NEPHROTIC SYNDROME

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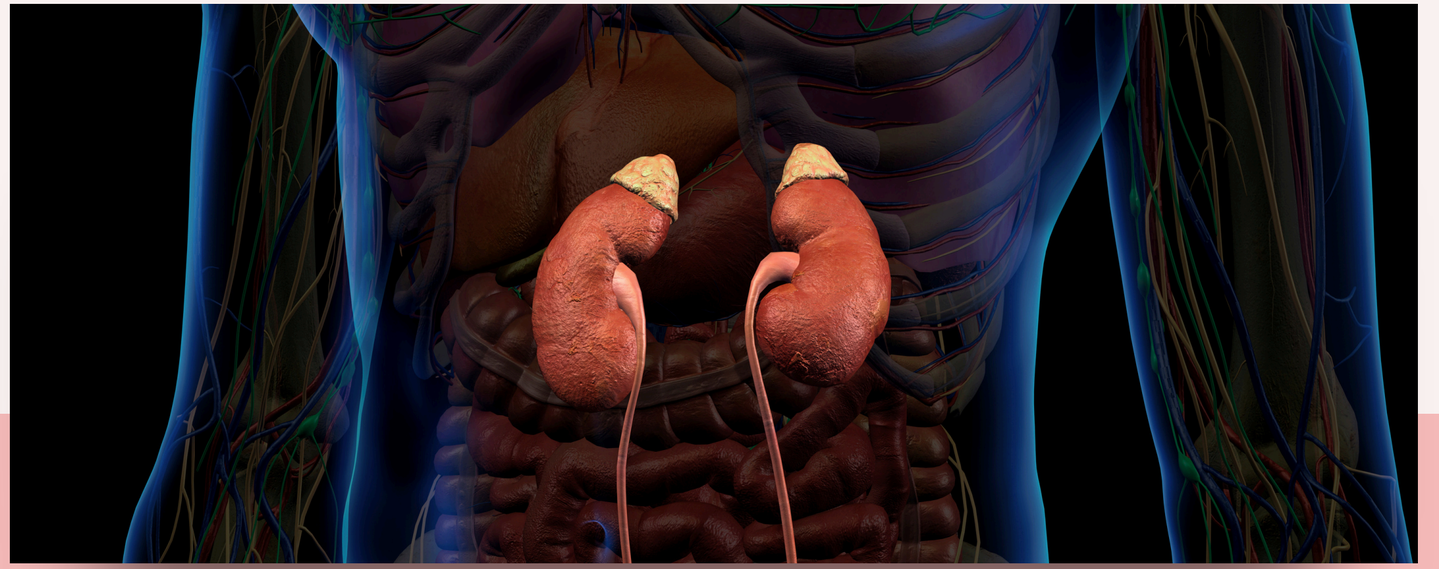
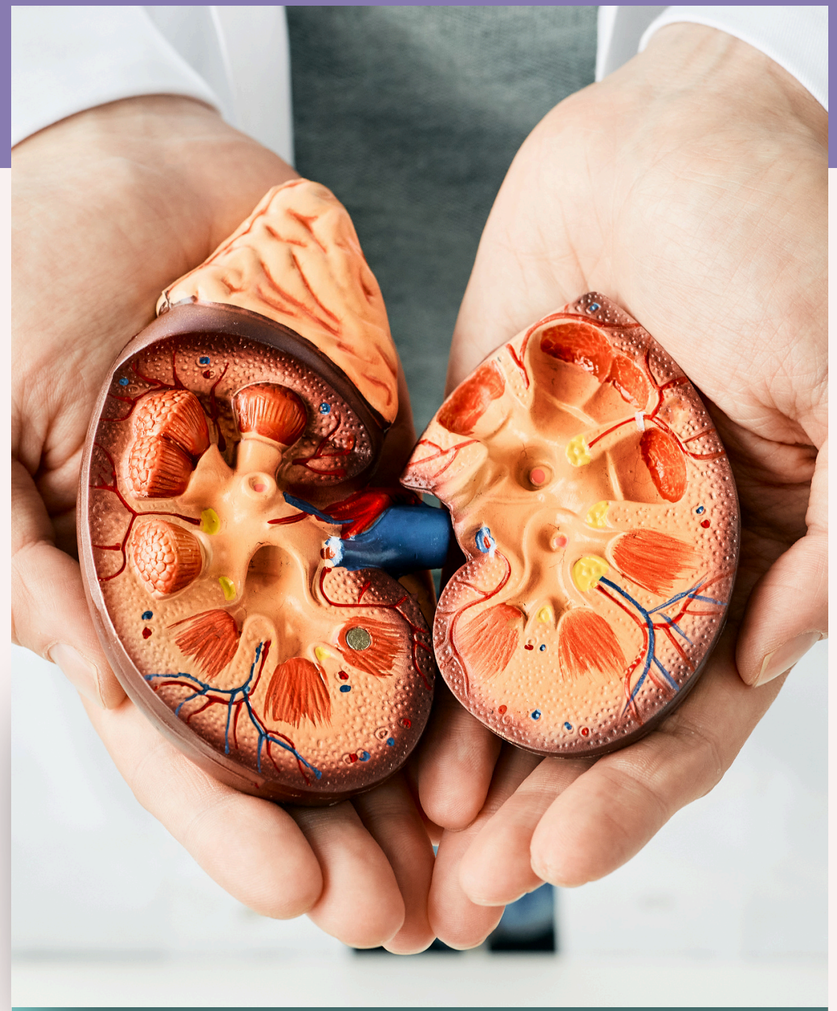
DEFINITIONS

- Nephrotic-range proteinuria: proteinuria > 3.5 g/24 hours
- Nephrotic syndrome:

1. **nephrotic-range proteinuria**
2. **hypoalbuminemia**
3. **edema**



ETIOLOGY



Nephrotic syndrome may be caused by primary glomerular disorders (80–90% of cases) and/or systemic diseases and toxic exposures (10–20% of cases).

- Primary (idiopathic) forms: The following types of nephrotic syndrome are commonly associated with other conditions.
  - Minimal change disease
  - Focal segmental glomerulosclerosis
  - Membranous nephropathy
  - Membranoproliferative glomerulonephritis (can manifest as nephrotic or nephritic syndrome)
- Secondary forms
  - Diabetic nephropathy
  - Amyloid nephropathy
  - Lupus nephritis (can manifest as nephrotic or nephritic syndrome)

MINIMAL CHANGE DISEASE (LIPOID NEPHROSIS)

- Most common cause of nephrotic syndrome in children

pathophysiology: cytokine-mediated damage of podocytes

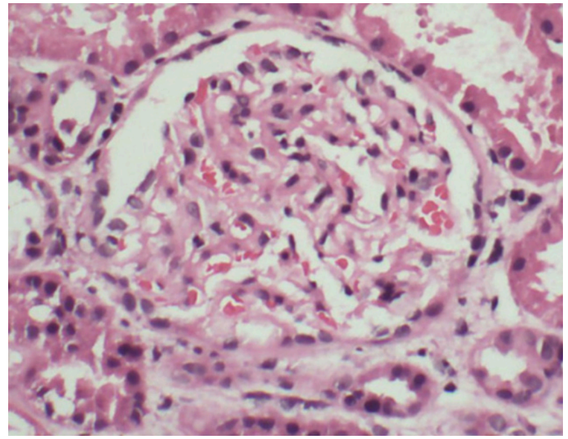
Associations

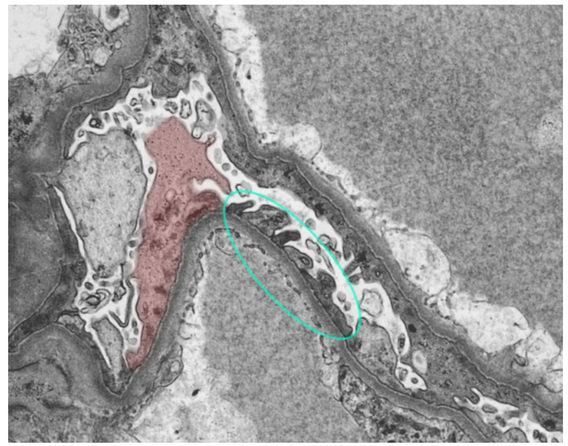
- Often idiopathic
- Secondary causes (rare):

1. Immune stimulus (e.g., infection, immunization)
2. Tumors (e.g., Hodgkin lymphoma)
3. Certain drugs (e.g., NSAIDs)

Findings

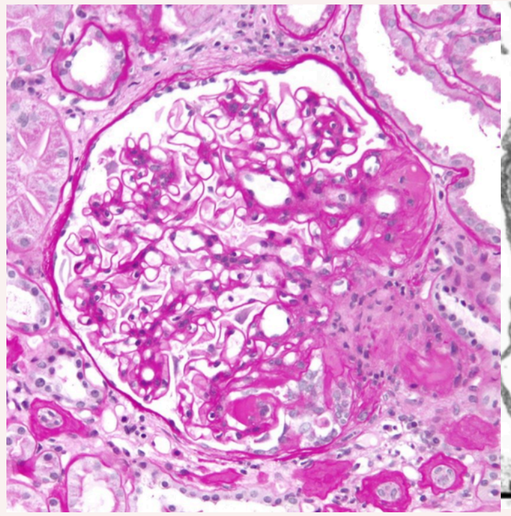
- LM: no changes(possibly fat bodies in some proximaltubular cells)
- IM: negative
- EM: effacement of podocyte foot processes
- Selective glomerular proteinuria

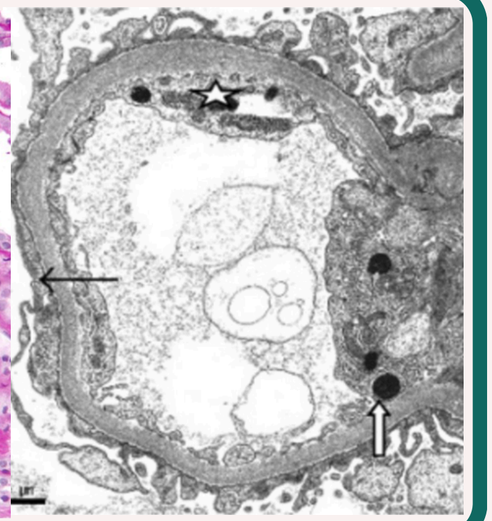




FOCAL SEGMENTAL GLOMERULOSCLEROSIS

- Most common cause of nephrotic syndrome in adults, especially in African American and Hispanic populations
- **Pathophysiology: sclerosis of glomeruli → damage and loss of podocytes**





Associations

- Can be idiopathic
- Heroin use
- HIV infection
- Sickle cell disease
- Massive obesity
- Interferontreatment
- Congenital malformations(e.g., Charcot-Marie-Tooth syndrome) [8][9]
- NPHS1 and NHPS2 mutations

Findings

- LM: segmental sclerosis and hyalinosis
- IM
  - Most commonly negative
  - Possibly IgM, C1, and C3 depositsinside the sclerotic regions
- EM: effacement of podocyte foot processes (similar to minimal change disease)

MEMBRANOUS NEPHROPATHY

Most common cause of nephrotic syndrome in adults of European, Middle Eastern, or North African descent

Pathophysiology

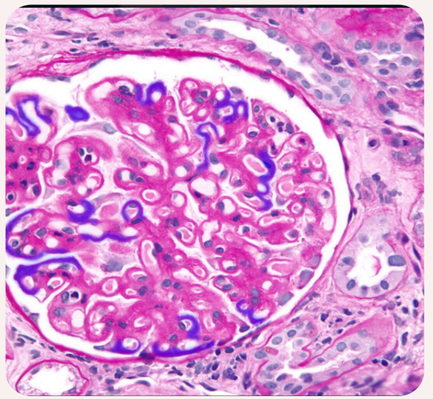
Anti-phospholipase A2 receptor antibodies (anti-PLA2R antibodies) bind to PLA2R (an autoantigen in glomerular podocytes) and thereby form immune complexes that activate the complement system, leading to podocyte injury.

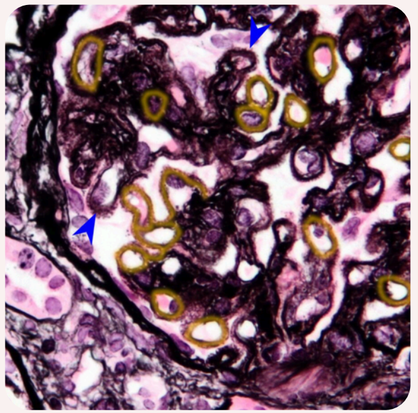
Associations

- Primary: **anti-PLA2R antibodies**
- Secondary:
  - Infections(HBV, HCV, malaria, syphilis)
  - Autoimmune diseases (e.g., SLE)
  - Tumors (e.g., lung cancer, prostate cancer)
  - Medications (e.g., NSAIDs, penicillamine, gold)

Findings

- LM:
- Diffuse thickened glomerularcapillary loops and basement membrane
- Granular subepithelial deposits of IgG and C3 (dense deposits) → **spike and dome appearance**





DIABETICNEPHROPATHY

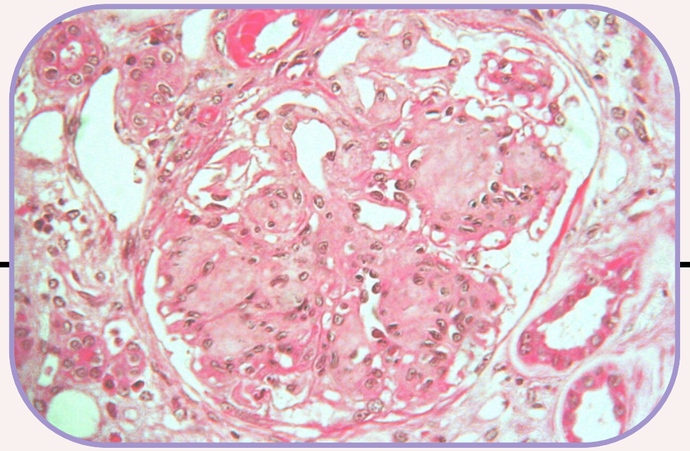
Pathophysiology

Chronic hyperglycemia → glycation (also called non-enzymatic glycosylation or NEG) of the basement membrane (protein glycation) → increased permeability and thickening of the basement membrane and stiffening of the efferent arteriole → hyperfiltration (increase in GFR) → increase in intraglomerular pressure → progressive glomerular hypertrophy, increase in renal size, and glomerular scarring (glomerulosclerosis) → worsening of filtration capacity

DIABETICNEPHROPATHY

ASSOCIATION

Usually additional signs of other organ system complications (e.g., retinopathy, neuropathy)



FINDING

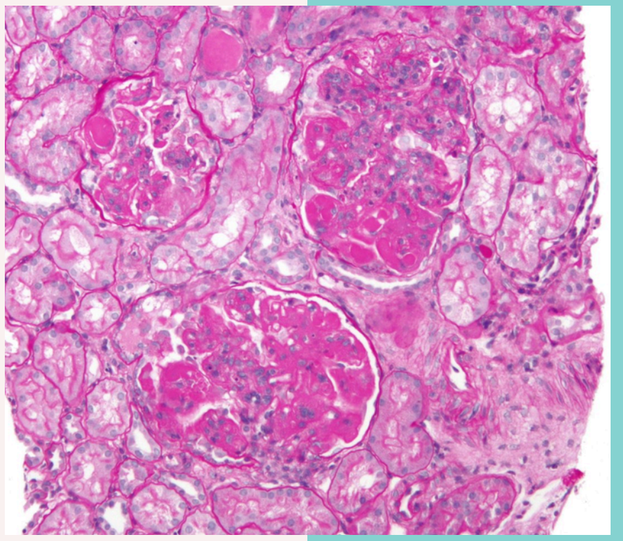
- LM
  - Thickening of the glomerular basement membrane(increased permeability)
  - Eosinophilic nodular glomerulosclerosis(Kimmelstiel-Wilson nodules)
- EM
  - Thickening of the glomerular basement membrane
  - Mesangial matrix expansion
  - Segmental effacement of podocyte foot processes

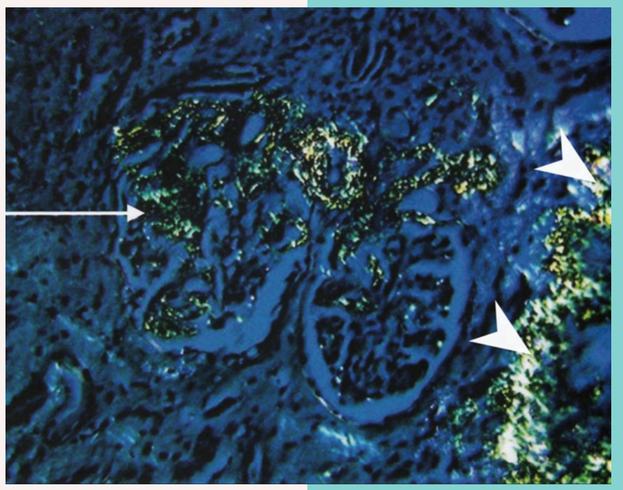
AMYLOID NEPHROPATHY

- The kidney is the most commonly affected organ in systemic amyloidosis.
- Other organs might be involved simultaneously (e.g., the heart).
- Multiple myeloma(AL amyloidosis)
- Chronic inflammatory disease, e.g., tuberculosis, rheumatoid arthritis (AA amyloidosis)

Finding:

1. **LM**
   - **Mesangial proliferation**
   - **Subendothelial and/or subepithelial immune complex deposition**
   - **Thickening of the capillary walls (appear as wire loops)**
   - **Congo red stain: amyloid deposition in the mesangium showing apple-green birefringence under polarized light**
   - **Nodular glomerulosclerosis**
2. **IM: positive for AA protein (AA amyloidosis), positive for kappa and lambda light chains (AL amyloidosis)**
3. **EM: amyloid fibrils**





CLINIC FEATURES

Edema

Massive proteinuria > 3.5 g/24 hours

frothy urine

Hypoalbuminemia —>Typically starts with periorbital edema

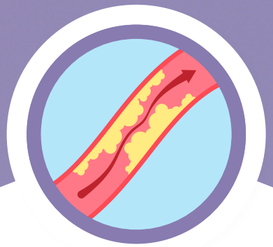
Peripheral edema (pitting)

Pleural effusion

Pericardial effusion

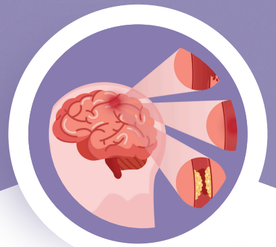
Ascites

In severe cases, **anasarca**



Hyperlipidemia

low serum albumin and oncotic pressure cause increases in lipoprotein synthesis from the liver LDL& VLDL —> cause high risk for CVA , MI , PAD by atherosclerosis

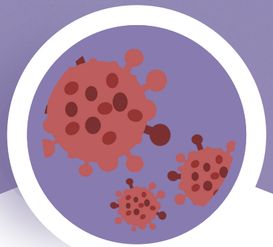


Hypercoagulable state

with increased risk of thrombosis and embolic events (e.g., pulmonary embolism, renal vein thrombosis)

Due to Loss of antithrombin III, protein C, and protein S,

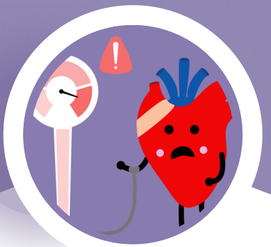
In Renal vein thrombosis patients present with flank pain, hematuria and decreased renal function , high LDH



Increased susceptibility to infection

due to high Proteinuria Loss of immunoglobulins → increased risk of infection, especially Streptococcus pneumoniae infection (pulmonary edema also increases the risk for S. pneumoniae infection)

Causes pneumonia, peritonitis, UTI



Hypertension

due to sodium retention and volume overload

- Symptoms of hypocalcemia (e.g., tetany, paresthesia, muscle spasms)
- Symptoms of the underlying disease (e.g., malar rash in lupus nephritis)

COMPLICATIONS

- **chronic kidney injury**

Chronic Injury to Glomerulus Leads to Glomerulosclerosis, —> low GFR, high Creatinine, high BUN
FSGS and membranous nephropathy in particular may progress to chronic kidney disease and ESRD.

- Loss of transport proteins

Loss of thyroglobulin transport protein → **thyroxin deficiency**
Vitamin D binding protein → **vitamin D deficiency**

APPROACH APATIENT WITH NEPHROTIC SYNDROME

HISTORY

Onset and duration: Acute vs. chronic

- Edema: Generalized (periorbital, lower limb, ascites)
- Urine changes: Frothy urine (suggestive of proteinuria)
- Systemic symptoms: Fatigue, weight gain, signs of infection

• RISK FACTORS:

- Recent infections (post-infectious glomerulonephritis)
- Medications (NSAIDs, penicillamine, gold, lithium)
- Autoimmune diseases (SLE, diabetes)
- Malignancies (solid tumors, Hodgkin’s lymphoma)

APPROACH APATIENT WITH NEPHROTIC SYNDROME

PHYSICAL EXAMINATION:

- Edema (pitting, periorbital, ascites)
- Hypertension or hypotension (volume status)
- Signs of secondary causes:
- Diabetes: Retinopathy
- Lupus: Rash, arthritis
- Infections: Hepatitis, HIV signs
- Malignancy: Lymphadenopathy, organomegaly

LABORATORY

URIN ANALYSIS

Confirmation of nephrotic-range proteinuria

- **Qualitative assessment by urine dipstick (commonly used for screening)**
  Usually shows ≥ 3+ proteins
- **Quantitative assessment of urine protein excretion**
  - **24-hour urine protein (test of choice): > 3.5 g/24 hours**
  - **Spot urine protein/creatinine ratio : > 3.5 g/g**

- **Urine sediment microscopy**
  - **Nephrotic sediment**
  - **Lipiduria, fatty casts with Maltese cross appearance under polarized light**

BLOOD TEST

CBC: ↑ Hb/Hct may indicate hemoconcentration
BMP: ↑ Cr and/or ↑ BUN may be seen
Serum protein: ↓ total protein, ↓ albumin (< 3 g/dL)
Coagulation factors: ↓ ATIII, ↓ protein S, ↓ plasminogen ; ↑ fibrinogen, ↑ D-dimer [28][29]
Lipid profile: Hyperlipidemia (↑ LDL, ↑ triglycerides) may be present.
Vitamin D levels: ↓ 25-OH Vit-D
Inflammatory markers: ↑ ESR, ↑ CRP may suggest underlying infection, inflammatory condition, or vasculitis.

RENAL BIOPSY

Indication: to confirm the diagnosis when the etiology of nephrotic syndrome is unclear and/or to guide management

Diagnostic Approach to Nephrotic Syndrome

Obtain
HbA1c, SPEP/UPEP +/- Fat pad Biopsy, and Anti-PLA2R antibody

Chronic DM
HbA1c (>6.5%)
(+) Retinopathy
→ Diabetic Nephropathy

(+)SPEP/UPEP
(+) Fat pad biopsy
→ Amyloid Nephropathy

(+)Anti-PLA2R → 1°Membranous Nephropathy

(-) Findings from above (e.g. diagnostic uncertainty)
Proteinuria and Renal function despite therapy (e.g. steroids)

Obtain
Renal Biopsy

Minimal change Disease

LM: Normal glomeruli
EM: Podocyte effacement
IF: Normal

Focal Segmental Glomerulosclerosis

LM: Sclerotic/hyalinotic glomeruli
EM: Podocyte effacement
IF: Normal

(+)HIV, Obesity,
Sickle cell, Heroin, IFN therapy?

No → 1° FSGS
Yes → 2° FSGS

Membranous Nephropathy

LM: Thick glomerular basement membrane (GBM)
EM: Subepithelial Deposits of Immune complexes
IF: Granular appearance of immune complexes

(+)HBV/HCV, (+) RPR,
(+)ANA and/or Anti-dsDNA, Malignancy?

No → 1° MN
Yes → 2° MN

Biopsy Findings of DM:
-LM: Kimmelstiel wilson nodules

Biopsy Findings of Amyloid:
-LM: Apple green birefringence on congo red stain

TREATMENT

Primary forms of nephrotic glomerulopathies: often treated with **immunosuppressive therapy**

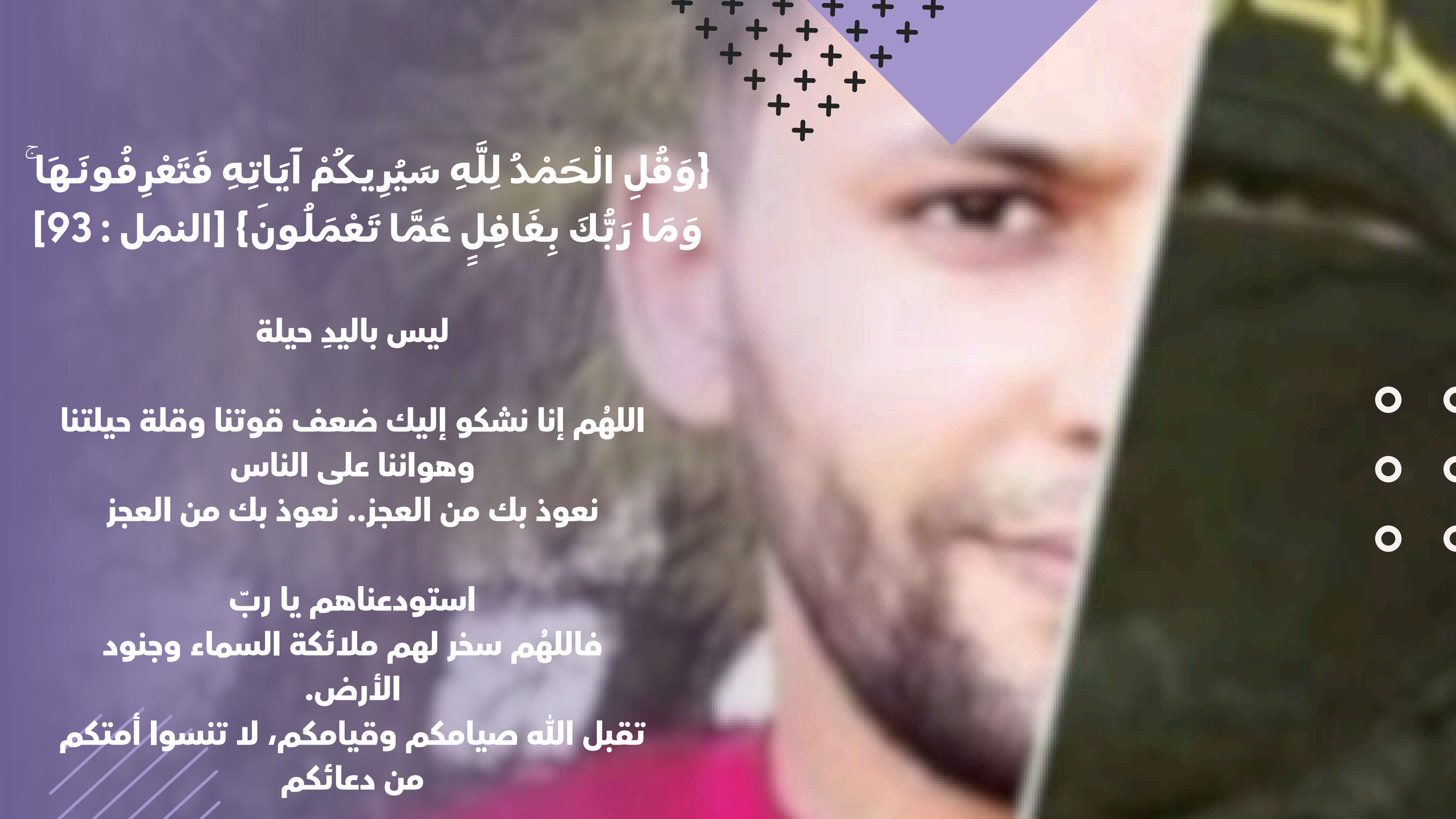
Immunosuppressive therapies may include:
Glucocorticoids (used initially)

Additional immunosuppressants (e.g.,**cyclophosphamide, calcineurin inhibitors**) in patients with steroid-resistant nephrotic syndrome or severe disease
Management in adults is usually guided by biopsy
-based histological diagnosis.
Children are often treated initially with empiric corticosteroids for presumed MCD

- **Secondary forms of nephrotic glomerulopathies: Treat the underlying cause.**

Treatment of **Glomerular Diseases**

Disorder	Treatment of Complications	Indications
Glomerular Disorders	Sodium restriction + Loop Diuretics	- Edema
	ACE-I or ARBs	- Hypertension & Proteinuria
	Statin therapy	- Hyperlipidemia
	Anticoagulation	- Hypercoagulability
	Pneumococcal vaccination	- Nephrotic Syndrome
	Dialysis	- Renal Failure Complications



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وَمَا رَبُّكَ بِغَافِلٍ عَمَّا تَعْمَلُونَ} [النمل : 93]

ليس باليدِ حيلة

اللهُم إنا نشكو إليك ضعف قوتنا وقلة حيلتنا
وهواننا على الناس
نعوذ بك من العجز.. نعوذ بك من العجز

استودعناهم يا ربّ
فاللهُم سخر لهم ملائكة السماء وجنود
الأرض.
تقبل الله صيامكم وقيامكم، لا تنسوا أمتكم
من دعائكم