figure 118.3** Gross pathological appearance of a kidney in case of lupus nephritis. The renal capsule has a characteritic flea-bitten appearance.

## TREATMENT

### MEDICATIONS

- Immunosuppressants
  - Corticosteroids; mycophenolate, cyclophosphamide

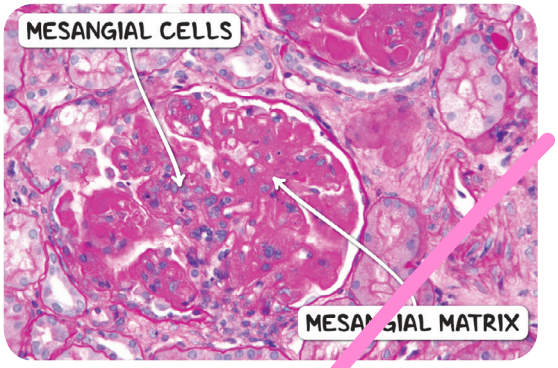


**Figure 118.4** Histological appearance of the glomerulus in a case of lupus nephritis. There is global mesangial cell proliferation and abundant mesangial matrix.

## LUPUS NEPHRITIS OVERVIEW

| | MICROSCOPIC APPEARANCE | KEY FACTS |
|---|---|---|
| CLASS I (MINIMAL MESANGIAL GLOMERULONEPHRITIS) | Normal appearance under light microscope; mesangial deposits under electron microscope | Mild clinical symptoms |
| CLASS II (MESANGIAL PROLIFERATIVE GLOMERULONEPHRITIS) | Mesangial hypercellularity, matrix expansion | Microscopic haematuria with/without proteinuria may occur |
| CLASS III (FOCAL GLOMERULONEPHRITIS) | Sclerotic lesions involving < 50% of glomeruli; subendothelial deposits under electron microscope | Haematuria, proteinuria with/without nephrotic syndrome, hypertension, elevated serum creatinine |
| CLASS IV (DIFFUSE PROLIFERATIVE NEPHRITIS) | > 50% of glomeruli involved; subendothelial deposits under electron microscope | Haematuria, proteinuria, frequently with nephrotic syndrome, hypertension, hypocomplementemia, elevated anti-dsDNA titres, elevated serum creatinine |
| CLASS V (MEMBRANOUS GLOMERULONEPHRITIS) | Diffuse thickening of glomerular capillary wall, diffuse membrane thickening, subepithelial deposits under electron microscope | Signs of nephrotic syndrome; microscopic haematuria, hypertension; may lead to thrombotic complications |
| CLASS VI (ADVANCED SCLEROSING LUPUS NEPHRITIS) | Global sclerosis involving > 90% of glomeruli | Slowly progressive kidney dysfunction |

# MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

osms.it/membrano-golmerulonephritis

## PATHOLOGY & CAUSES

- Type of nephrotic syndrome; inflammation of glomerular basement membrane, mesangium → decreased kidney function, proteinuria
- Immune complex/complement deposits trigger immune reactions
  - Activates complement system → enzyme cascade → membrane attack complex → damage to podocytes, mesangial cells
  - Recruits inflammatory cells → proteases, oxidants release → basement membrane damage → proteins leak into urine → nephrotic syndrome

### TYPES

- Appearance under light microscopy
  - Type I, II, II
  - All three can present as nephrotic, nephritic syndrome
- *Immunofluorescence:* immune complex-mediated MPGN, complement-mediated MPGN

### CAUSES

#### Type I

- Chronic infection (e.g. hepatitis B, hepatitis C)
  - Antigens released → bind antibodies in blood → immune complexes deposit in glomerular basement membrane → activate classical complement pathway → complement protein + immune complex deposits
- Inappropriate activation of alternative pathway of complement
  - Mutation in proteins that regulate pathway
  - Presence of autoantibodies against proteins that regulate pathway
- Nephritic factor (C3NeF)
  - IgG antibody, binds to C3 convertase → C3 convertase more stable, active longer
  - Only complement deposits, no immune complex deposits
  - *Autoimmune diseases:* systemic lupus erythematosus, scleroderma, Sjögren syndrome, sarcoidosis
  - *Cancer:* leukemia, lymphoma

#### Type II

- Nephritic factor (C3NeF)
  - IgG antibody binds to C3 convertase → C3 convertase more stable, active longer

#### Type III

- Idiopathic

### RISK FACTORS

- Dysregulation of complement system

### COMPLICATIONS

- Chronic renal failure, hypertension

## SIGNS & SYMPTOMS

- Nephrotic syndrome
  - Proteinuria, peripheral edema, foamy urine, hyperlipidemia, lipiduria
- Nephritic syndrome (more common)
  - Hematuria, oliguria (low production of urine), hypertension

## DIAGNOSIS

### LAB RESULTS

#### Kidney biopsy

#### Electron microscopy

- Type I
  - Subendothelial deposits
  - Thickening of basement membrane
  - Mesangial interposition: mesangial cells reach cytoplasmic arms through thick basement membrane, split lengthwise → duplicate basement membrane → "tram-track" appearance
- Type II
  - Complement deposits along basement membrane of glomeruli, tubules, Bowman's capsule
- Type III
  - Subepithelial deposits in mesangium, subendothelial space

## TREATMENT

### MEDICATIONS

- Treatment of underlying cause (e.g. antiviral therapy for hepatitis B virus)
- If underlying cause ruled out/nephrotic range proteinuria
  - Immunosuppressive therapy (steroids)

# MEMBRANOUS GLOMERULONEPHRITIS

**osms.it/membranous-glomerulonephritis**

## PATHOLOGY & CAUSES

- Inflammation of glomerular basement membrane triggered by immune complex deposits → increased permeability, proteinuria → nephrotic syndrome
- Glomerular basement membrane damaged by immune complex deposits; sandwiched between epithelial cells of podocytes, glomerular basement membrane (subendothelial deposits)
- Autoantibodies target glomerular basement membrane
  - *Two major antigen targets on podocytes:* M-type phospholipase A2 receptor, neural endopeptidase
- Complexes outside kidney, carried through blood, deposit in basement membrane
  - *Possible antigens:* cationic bovine serum albumin (cow's milk, beef protein)
- Immune complex deposits → immune reactions
  - Activates complement system → enzyme cascade → membrane attack complex → damage to podocytes, mesangial cells
  - Recruits inflammatory cells → proteases, oxidants release → basement membrane damage → proteins leak into urine → nephrotic syndrome
- Often benign
  - *Spontaneous complete remission:* 5–30% at five years
  - *Spontaneous partial remission:* 25–40% at five years

### CAUSES

#### Primary

- Mostly idiopathic
- Associated with human leukocyte antigen (HLA) alleles (e.g. HLA-DQA1)

### Secondary

- Auto-antibodies generated in response to underlying conditions
- Infections
  - Hepatitis B virus, hepatitis C virus, syphilis
- Medications
  - NSAIDs, penicillamine, gold
- Autoimmune
  - Systemic lupus erythematosus
- Malignancy

## RISK FACTORS

- White people of European descent
- Increase risk of end-stage renal disease
  - Older age at onset (> 50 years), individuals who are biologically male, nephrotic-range proteinuria (> 8–10g/day), increased serum creatinine

## COMPLICATIONS

- Chronic kidney failure, if untreated + nephrotic range proteinuria

# SIGNS & SYMPTOMS

- Often asymptomatic, discovered incidentally
- Proteinuria, hypoalbuminemia, edema, hyperlipidemia, lipiduria, hypercoagulability; develop gradually over months

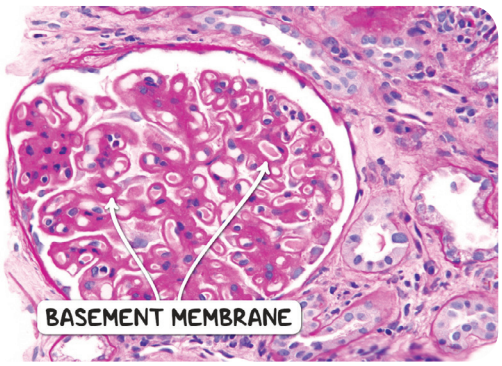


**Figure 118.5** Histological appearance of membranous glomerulonephritis. The basement membrane of the glomerulus is markedly thickened.

# DIAGNOSIS

## LAB RESULTS

- Proteinuria

### Renal biopsy

- Light microscopy
  - Diffuse thickening of glomerular basement membrane
- Electron microscopy
  - "Spike and dome" appearance due to glomerular basement matrix on top of subepithelial deposits; effacement of podocytes
- Immunofluorescence
  - Deposits appear granular throughout glomerular basement membrane
- If kidney biopsy not an option
  - *Serum:* assayed for antibodies associated with membranous glomerulonephritis (anti-PLA2R antibody)

# TREATMENT

## MEDICATIONS

### Primary cause

- Diuretics (furosemide), ACE inhibitors, heparin, antibacterial drugs
  - Symptomatic therapy
- Close observation, no immunosuppression
  - If at low risk of end-stage renal disorder (i.e. proteinuria < 3.5g/day)
- Prednisone + calcineurin inhibitor (e.g. tacrolimus, cyclosporine)/cytotoxic agent (e.g. cyclophosphamide)
  - If at moderate/high risk of end-stage renal disorder
- Rituximab

### Secondary cause

- Treat underlying condition

## OTHER INTERVENTIONS

- Lifestyle changes
  - Medical nutrition therapy, reduce cholesterol, saturated fat intake

# MINIMAL CHANGE DISEASE

osms.it/minimal-change-disease

## PATHOLOGY & CAUSES

- Type of glomerulonephritis; podocytes in glomeruli damaged by T cells cytokines
- Foot processes of podocytes damaged, flattened (AKA effacement) → lose function as barrier → albumin permeates, bigger proteins cannot get through (selective proteinuria)

### CAUSES

- Unknown; T cells release cytokines, may cause effacement of podocytes

### RISK FACTORS

- Recent infection; immunization; immune stimulus; medications: nonsteroidal anti-inflammatory drugs (NSAIDs)
- Hematologic malignancies (e.g. Hodgkin's lymphoma)
- Most common nephrotic syndrome in children

### COMPLICATIONS

- Relatively benign, does not affect kidney function

## SIGNS & SYMPTOMS

- Proteinuria, hypoalbuminemia, edema, hyperlipidemia, lipiduria, hypercoagulability
- Onset more rapid (days to weeks) than other nephrotic syndromes

## DIAGNOSIS

### LAB RESULTS

- Protein in urine > 3.5g/day

#### Kidney biopsy

- Corticosteroid resistant patients
- Light microscopy
  - Glomeruli appear normal, hence "minimal change disease"
- Electron microscopy
  - Effacement of foot processes.
- Immunofluorescence
  - Negative (no immune complex deposition)

## TREATMENT

### MEDICATIONS

- Prednisone therapy
  - Excellent response, more quickly in children than adults; potential relapse

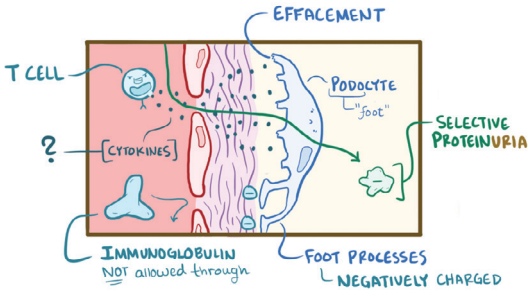


**Figure 118.6** An illustration demonstrating the pathophysiology of minimal change disease.