

Nephrotic Syndrome

Glomerular permeability, systemic consequences, and clinicopathologic classification

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Learning objectives

- Define the nephrotic syndrome and distinguish it from isolated proteinuria.
- Trace glomerular protein leakage to hypoalbuminemia, edema, lipid abnormalities, and complications.
- Classify major primary and systemic causes using age and morphology.
- Interpret the roles of light, immunofluorescence, and electron microscopy.

Nephrotic syndrome is a clinical pattern, not one disease

- Multiple glomerular lesions can produce the same permeability phenotype.
- The shared functional lesion is increased glomerular capillary permeability to plasma proteins.
- Etiology, microscopic pattern, renal function, and prognosis vary among causes.
- A clinical syndrome directs the search for an underlying glomerular or systemic disease.

The four cardinal manifestations

Heavy
Proteinuria

Hypo-
Albuminemia

Generalized
Edema

Hyperlipidemia
And lipiduria

A linked set of findings; Edema and dyslipidemia arise downstream of glomerular protein leakage.

Core diagnostic thresholds

Heavy proteinuria

Daily loss ≥ 3.5 g of protein

Pediatric thresholds differ

Hypoalbuminemia

Plasma albumin < 3 g/dL

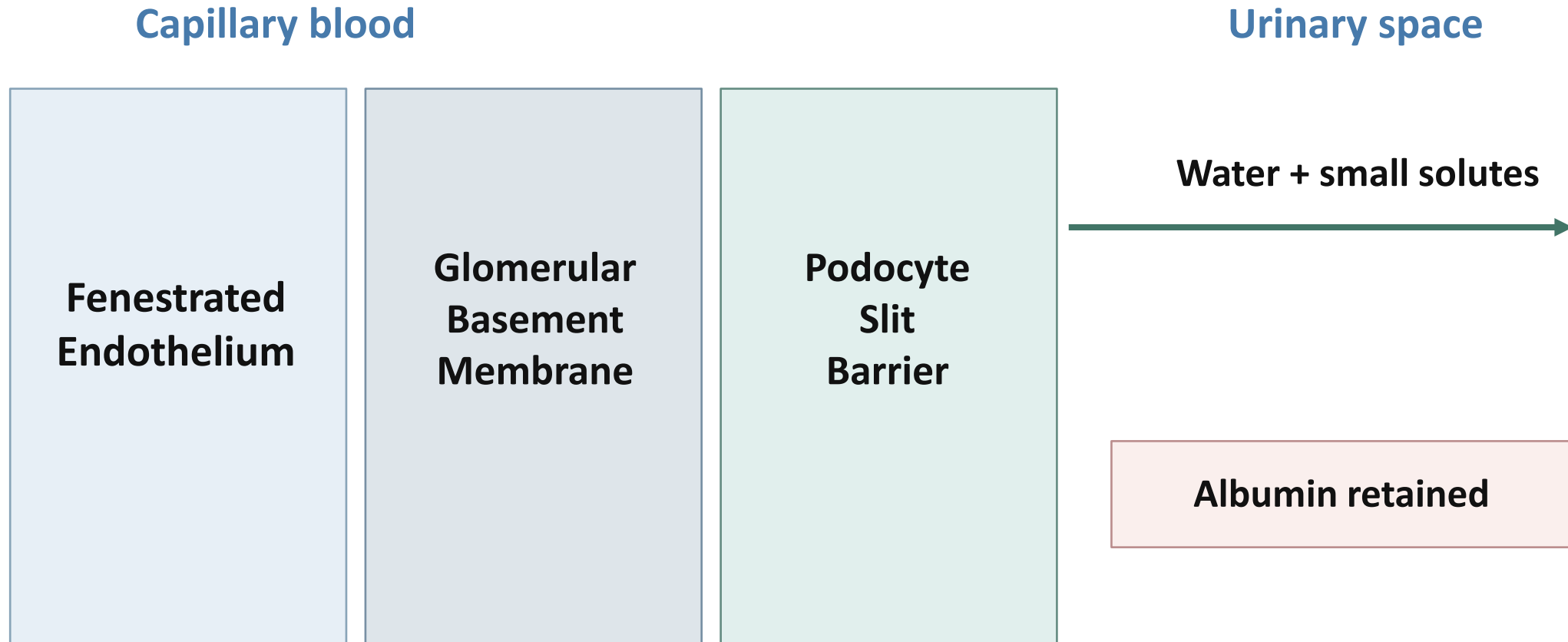
Interpret alongside edema and lipid findings

Nephrotic-range proteinuria alone does not establish the complete syndrome.

Nephrotic-range proteinuria is not synonymous with the syndrome

- “Nephrotic range” describes the magnitude of protein excretion.
- “Nephrotic syndrome” describes proteinuria with the characteristic systemic biochemical and clinical constellation.
- Severity of edema and dyslipidemia does not map perfectly to any single protein measurement.
- An underlying lesion remains to be identified.

Three layers form the glomerular filtration barrier



Schematic: Compartments and barrier function; Not an electron micrograph.

Fenestrated endothelium permits high-volume ultrafiltration

- The endothelial layer contains fenestrae allowing passage of water and small solutes.
- Endothelium is the blood-facing component of the capillary filtration wall.
- Normal barrier function depends on coordinated endothelial, basement-membrane, and podocyte integrity.
- Protein restriction cannot be assigned to the endothelial layer alone.

GBM matrix contributes to selective permeability

- The glomerular basement membrane contains type IV collagen, laminin, and proteoglycans.
- Its extracellular matrix supports the structural integrity of capillary loops.
- Size- and charge-dependent restriction arise from the composite filtration barrier.
- Changes in matrix architecture can accompany proteinuric glomerular disease.

Podocyte slit diaphragms form a distal protein barrier

- Interdigitating podocyte foot processes delimit filtration slits.
- Slit diaphragms bridge these spaces and maintain selective protein restriction.
- Nephrin, podocin, and associated proteins connect the junction to the actin cytoskeleton.
- Podocyte injury or defective slit architecture can cause severe proteinuria.

The normal filter discriminates by size and charge

Size selectivity

Larger plasma proteins are less permeable

Slit diaphragm is a distal size-selective barrier

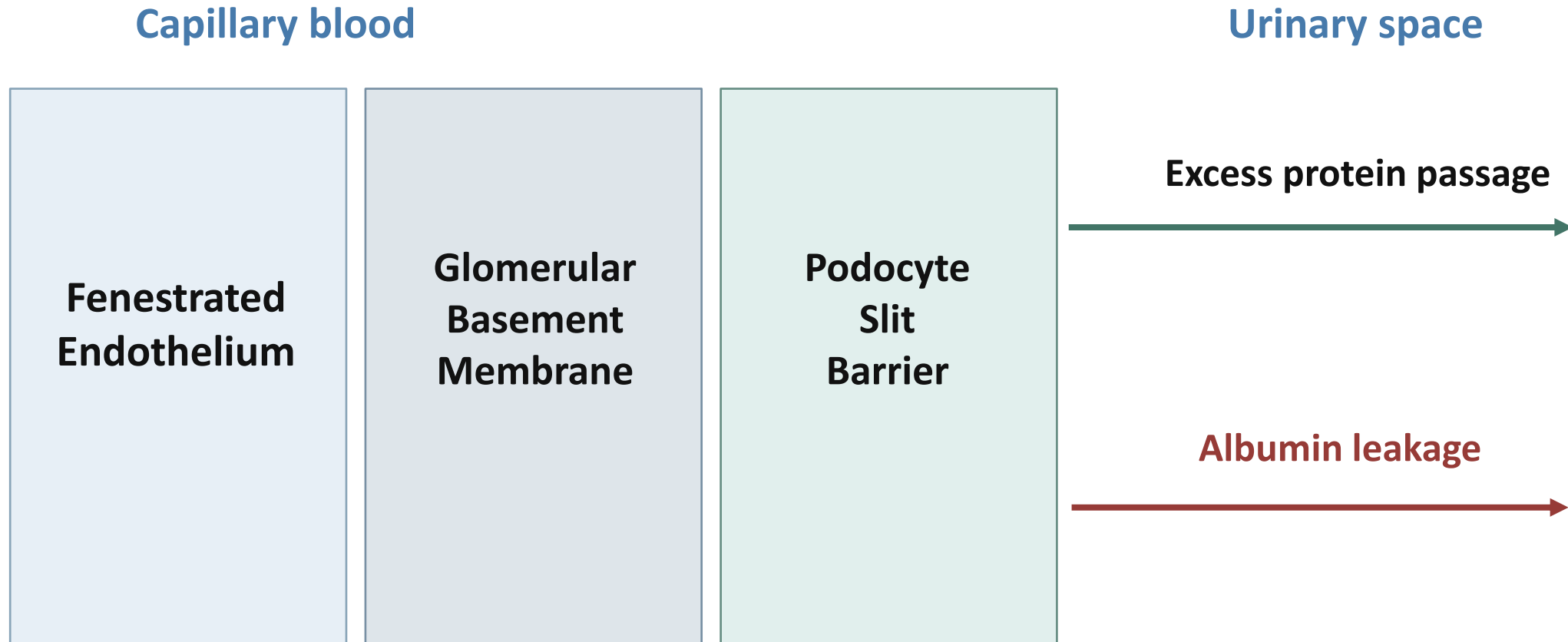
Charge selectivity

Anionic albumin is normally excluded

Glomerular barrier properties restrict anionic proteins

The intact filtration wall as a combined size- and charge-selective barrier.

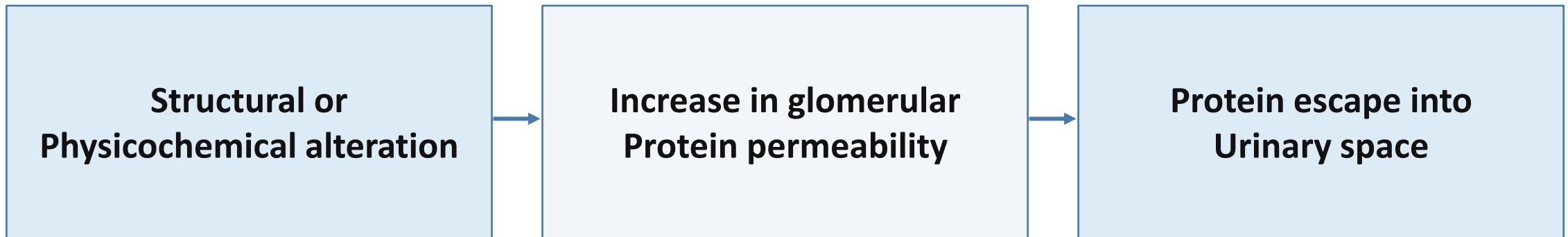
Loss of barrier integrity permits albumin escape



Schematic: Compartments and barrier function; Not an electron micrograph.

Structural and physicochemical injury converge on proteinuria

Different initiating lesions can share the same final pathway.



Heavy urinary losses are dominated by albumin, with variable globulin excretion.

Protein selectivity reflects the filtration lesion

Highly selective

Mainly lower-molecular-weight proteins

Albumin and transferrin predominate

Often seen with minimal change disease

Poorly selective

Larger globulins accompany albumin

Reflects broader permeability

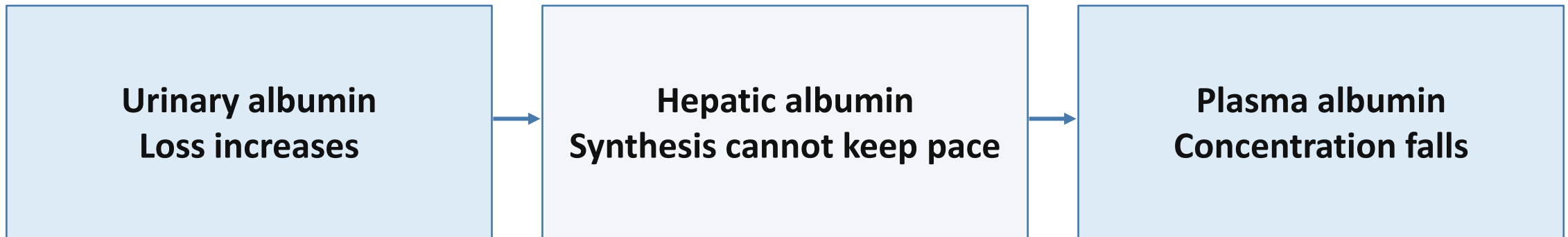
Often seen with FSGS or membranous disease

Urinary protein loss is mainly albumin

- Albumin represents the largest proportion of urinary protein loss in many nephrotic patients.
- Globulins are also excreted when the filter becomes poorly selective.
- The molecular-weight composition of urine protein provides clues to filtration-barrier injury.
- Protein loss has both plasma-concentration and systemic consequences.

Proteinuria overwhelms hepatic compensation

Net albumin balance determines circulating albumin concentration.



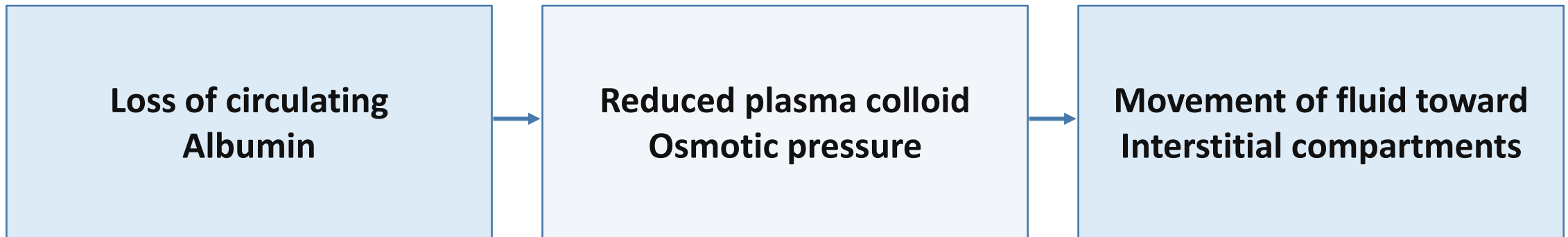
Increased renal catabolism of filtered albumin additionally contributes to hypoalbuminemia.

Tubular handling of filtered albumin adds to depletion

- Filtered albumin may be reabsorbed and catabolized by renal tubules.
- Increased renal catabolism is an additional mechanism of hypoalbuminemia.
- Tubular protein droplets may accompany marked glomerular protein leakage.
- The major driver of circulating albumin depletion remains heavy proteinuria.

Hypoalbuminemia lowers plasma oncotic pressure

Albumin contributes substantially to intravascular oncotic pressure.



The clinical result is soft, pitting edema—often periorbital or dependent.

Two processes amplify nephrotic edema

Fluid redistribution

Reduced plasma oncotic pressure

Fluid shifts toward interstitium

Intravascular underfilling may occur

Renal sodium–water retention

Renin–aldosterone stimulation

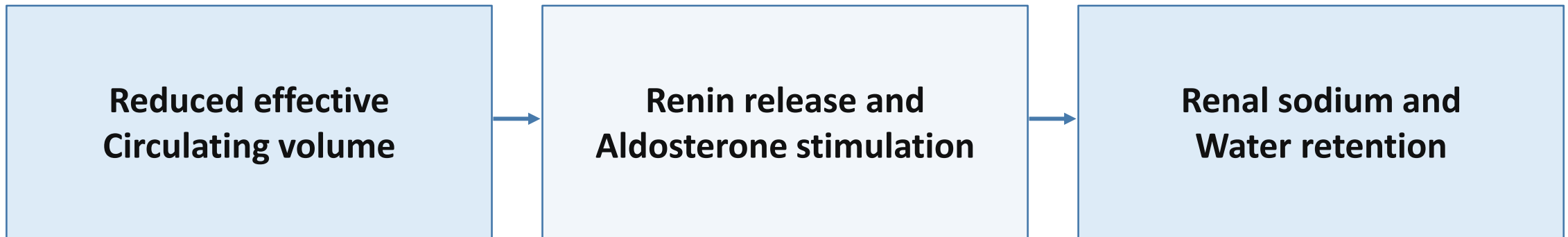
Sympathetic activity / reduced natriuresis

Further expands edema

Both are mechanisms; Their relative importance can vary.

Renin–aldosterone signaling can aggravate edema

A compensatory response can intensify edema.



The textbook also identifies sympathetic activity and reduced natriuretic influences.

Other neurohumoral pathways encourage retention

- Enhanced sympathetic nervous system activity supports renal salt and water conservation.
- Reduced secretion of natriuretic factors can diminish sodium excretion.
- These responses interact with changes in effective intravascular volume.
- The net effect is increased extracellular fluid accumulation.

Edema distribution has a physiologic basis

- Periorbital swelling is a characteristic early or prominent location.
- Dependent tissues accumulate fluid under the influence of gravity.
- Soft, pitting edema reflects freely mobile interstitial fluid.
- Distribution and severity depend on oncotic pressure, salt balance, and posture.

Severe hypoalbuminemia may cause serous effusions

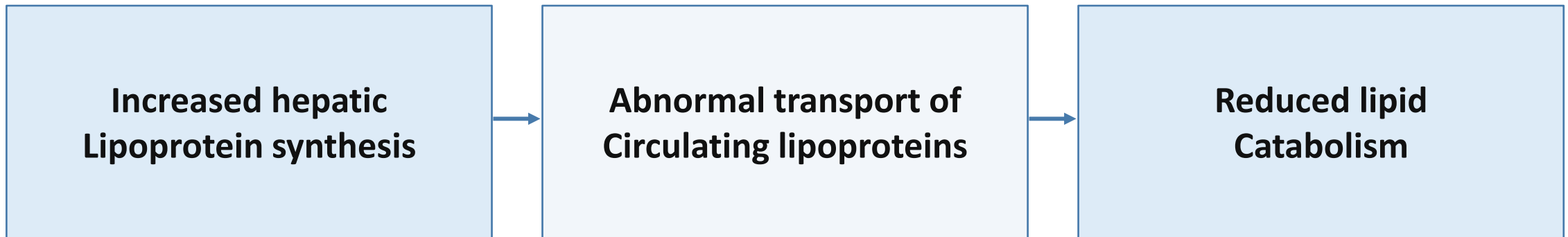
- Reduction of plasma oncotic pressure may lead to clinically important third-spacing.
- Pleural effusions may accumulate around the lungs.
- Ascites may develop when fluid collects in the peritoneal cavity.
- These findings are consequences of systemic fluid imbalance—not separate glomerular lesions.

Nephrotic dyslipidemia affects multiple lipoproteins

- Cholesterol and triglyceride levels are often increased.
- Very-low-density and low-density lipoproteins may rise.
- Lipoprotein(a) and apoprotein concentrations may also increase.
- High-density lipoprotein concentration can decrease in some patients.

Hyperlipidemia has more than one mechanism

The combined disturbance yields elevated circulating cholesterol and triglycerides.



It is not explained solely by albumin synthesis in the liver.

Altered lipid transport sustains circulating lipoproteins

- The dyslipidemic state reflects disturbed synthesis, distribution, and clearance.
- Changes in apoproteins and transport contribute to the altered plasma profile.
- Lipid abnormalities can persist while urinary protein loss remains heavy.
- Interpret lipid changes as part of the systemic response to nephrosis.

Hyperlipidemia and a leaky barrier cause lipiduria

Lipiduria arises from combined plasma and glomerular abnormalities.

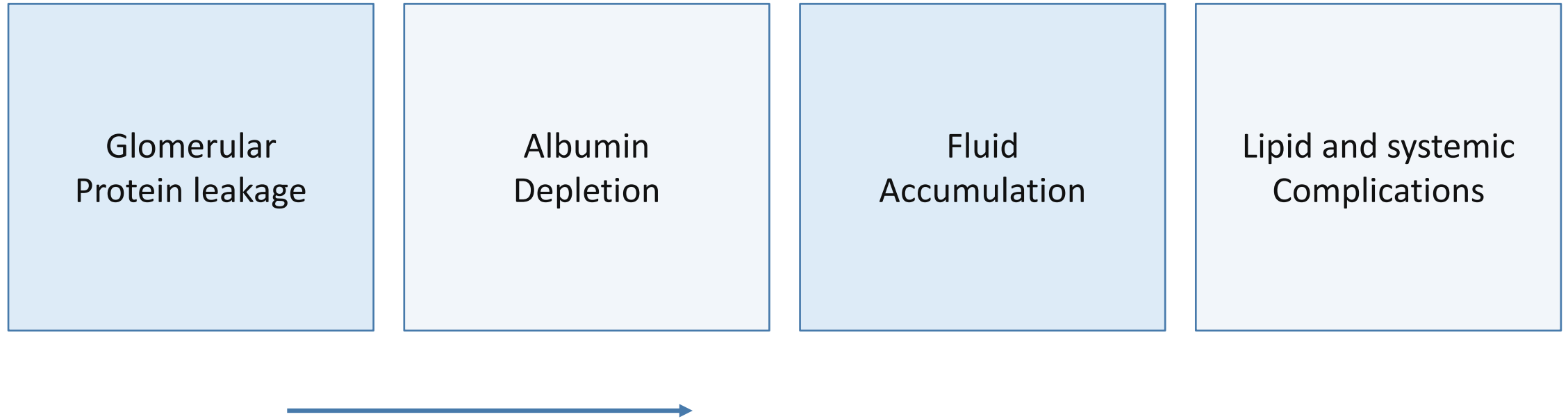


Urinary lipid may be free fat or contained in exfoliated tubular epithelial cells.

Oval fat bodies reflect tubular uptake of lipid

- Filtered lipoproteins are reabsorbed by tubular epithelial cells.
- Lipid-laden tubular cells may detach and enter urinary sediment.
- Such cells appear as oval fat bodies in a nephrotic urine sample.
- Their presence reflects lipid handling downstream of glomerular leakage.

Clinical findings form one causal network



Permeability defect is upstream; Later features are linked but not identical.

Urinary immunoglobulin loss increases infection risk

- Loss of plasma proteins can include immunoglobulins.
- Reduced host-defense components contribute to susceptibility to infection.
- Nephrotic patients may be particularly vulnerable to bacterial infections.
- Infection risk is a systemic complication, not simply a urinary tract issue.

Staphylococcal and pneumococcal infections merit attention

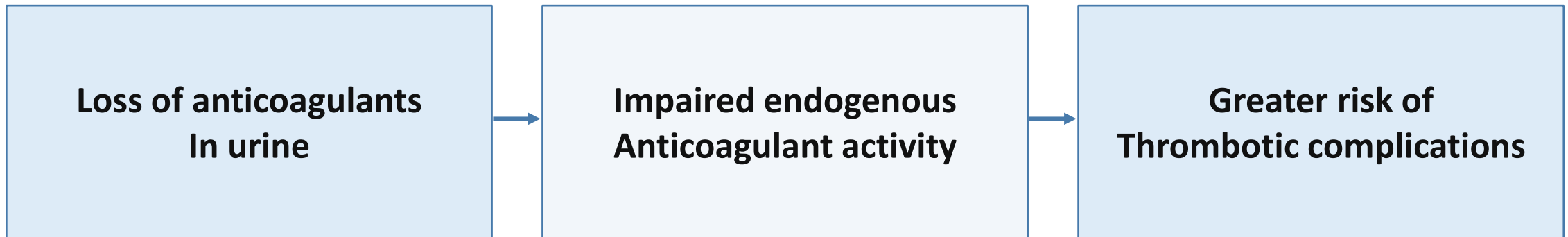
- Robbins specifically highlights staphylococcal infections.
- Pneumococcal infections are another characteristic concern.
- Protein losses provide a plausible link between nephrosis and impaired humoral defense.
- A febrile patient with active nephrosis should not be assessed as having edema alone.

Nephrosis can create a hypercoagulable state

- Loss of endogenous anticoagulants contributes to increased thrombotic risk.
- Antithrombin III is a specifically described urinary loss.
- Thrombotic and thromboembolic complications occur in nephrotic patients.
- Proteinuria therefore produces consequences beyond low oncotic pressure.

Urinary antithrombin loss can promote thrombosis

The renal lesion can alter systemic hemostasis.



Antithrombin III loss is one contributor; It is not the only determinant of risk.

Renal vein thrombosis: Complication rather than primary cause

- Renal vein thrombosis was historically regarded as a possible cause of nephrosis.
- It is usually a consequence of the hypercoagulable state.
- The association is particularly important in membranous nephropathy.
- Do not invert the causal direction when interpreting nephrotic presentations.

Four domains of nephrotic morbidity

Fluid overload
And effusions

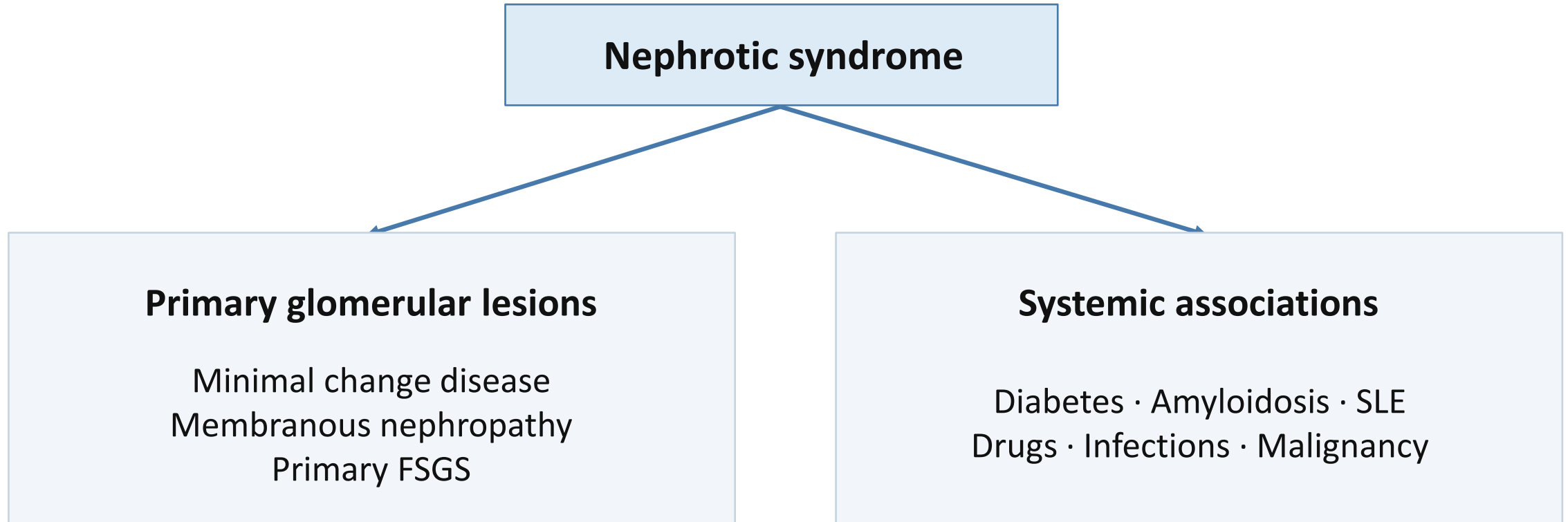
Dyslipidemia
And lipiduria

Infection
Susceptibility

Venous thrombosis
And embolism

All trace back to glomerular injury and its biochemical/systemic effects.

Classify causes as primary or associated with systemic disease



The list is representative, not exhaustive.

Age changes the differential diagnosis

- In North American children, nephrosis is usually due to a primary glomerular lesion.
- Systemic disease is a relatively more important source in adults.
- Minimal change disease dominates childhood primary patterns.
- Membranous nephropathy and FSGS become more prominent in adult etiologic assessment.

Primary childhood patterns: Use age to prioritize

Textbook estimates for primary causes in children; Do not generalize across populations.

Lesion	Approximate share*	Teaching implication
Minimal change disease	75%	Most frequent primary lesion
FSGS	10%	Significant alternative
Membranous nephropathy	3%	Relatively uncommon
MPGN / other GN	≈12% combined	May show mixed manifestations

Adult primary lesions show a different distribution

Textbook composite estimates among primary causes; Systemic disease is separately considered.

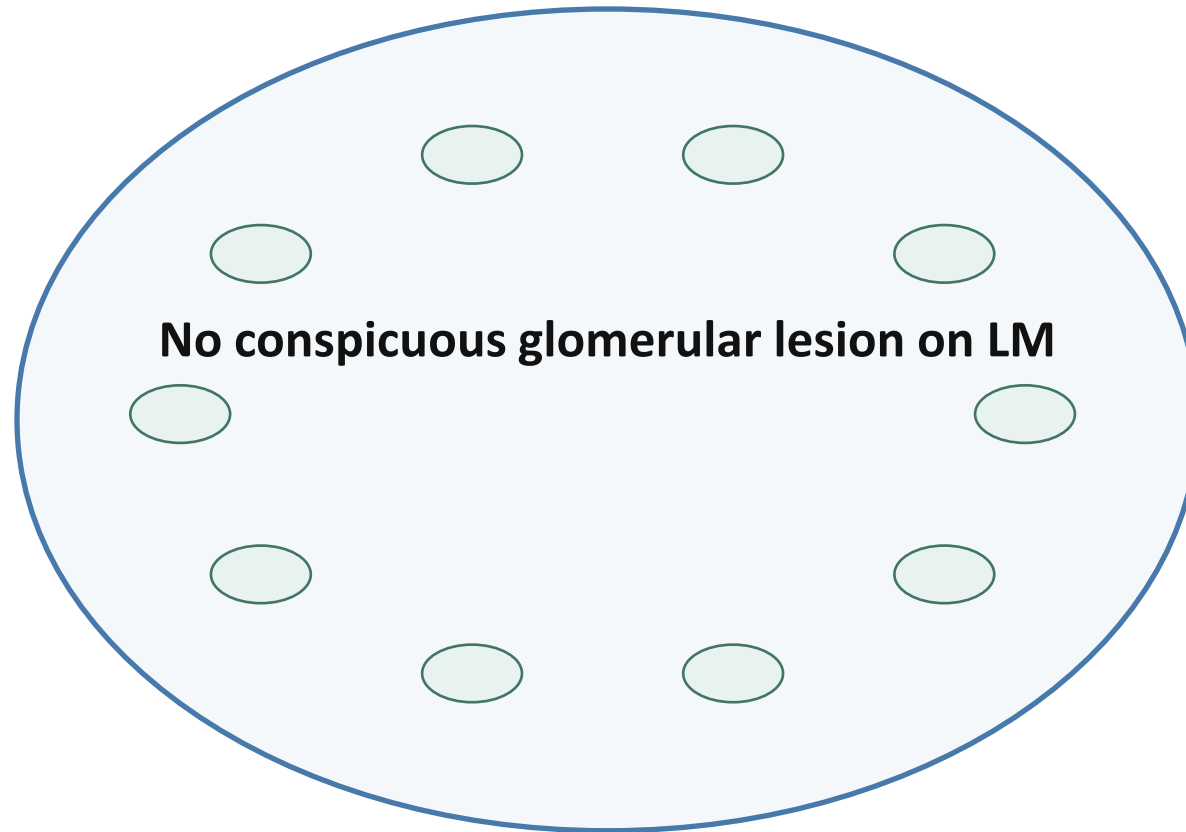
Lesion	Approximate share*	Interpretive point
FSGS	35%	Common adult pattern
Membranous nephropathy	30%	Important adult lesion
Minimal change disease	8%	Less dominant than in children
MPGN / other GN	≈27% combined	May overlap nephritic pattern

Three primary lesions: Distinguishing pathology

These are prototypic morphology patterns, not stand-alone diagnoses.

Disease	Light microscopy	Electron microscopy
Minimal change	Glomeruli often normal	Diffuse foot-process effacement
Membranous	Capillary-wall thickening	Subepithelial deposits
Primary FSGS	Focal segmental sclerosis	Effacement; Podocyte loss

Minimal change disease: LM can appear normal



Simplified morphology schematic — not a clinical/histologic specimen

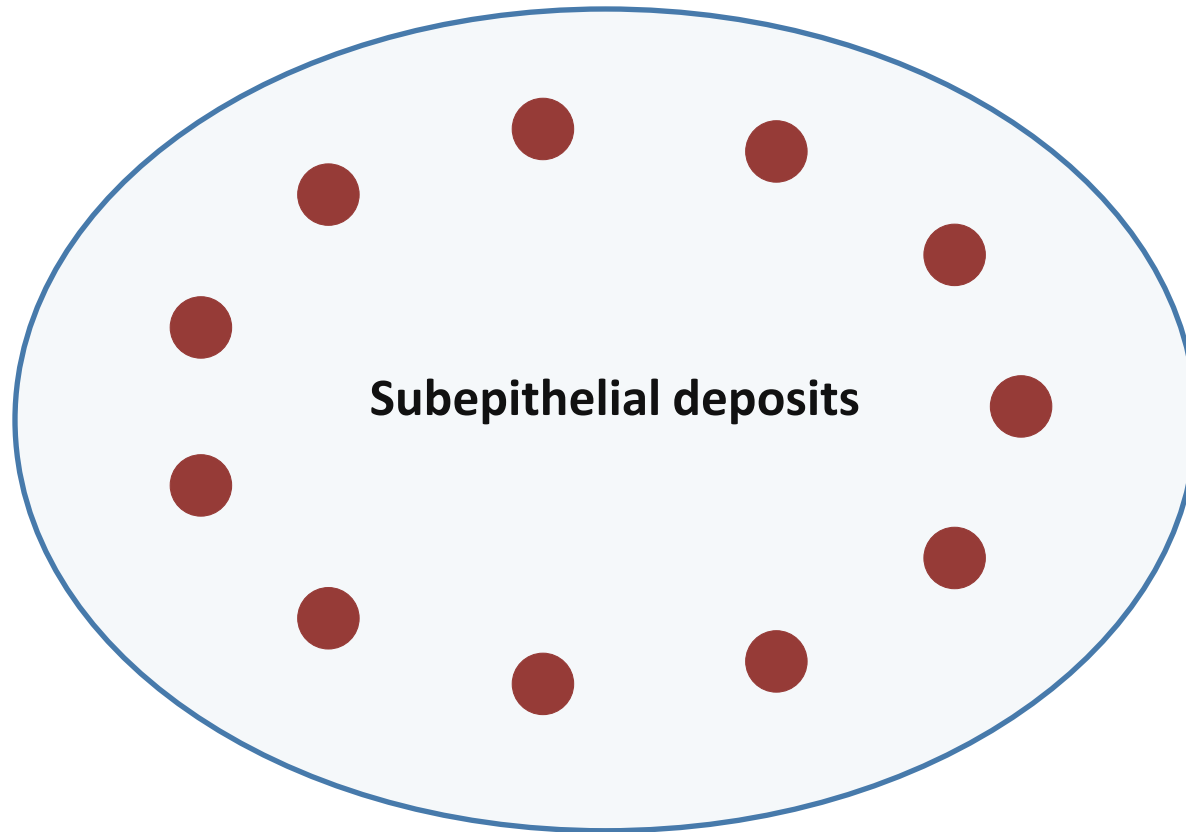
Minimal change disease centers on podocyte injury

Anti-nephrin antibodies are implicated in a subset of cases.



The classic EM picture lacks electron-dense immune-complex deposits.

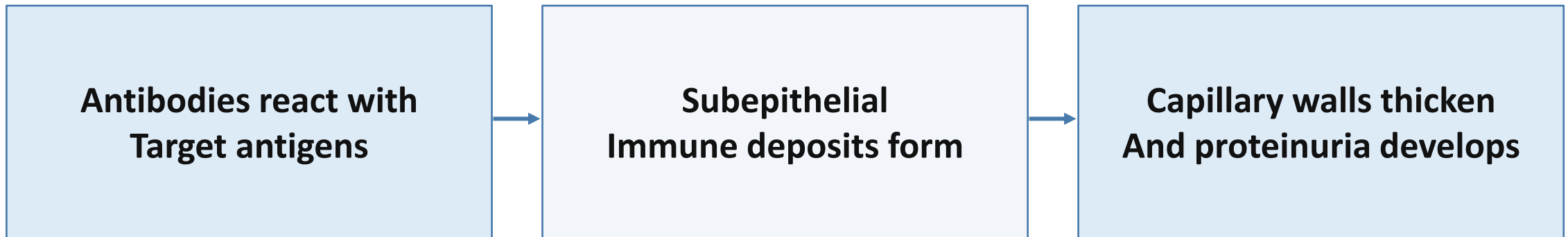
Membranous nephropathy: Subepithelial deposits



Simplified morphology schematic — not a clinical/histologic specimen

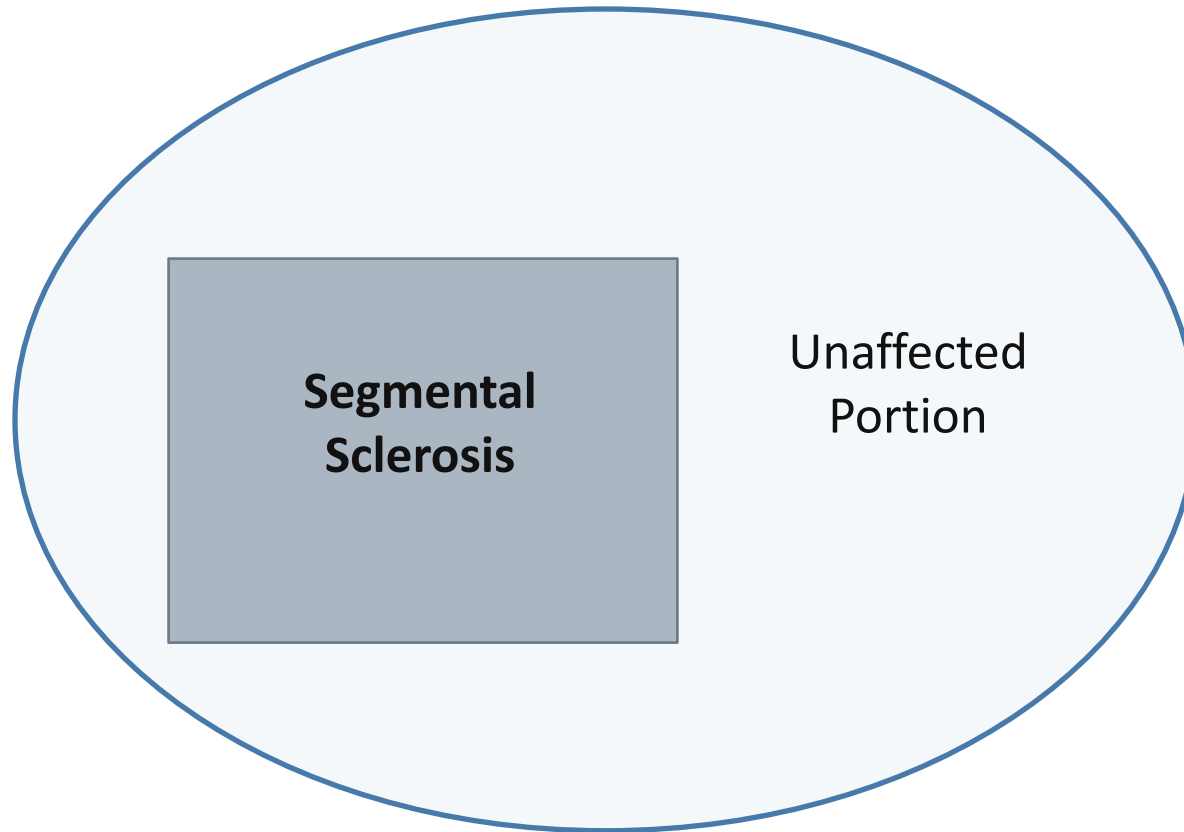
Membranous nephropathy links deposits to barrier injury

PLA2R is a major antigen in primary membranous nephropathy.



Granular immunoglobulin/complement staining and GBM spikes support the lesion.

FSGS: Sclerosis is both focal and segmental



Simplified morphology schematic — not a clinical/histologic specimen

FSGS progresses from podocyte loss to sclerosis

Focal: Only some glomeruli; Segmental: Only part of an affected tuft.



Primary FSGS is only one etiologic category; Adaptive, genetic, and other forms exist.

LM, IF, and EM answer different questions

A nephrotic clinical pattern may have very different microscopic substrates.

Method	Question	Examples
Light microscopy	What is the tissue architecture?	Normal LM in MCD; Sclerosis in FSGS
Immunofluorescence	Which immune reactants are present?	Granular IgG in membranous lesion
Electron microscopy	Where are deposits / podocyte changes?	Effacement; Subepithelial deposits

Diabetes mellitus is an important systemic cause

- Diabetes is among the major systemic causes of nephrotic syndrome.
- The etiologic classification must therefore include non-primary renal disorders.
- Clinical context and renal pathology are interpreted together.
- The nephrotic phenotype does not by itself establish diabetic nephropathy.

Amyloidosis belongs in the systemic differential

- Amyloidosis is a frequently cited systemic association of nephrotic syndrome.
- Heavy proteinuria can be the dominant renal manifestation.
- A systemic disease history changes the diagnostic question from lesion pattern alone to underlying etiology.
- Specific morphologic proof requires tissue evaluation, not clinical syndrome recognition alone.

SLE can present with a nephrotic phenotype

- Systemic lupus erythematosus is a major systemic cause listed by Robbins.
- Not every lupus glomerular lesion produces the same clinical syndrome.
- A membranous lesion is one mechanism of nephrotic presentation in SLE.
- Clinical serology, systemic findings, and renal pathology must be integrated.

Secondary causes extend beyond metabolic and autoimmune disease

- Drugs include nonsteroidal anti-inflammatory drugs and penicillamine.
- Infections listed include malaria, syphilis, viral hepatitis, and HIV.
- Malignant neoplasms, including carcinomas and lymphoma, may be associated.
- These are etiologic categories to investigate, not presumptive diagnoses.

Nephrotic and nephritic patterns answer different questions

Nephrotic pattern

Heavy proteinuria dominates

Hypoalbuminemia with edema

Hyperlipidemia / lipiduria

Nephritic pattern

Hematuria with RBC casts

Oliguria or azotemia

Hypertension; Often inflammatory lesion

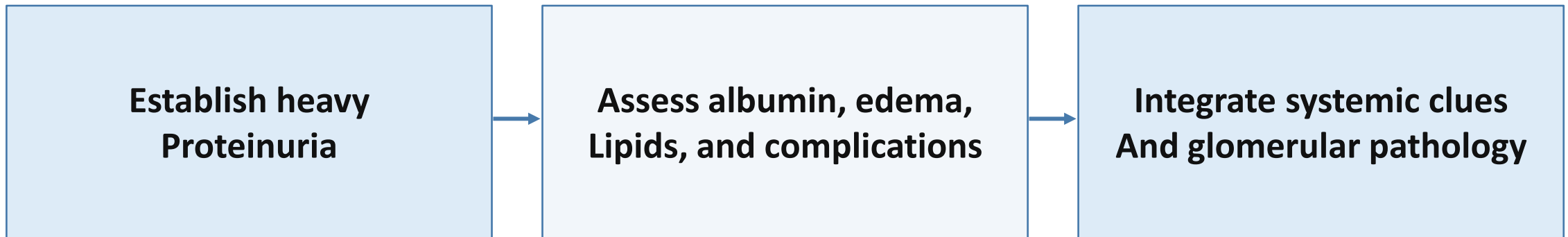
Some glomerular diseases generate mixed nephritic–nephrotic syndromes.

Mixed nephritic–nephrotic presentations occur

- Proliferative glomerular diseases may produce substantial protein loss.
- Membranoproliferative patterns can combine nephritic and nephrotic manifestations.
- IgA nephropathy and other proliferative lesions may also enter the differential.
- Urine sediment and renal function help detect an inflammatory component.

Clinical evaluation proceeds from phenotype to etiology

A conceptual diagnostic sequence, not a formal treatment guideline.



The clinical syndrome is a starting point; Morphology and context refine the diagnosis.

Quantify urine protein before attributing its cause

- A measurement of daily protein excretion allows comparison with the nephrotic-range threshold.
- Total protein quantity and molecular composition answer different questions.
- Identify whether the urinary proteins are predominantly albumin or include larger globulins.
- Interpret quantitative results alongside clinical edema and serum albumin.

Urinary sediment provides mechanistic clues

- Lipiduria and oval fat bodies are compatible with a nephrotic phenotype.
- Red cell casts and prominent hematuria suggest a nephritic component.
- Sediment characteristics do not replace etiologic diagnosis.
- Tubular protein or lipid reabsorption reflects downstream effects of glomerular leakage.

Laboratory findings map to the causal pathways

Finding	Underlying process	Interpretation
Heavy proteinuria	Increased permeability	Primary functional defect
Low albumin	Protein depletion / catabolism	Contributes to edema
High plasma lipids	Altered lipoprotein balance	Systemic metabolic effect
Lipiduria	Lipoprotein passage / cells	Downstream tubular effect

Biopsy patterns identify the lesion, not merely the syndrome

- Normal-appearing glomeruli by LM do not exclude a major podocytopathy.
- IF and EM may reveal deposits or diffuse foot-process effacement.
- Membranous disease illustrates immune deposits with capillary-wall changes.
- FSGS illustrates loss of podocytes and formation of segmental scars.

Application: A child with selective proteinuria

A preschool-aged child develops marked pitting edema, heavy predominantly albumin proteinuria, and preserved renal function.

Interpretation

- Which lesion is common in this age group?
- What would you expect by light and electron microscopy?

Application: An adult with subepithelial deposits

An adult presents with nephrotic syndrome. Renal biopsy shows capillary-wall thickening and subepithelial electron-dense deposits.

Interpretation

- Which primary glomerular lesion is suggested?
- Which immunofluorescence distribution supports it?

Application: Edema with renal-vein thrombosis

A patient with severe nephrotic proteinuria develops renal-vein thrombosis. The question is whether thrombosis caused the syndrome.

Interpretation

- What causal direction is emphasized by Robbins?
- Which urinary loss contributes to hypercoagulability?

Integrated clinicopathologic reasoning

Observation	Mechanistic inference	Next interpretive step
Proteinuria + low albumin	Damaged glomerular filter	Investigate lesion
Edema	Oncotic / sodium mechanisms	Assess fluid burden
Lipiduria	Lipoprotein filtration	Correlate plasma lipids
Thrombosis	Procoagulant state	Recognize complication

Link each nephrotic feature to its mechanism

Feature	Mechanistic explanation
Proteinuria	Increased glomerular capillary-wall permeability
Hypoalbuminemia	Urinary loss outstrips synthesis; Catabolism contributes
Edema	Low oncotic pressure and renal sodium retention
Hyperlipidemia	Changed synthesis, transport, and clearance
Infections / thrombosis	Loss of immunoglobulins and anticoagulants

Synthesis: Phenotype, mechanism, and etiologic diagnosis

- Nephrotic syndrome begins with excessive glomerular permeability to proteins.
- Albumin depletion, fluid retention, lipid abnormalities, and systemic complications are interconnected.
- Primary podocytopathies and deposit diseases coexist in the differential with systemic disorders.
- LM, IF, and EM explain why the same clinical syndrome arises from different lesions.

Principal reference

Robbins, Cotran & Kumar

Pathologic Basis of Disease

Core nephrotic syndrome discussion and glomerular disease context

Nephrotic Syndrome; adjacent sections on glomerular structure, membranous nephropathy, minimal change disease, and FSGS.