Nephrotic Syndrome

Nephrotic syndrome is a clinical syndrome characterized by significant proteinuria, hypoalbuminemia, edema, and hyperlipidemia, often leading to complications if untreated. This document provides a comprehensive overview for physician assistant (PA) students in a hospital setting.

Definition and Epidemiology

Definition:

Nephrotic syndrome (NS) is a kidney disorder defined by:

• **Proteinuria:** >3.5 g/day (or spot urine protein-to-creatinine ratio >2 mg/mg in adults, >2 mg/mg in children).

• **Hypoalbuminemia:** Serum albumin <3 g/dL.

• **Edema:** Often periorbital, lower extremity, or anasarca.

• **Hyperlipidemia:** Elevated cholesterol and triglycerides.

• **Additional features:** Hypercoagulability (due to urinary loss of antithrombin III), increased infection risk (loss of immunoglobulins), and hypocalcemia (due to vitamin D deficiency).

Epidemiology:

• **Incidence:** ~3 per 100,000 adults/year; more common in children (15-20 per 100,000/year, peak age 2-6 years).

• **Primary Causes in Children:** Minimal change disease (MCD) accounts for 70-90% of cases in children <10 years.

• **Primary Causes in Adults:** Focal segmental glomerulosclerosis (FSGS, 35%), membranous nephropathy (MN, 30%), MCD (10-15%).

• **Secondary Causes:** Diabetes mellitus, systemic lupus erythematosus (SLE), amyloidosis, and drugs (e.g., NSAIDs, gold).

• **Risk Factors:** Family history of kidney disease, diabetes, hypertension, obesity, infections (e.g., HIV, hepatitis B/C), and certain medications.

Pathophysiology

Mechanisms:

• **Podocyte Injury:** Damage to glomerular podocytes (e.g., in MCD, FSGS, MN) disrupts the filtration barrier, allowing massive protein leakage into the urine.

• **Proteinuria:** Loss of albumin and other proteins (e.g., antithrombin III, immunoglobulins) leads to downstream effects.

• **Hypoalbuminemia:** Urinary protein loss exceeds liver synthesis capacity (normal albumin half-life ~20 days), reducing oncotic pressure.

• **Edema:** ↓ Oncotic pressure → Fluid extravasation into interstitial space; secondary hyperaldosteronism (due to hypovolemia) exacerbates sodium retention.

• **Hyperlipidemia:** Hypoalbuminemia stimulates hepatic lipoprotein synthesis (↑ LDL, VLDL); ↓ lipoprotein lipase activity impairs lipid clearance.

• **Hypercoagulability:** Urinary loss of antithrombin III, protein C/S, and ↑ hepatic synthesis of clotting factors (e.g., fibrinogen) → Prothrombotic state.

• **Infection Risk:** Loss of immunoglobulins and complement proteins → Impaired immunity (e.g., ↑ risk of pneumococcal infections).

• **Hypocalcemia:** Loss of vitamin D-binding protein and 25-hydroxyvitamin D → ↓ Calcium absorption, secondary hyperparathyroidism.

Key Pathway:

Podocyte injury → Proteinuria → Hypoalbuminemia → Edema, hyperlipidemia, hypercoagulability, infection risk.

Causes of Nephrotic Syndrome

Category Causes Notes

Category	Causes	Notes
Primary Glomerular Diseases	Minimal Change Disease (MCD), Focal Segmental Glomerulosclerosis (FSGS), Membranous Nephropathy (MN)	MCD: Common in children, steroid-responsive. FSGS: Common in adults, progressive. MN: Anti-PLA2R positive in 70-80%.

Category	Causes	Notes
Systemic Diseases	Diabetes Mellitus, Systemic Lupus Erythematosus (SLE), Amyloidosis (AL/AA), Multiple Myeloma, Preeclampsia	Diabetes: Nodular glomerulosclerosis. SLE: Class V lupus nephritis. Amyloidosis: Congo red staining.
Infections	Hepatitis B/C (HBV/HCV), HIV (HIVAN), Syphilis, Malaria, Schistosomiasis	HBV/HCV: MN pattern. HIVAN: Collapsing FSGS, common in African descent.
Drugs/Toxins	NSAIDs, Gold, Penicillamine, Heroin, Lithium, Pamidronate	NSAIDs: MCD pattern. Gold/Penicillamine: MN pattern.
Other	Hereditary (e.g., NPHS1/NPHS2 mutations), Malignancy (e.g., lymphoma, solid tumors), Obesity, Sickle Cell Disease	Hereditary: Familial FSGS. Malignancy: MN (solid tumors), MCD (lymphoma).

Common Drugs Causing Nephrotic Syndrome

Drug Mechanism Notes

Drug	Mechanism	Notes
NSAIDs	Podocyte injury (MCD pattern)	E.g., ibuprofen, naproxen; reversible with cessation.
Gold	Immune complex deposition (MN pattern)	Used in RA; rare with modern therapies.
Penicillamine	Immune complex deposition (MN pattern)	Used in Wilson's disease, RA; monitor proteinuria.
Heroin	Direct toxicity, collapsing FSGS	Common in IV drug users; poor prognosis.
Lithium	Podocyte injury (MCD, FSGS)	Long-term use; monitor renal function.
Pamidronate	Collapsing FSGS	Bisphosphonate; used in hypercalcemia, osteoporosis.

Clinical Presentation

Symptoms:

• **Edema:** Periorbital (early), lower extremity, anasarca; often the presenting symptom.

• **Foamy Urine:** Due to high proteinuria.

• **Fatigue/Weakness:** From hypoalbuminemia, anemia (if chronic kidney disease present).

• **Infections:** Recurrent infections (e.g., cellulitis, peritonitis), especially in children.

• **Thrombotic Events:** Deep vein thrombosis (DVT), renal vein thrombosis (RVT), pulmonary embolism (PE).

Physical Exam:

• **Edema:** Pitting edema (legs, feet), periorbital edema, ascites, pleural effusions.

• **Hypertension:** Common in FSGS, diabetic nephropathy; less common in MCD.

• **Signs of Underlying Disease:** Malar rash (SLE), neuropathy (amyloidosis), retinopathy (diabetes).

• **Thrombosis Signs:** leg swelling (DVT), flank pain/hematuria (RVT), hypoxia/tachycardia (PE).

Red Flags:

• Gross hematuria, rapid renal decline → Suspect glomerulonephritis (e.g., lupus nephritis, post-infectious).

• Acute flank pain, hematuria → Consider renal vein thrombosis.

• Severe infections (e.g., peritonitis) → Urgent antibiotics, supportive care.

Diagnostic Workup

Initial Labs:

• **Urinalysis:** Proteinuria (3+ to 4+ on dipstick), microscopic hematuria (if glomerulonephritis), oval fat bodies, Maltese cross (lipiduria).

• **Spot Urine Protein-to-Creatinine Ratio (UPCR):** >2 mg/mg confirms nephrotic-range proteinuria.

• **24-Hour Urine Protein:** >3.5 g/day (gold standard but cumbersome).

• **Serum Albumin:** <3 g/dL (often 1-2 g/dL in severe cases).

• **Lipid Panel:** ↑ Total cholesterol, LDL, triglycerides.

• **Serum Creatinine/eGFR:** Assess renal function; often normal in MCD, elevated in FSGS, diabetic nephropathy.

• **Electrolytes:** Hypocalcemia (↓ vitamin D), hyponatremia (edema-related dilution).

Specific Tests:

- **Serologies:**
  - ANA, anti-dsDNA (SLE).
  - Hepatitis B/C serologies (HBV/HCV-associated MN).
  - HIV (FSGS in HIVAN).
  - **Complement (C3, C4):** Low in SLE, post-infectious GN.
  - **SPEP/UPEP:** Monoclonal spike in amyloidosis, multiple myeloma.
  - **Anti-PLA2R Antibodies:** Positive in 70-80% of primary membranous nephropathy.
  - **Serum Free Light Chains:** For amyloidosis, multiple myeloma.
  - **Genetic Testing:** If familial FSGS suspected (e.g., NPHS1, NPHS2 mutations).
- Imaging:
  - **Renal Ultrasound:** Rule out obstruction, assess kidney size (small in chronic disease, normal/large in acute).
  - **Doppler Ultrasound:** If renal vein thrombosis suspected (flank pain, hematuria).
  - **CT Chest/Extremities:** If PE or DVT suspected.

Renal Biopsy:

- **Indications:** Adults with NS (most cases); children if atypical features (e.g., hematuria, hypertension, poor steroid response).
  - **Findings:**
    - **MCD:** Normal light microscopy, podocyte effacement on electron microscopy (EM).
    - **FSGS:** Segmental scarring, podocyte injury on EM.
    - **MN:** Subepithelial deposits, "spike and dome" on EM.
    - **Diabetic Nephropathy:** Nodular glomerulosclerosis (Kimmelstiel-Wilson nodules).
    - **Amyloidosis:** Congo red staining, amyloid fibrils on EM.

Key Tips:

• UPCR first to confirm proteinuria; 24-hour collection if UPCR equivocal.

• Serologies to identify secondary causes (SLE, HBV, HIV).

• Biopsy in adults; often deferred in children with MCD (presumed if steroid-responsive).

Diagnostic Flowsheet: Nephrotic Syndrome

Step 1: Urinalysis/UPCR: Proteinuria: Dipstick 3+/4+, UPCR >2mg. 24-hour urine: >3.5 g/day.

Step	Description
Step 1: Urinalysis/ UPCR:	Proteinuria: Dipstick 3+/4+, UPCR >2mg. 24-hour urine: >3.5 g/day.
Step 2: Serum Labs	-Albumin: <3 g/dL. -Lipids: ↑ Cholesterol, triglycerides. -Creatinine/eGFR: Assess renal function.
Step 3: Serologies/ Imaging	-ANA, anti-dsDNA (SLE). -HBV/HCV, HIV. -Anti-PLA2R (MN). -Renal US: Rule out obstruction, RVT.
Step 4: Biopsy (Adults)	Children: Presume MCD if steroid-responsive. Adults: MCD, FSGS, MN, diabetic nephropathy.
Step 5: Confirm Diagnosis	-MCD: Steroid response, podocyte effacement. -FSGS: Segmental scarring. -MN: Anti-PLA2R, subepithelial deposits.

Treatment

General Principles:

Reduce proteinuria, manage complications (edema, hyperlipidemia, thrombosis, infections), and treat the underlying cause.

Supportive Care:

- Edema:
  - **Sodium Restriction:** <2 g/day.
  - **Diuretics:** Furosemide 40-80 mg IV/PO daily (loop diuretic); add spironolactone 25-50 mg daily if refractory.
  - **Fluid Restriction:** 1-1.5 L/day if severe edema.
  - **Monitor:** Daily weights, urine output; avoid over-diuresis (risk of AKI).
- Hyperlipidemia:
  - **Statins:** Atorvastatin 20-40 mg daily (LDL >100 mg/dL).
  - **Dietary Counseling:** Low saturated fat, high fiber.
- Thrombosis Prophylaxis:
  - **Anticoagulation:** Prophylactic heparin (e.g., enoxaparin 40 mg SC daily) if albumin <2 g/dL, immobile, or history of thrombosis.
  - **Monitor:** Doppler US if DVT/RVT suspected; CT chest if PE suspected.
- Infection Prevention:
  - **Vacines:** Pneumococcal (PCV20), influenza (annually).

- **Prophylaxis:** Consider antibiotics (e.g., penicillin) in children with severe hypoalbuminemia.
- **Dietary Protein:** 0.8-1 g/kg/day (avoid high protein; does not correct hypoalbuminemia, may worsen proteinuria).
- **Vitamin D/Calcium:** Vitamin D3 1000-2000 IU daily, calcium 1000 mg daily (correct hypocalcemia, prevent osteoporosis).

Specific Therapy:

- Minimal Change Disease (MCD):
  - **Steroids:** Prednisone 1 mg/kg/day (max 80 mg) x 4-8 weeks, then taper over 2-3 months.
    - **Response:** 80-90% of children, 50-70% of adults respond within 4-8 weeks.
    - **Relapse:** Cyclophosphamide 2 mg/kg/day x 8-12 weeks or calcineurin inhibitors (e.g., tacrolimus 0.05-0.1 mg/kg/day).
- Focal Segmental Glomerulosclerosis (FSGS):
  - **Steroids:** Prednisone 1 mg/kg/day x 8-16 weeks (less responsive than MCD).
  - **Adjunctive:** Cyclosporine 3-5 mg/kg/day or tacrolimus (if steroid-resistant).
  - **ACEi/ARBs:** Lisinopril 10-40 mg daily (reduce proteinuria, renoprotective).
- Membranous Nephropathy (MN):
  - **Risk Stratification:** Anti-PLA2R titers, proteinuria severity.
    - **Low Risk:** Supportive care (ACEi/ARBs, statins).
    - **High Risk:** Cyclophosphamide + steroids (Ponticelli regimen: methylprednisolone 1 g IV x 3 days, then prednisone 0.5 mg/kg/day, alternate with cyclophosphamide 2 mg/kg/day x 6 months) or rituximab 375 mg/m² weekly x 4 doses.
- Diabetic Nephropathy:
  - **Glycemic Control:** HbA1c <7% (insulin, metformin).
  - **BP Control:** ACEi/ARBs (e.g., losartan 50-100 mg daily), target BP <130/80 mmHg.
  - **SGLT2 Inhibitors:** Empagliflozin 10-25 mg daily (reduces proteinuria, slows progression).
- Lupus Nephritis (Class V):
  - **Immunosuppression:** Prednisone 0.5-1 mg/kg/day + mycophenolate mofetil (MMF) 1-2 g/day.
  - **Monitor:** Anti-dsDNA, C3/C4, proteinuria.

- Amyloidosis:
  - **Treat Underlying Cause:** Chemotherapy for AL amyloidosis (e.g., bortezomib, dexamethasone); anti-inflammatory for AA amyloidosis (e.g., colchicine in FMF).
  - **Supportive:** Diuretics, ACEi/ARBs.
- Infection-Associated (e.g., HBV, HCV):
  - **Antivirals:** Teno`fovir 300 mg daily (HBV), sofosbuvir/ledipasvir (HCV).
- **o Immunosuppression:** Avoid unless severe (risk of viral replication).
- Renin-Angiotensin System (RAS) Blockade:
- **o ACEi/ARBs:** Start in all patients (e.g., lisinopril 10 mg daily); reduces intraglomerular pressure, proteinuria.
- **o Monitor:** Serum potassium, creatinine (30% rise in Cr acceptable initially).

Key Tips:

• **Children with MCD:** Start steroids empirically; biopsy if no response in 8 weeks.

• **Adults:** Biopsy first, then tailor therapy (e.g., rituximab for MN, MMF for lupus).

• Thrombosis risk highest when albumin <2 g/dL; prioritize prophylaxis.

Examples

Case 1: Minimal Change Disease (Child)

Presentation: 4 y/o M, periorbital edema, weight gain, UPCR 3.5 mg/mg, albumin 2.2 g/dL, cholesterol 300 mg/dL, normal creatinine.

Interpretation: Nephrotic syndrome, likely MCD (child, no hematuria/hypertension).

Management: Prednisone 1 mg/kg/day x 6 weeks, then taper; sodium restriction, furosemide 1 mg/kg/day for edema, pneumococcal vaccine, monitor UPCR weekly.

Case 2: FSGS (Adult)

Presentation: 35 y/o M, leg edema, HTN, UPCR 4.2 mg/mg, albumin 1.8 g/dL, creatinine 1.5 mg/dL, biopsy: FSGS.

Interpretation: Nephrotic syndrome, primary FSGS (adult, HTN, renal dysfunction).

Management: Prednisone 1 mg/kg/day x 12 weeks, lisinopril 20 mg daily, atorvastatin 20 mg daily, enoxaparin 40 mg SC daily (albumin <2 g/dL), monitor creatinine, proteinuria.

Case 3: Membranous Nephropathy (Anti-PLA2R Positive)

Presentation: 50 y/o F, anasarca, UPCR 5 mg/mg, albumin 1.5 g/dL, anti-PLA2R positive, biopsy: MN.

Interpretation: Nephrotic syndrome, primary MN (anti-PLA2R positive).

Management: Rituximab 375 mg/m² weekly x 4, lisinopril 10 mg daily, furosemide 40 mg daily, atorvastatin 40 mg daily, enoxaparin prophylaxis, monitor anti-PLA2R titers.

Case 4: Diabetic Nephropathy

Presentation: 60 y/o M, T2DM, HTN, leg edema, UPCR 3.8 mg/mg, albumin 2.5 g/dL, creatinine 2.0 mg/dL, HbA1c 8.5%.

Interpretation: Nephrotic syndrome, diabetic nephropathy (DM, HTN, renal dysfunction).

Management: Optimize glycemic control (insulin), losartan 50 mg daily, empagliflozin 10 mg daily, furosemide 40 mg daily, atorvastatin 20 mg daily, monitor eGFR, HbA1c.

Case 5: Lupus Nephritis (Class V)

Presentation: 28 y/o F, malar rash, edema, UPCR 4 mg/mg, albumin 2.0 g/dL, ANA positive, low C3/C4, biopsy: lupus nephritis (Class V).

Interpretation: Nephrotic syndrome, secondary to SLE.

Management: Prednisone 0.5 mg/kg/day + MMF 1 g BID, lisinopril 10 mg daily, furosemide 40 mg daily, hydroxychloroquine 200 mg BID, monitor anti-dsDNA, C3/C4.

Complications

Acute:

• **Thrombosis:** Renal vein thrombosis (10-20% in MN), DVT/PE (albumin <2 g/dL increases risk).

• **Infections:** Pneumococcal peritonitis, cellulitis (loss of IgG, complement).

• **Acute Kidney Injury (AKI):** Hypovolemia (over-diuresis), renal vein thrombosis, or progression of underlying disease.

• **Hypovolemia:** From severe hypoalbuminemia, over-diuresis → Hypotension, AKI.

Long-Term:

• **Chronic Kidney Disease (CKD):** Progressive decline in eGFR (esp. FSGS, diabetic nephropathy).

• **Cardiovascular Disease:** Hyperlipidemia → Atherosclerosis, MI, stroke.

• **Osteoporosis:** Vitamin D deficiency, steroid use → Bone loss, fractures.

• **End-Stage Renal Disease (ESRD):** 20-30% of FSGS patients progress to ESRD within 5-10 years.

Prognosis

Remission Rates:

• **MCD:** 80-90% of children achieve remission with steroids; 50-70% of adults. Relapse common (50% in children).

• **FSGS:** 20-40% achieve remission with treatment; 30-50% progress to ESRD in 5-10 years.

• **MN:** 30-40% spontaneous remission; 30% progress to ESRD if untreated. Rituximab improves outcomes.

• **Diabetic Nephropathy:** Slow progression with RAS blockade, SGLT2 inhibitors; 20-40% reach ESRD in 10-15 years.

Mortality:

• **Infections/Thrombosis:** Leading causes of death in untreated NS (5-10% mortality if complications occur).

• **ESRD:** Higher mortality on dialysis (20-30% 5-year mortality).

Key Factors:

• Early immunosuppression (e.g., steroids, rituximab) improves remission rates.

• Control of proteinuria (<0.5 g/day) slows CKD progression.

• Secondary causes (e.g., SLE, diabetes) have worse prognosis if untreated.

Key Pearls

• **Nephrotic syndrome:** Proteinuria (>3.5 g/day), hypoalbuminemia (<3 g/dL), edema, hyperlipidemia.

• **Children:** Presume MCD, start steroids; biopsy if no response in 8 weeks.

• **Adults:** Biopsy first; tailor therapy (e.g., rituximab for MN, MMF for lupus).

• **Thrombosis risk:** Prophylactic anticoagulation if albumin <2 g/dL.

• **Edema:** Sodium restriction, diuretics; avoid over-diuresis (AKI risk).

• **Monitor:** UPCR, albumin, creatinine, lipids; treat complications (infections, thrombosis).

References

• UpToDate: "Nephrotic Syndrome" (2025).

• KDIGO: "Glomerular Diseases Guidelines" (2021).

• NEJM: "Rituximab in Membranous Nephropathy (MENTOR Trial)" (2019).

• JASN: "Management of FSGS" (2023).

• Lancet: "Diabetic Nephropathy: Advances in Treatment" (2024).

Visit: medcheatsheets.com for more education, fun resources and 10 category 1 AAPA CME credit!