

Minimal Change Disease

Diffuse podocytopathy with minimal changes

Podocyte injury · Nephrotic syndrome · Renal biopsy

Pathology lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

Explain how podocyte slit-diaphragm injury produces selective albuminuria.

Recognize the integrated light microscopy, electron microscopy, and immunofluorescence pattern.

Distinguish MCD from membranous nephropathy and FSGS.

Relate corticosteroid responsiveness, relapse, and prognosis to the lesion.

The defining clinicopathologic paradox

Clinical

Marked albumin-rich proteinuria

Light microscopy

Glomeruli appear normal by light microscopy

Electron microscopy

Diffuse podocyte injury visible by electron microscopy

Interpret all modalities together; No single finding alone is sufficient.

Minimal change disease is a podocytopathy

Primary injury localizes to the visceral glomerular epithelial cells: Podocytes.

The major structural abnormality is widespread simplification of foot processes.

There is generally no destructive inflammatory or sclerosing glomerular lesion at presentation.

Protein permeability is profoundly altered despite preserved capillary architecture.

Clinical context: The nephrotic syndrome

MCD classically presents as a nephrotic, not a nephritic, glomerular syndrome.

Heavy protein loss generates hypoalbuminemia, edema, and disordered lipid handling.

The urine may contain lipids or lipid-laden elements.

Renal filtration function is often relatively preserved.

The core nephrotic phenotype

Heavy proteinuria

Low serum albumin

Generalized edema

Hyperlipidemia and lipiduria

Why children are especially affected

MCD is the most frequent cause of nephrotic syndrome in childhood.

Its highest incidence occurs from 2 to 6 years of age.

It also occurs in adults but represents a smaller share of their nephrotic disorders.

Age helps frame the differential; It does not establish the diagnosis alone.

Preceding events and associations

A respiratory infection may precede the onset of nephrotic syndrome.

MCD may occur after routine immunization.

These temporal associations do not define a single universal pathogenic mechanism.

The disease can occur without an identifiable precipitating event.

Adult-associated minimal change disease

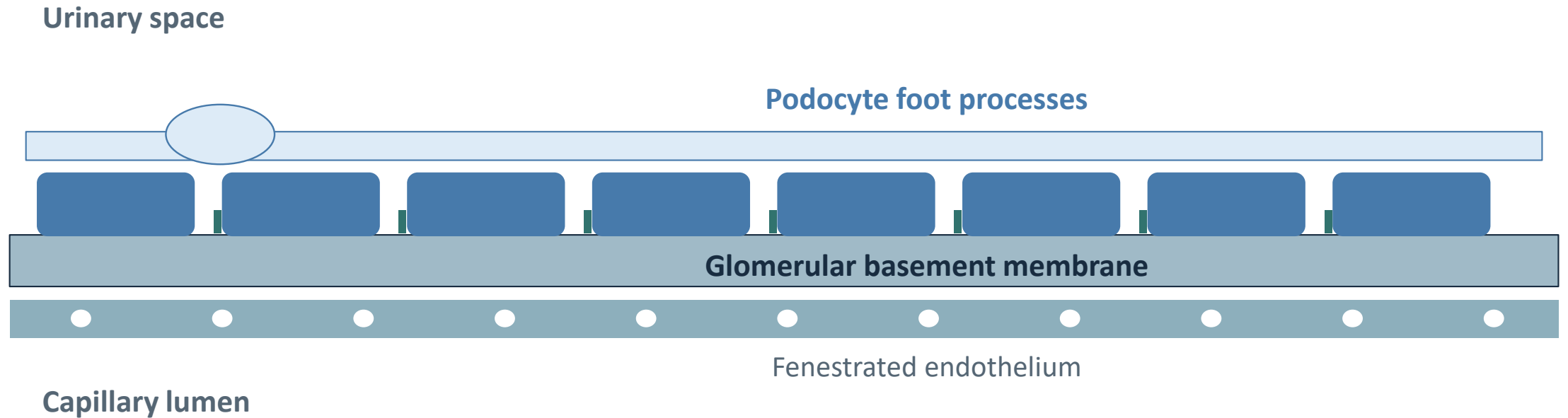
Hodgkin lymphoma is a recognized clinical association.

Other lymphomas and leukemias are less frequent associations.

MCD is reported with nonsteroidal anti-inflammatory drug exposure.

Infection or vaccination may precede adult as well as pediatric cases.

Glomerular filtration barrier: Three layers



Schematic: Not diagnostic tissue imagery

Fenestrated endothelium • Glomerular basement membrane • Podocyte foot processes and slit diaphragms

The podocyte is an active filtration structure

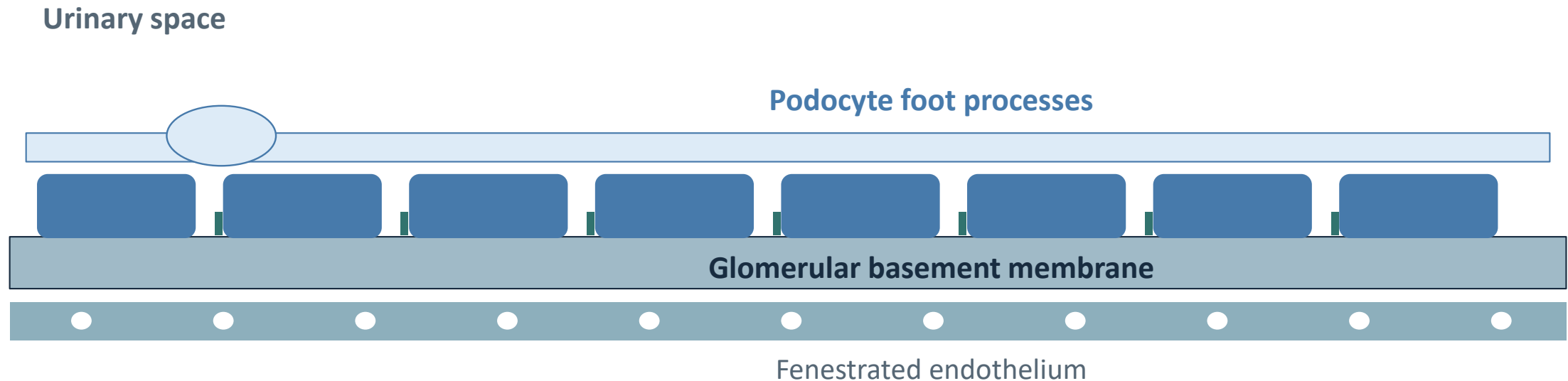
Visceral epithelial cell processes envelop the outer surface of capillary loops.

Neighboring foot processes interdigitate along the glomerular basement membrane.

Filtration slits are bridged by specialized slit diaphragms.

The podocyte cytoskeleton helps maintain this highly organized architecture.

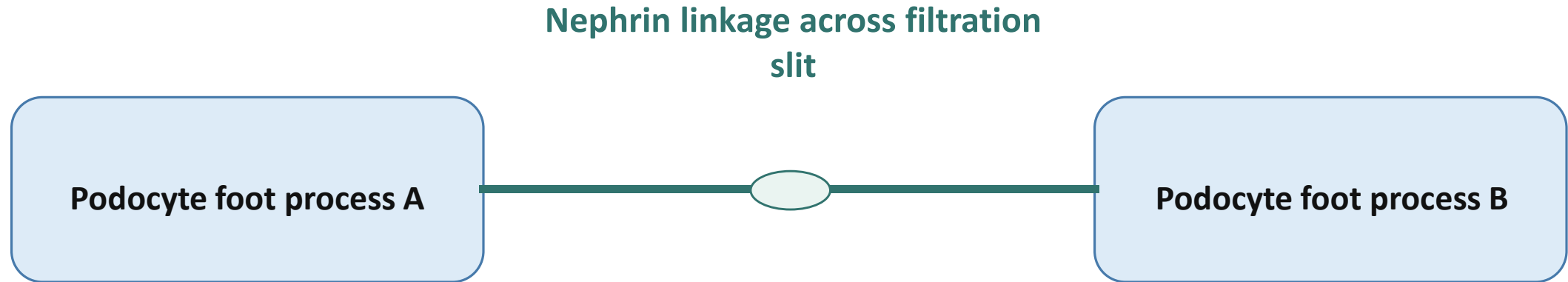
Filtration slits enforce protein selectivity



Schematic: Not diagnostic tissue imagery

Slit diaphragms bridge spaces between adjacent foot processes. • Their organization creates an important distal barrier to plasma proteins. • Structural stability depends on membrane proteins coupled to the actin network.

Nephrin forms the slit-diaphragm scaffold



Intracellularly: Nephrin → podocin/CD2AP → actin cytoskeleton

Schematic; Molecular geometry simplified Nephrin spans podocyte membranes at the filtration slit.

The actin scaffold preserves podocyte shape

Slit diaphragm junctions are linked to intracellular actin architecture.

This coupling stabilizes foot-process position and spacing.

Loss of this support can flatten and retract processes.

Morphologic foot-process effacement is therefore a cellular-architecture change.

Size and charge shape protein filtration

The capillary wall normally restricts entry of large plasma proteins.

Charge-selective effects also influence passage of anionic albumin.

Podocyte slit-diaphragm integrity is essential to effective size selectivity.

MCD disproportionately disrupts protein selectivity rather than gross architecture.

A changing model of MCD pathogenesis

Historical interpretation

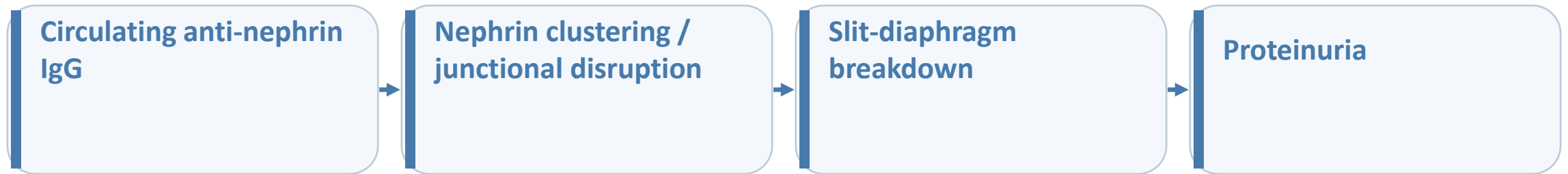
Absent conventional deposits argued against antibody-mediated injury.

Current Robbins hypothesis

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

Compare the underlying morphologic mechanisms.

Anti-nephrin antibodies: Proposed mechanism



Current hypothesis for a subset, not a proven universal mechanism

Anti-nephrin is not a universal explanation

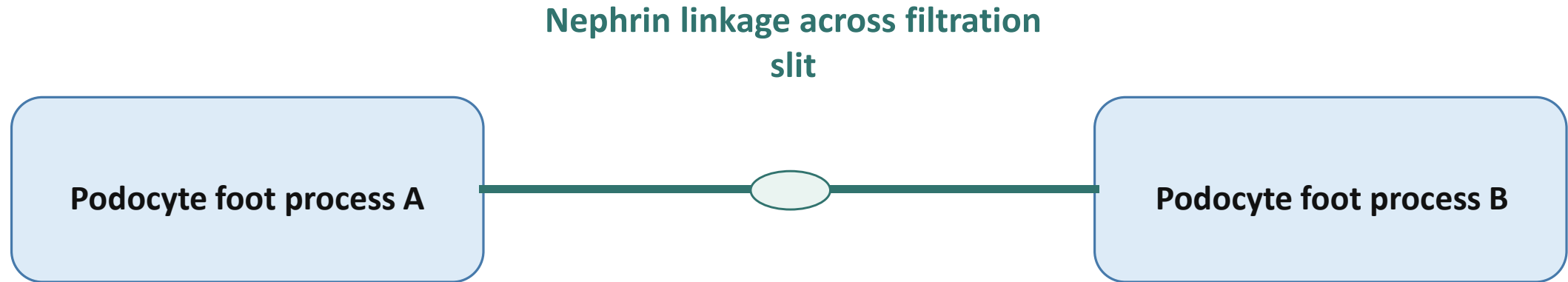
Anti-nephrin-mediated disease as a hypothesis for a subset.

The presence and visibility of glomerular IgG can vary among patients.

Absence of detectable glomerular staining does not exclude an MCD pattern.

The disease remains a morphologic and clinicopathologic diagnosis.

Nephrin crosslinking becomes abnormal



Extracellular nephrin interactions connect neighboring processes

Intracellularly: Nephrin → podocin/CD2AP → actin cytoskeleton

Schematic; Molecular geometry simplified Antibodies may interfere with physiologic nephrin interactions.

From slit failure to albumin leakage



Mechanistic summary drawn from MCD pathogenesis

Effacement begins at the cytoskeleton

Podocyte actin architecture collapses or reorganizes.

Processes retract, swell, and flatten over the basement membrane.

The normal spaces between processes become less recognizable.

These changes may be structurally reversible after successful treatment.

Foot-process effacement is not fusion

Misleading shorthand

“Fusion” suggests adjacent processes simply merge.

Accurate morphologic meaning

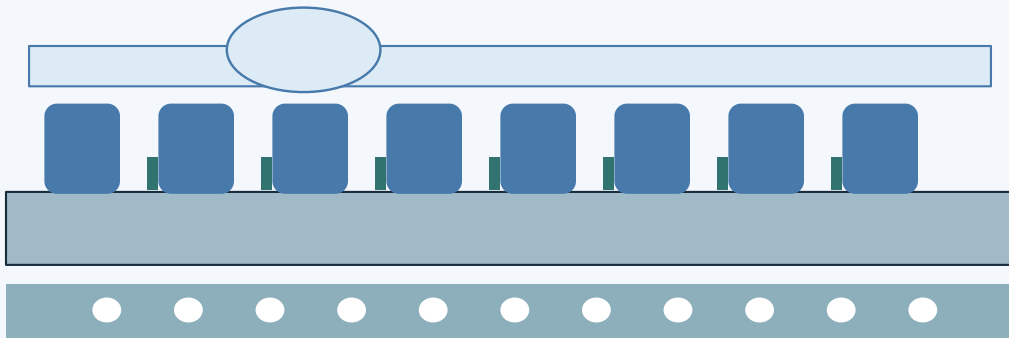
Processes simplify through retraction, flattening, and cytoskeletal collapse.

Compare the underlying morphologic mechanisms.

Normal versus effaced foot processes

Preserved filtration slits

Urinary space



Capillary lumen

Interdigitating processes; Slit diaphragms intact

Schematic comparison — not an electron micrograph

Minimal change disease

Urinary space



Capillary lumen

Diffusely simplified processes; Slit loss

A potential contribution from surface charge

Experimental observations suggest loss of glomerular polyanions.

Reduced anionic barrier function may facilitate albumin filtration.

This is a contributory hypothesis rather than a fully resolved causal pathway.

The prominent ultrastructural lesion remains podocyte effacement.

Albumin-rich proteinuria reflects selectivity loss

Proteinuria is typically highly selective in classic MCD.

Most of the urinary protein is albumin.

Disruption of slit-diaphragm organization permits excessive plasma-protein passage.

Urinary protein loss can be severe despite normal appearing light-microscopic glomeruli.

Pathology requires three complementary modalities

Light microscopy

Normal glomerular tuft

Electron microscopy

Diffuse foot-process effacement; No dense deposits

Immunofluorescence

Often negative; Sometimes subtle podocyte IgG

Interpret all modalities together; No single finding alone is sufficient.

Light microscopy: Glomeruli appear normal

Glomerular capillary walls retain their usual architecture.

No characteristic mesangial or endocapillary proliferation is present.

No diffuse wall thickening is required to explain the proteinuria.

The key lesion is below the resolving power of conventional light microscopy.

Light microscopy: What should be absent?

A proliferative glomerular lesion is not typical of uncomplicated MCD.

Segmental tuft scarring suggests consideration of FSGS.

Prominent capillary-wall thickening raises other nephrotic diagnoses.

Interpret the entire biopsy; A normal-looking tuft is not sufficient alone.

Tubular lipid and protein reabsorption

Filtered plasma proteins enter proximal tubular lumina.

Proximal tubular epithelial cells reabsorb filtered lipoproteins.

Cytoplasmic lipid and protein accumulation can therefore accompany MCD.

The historic term “lipoid nephrosis” refers to this tubular appearance.

Electron microscopy: The GBM is intact

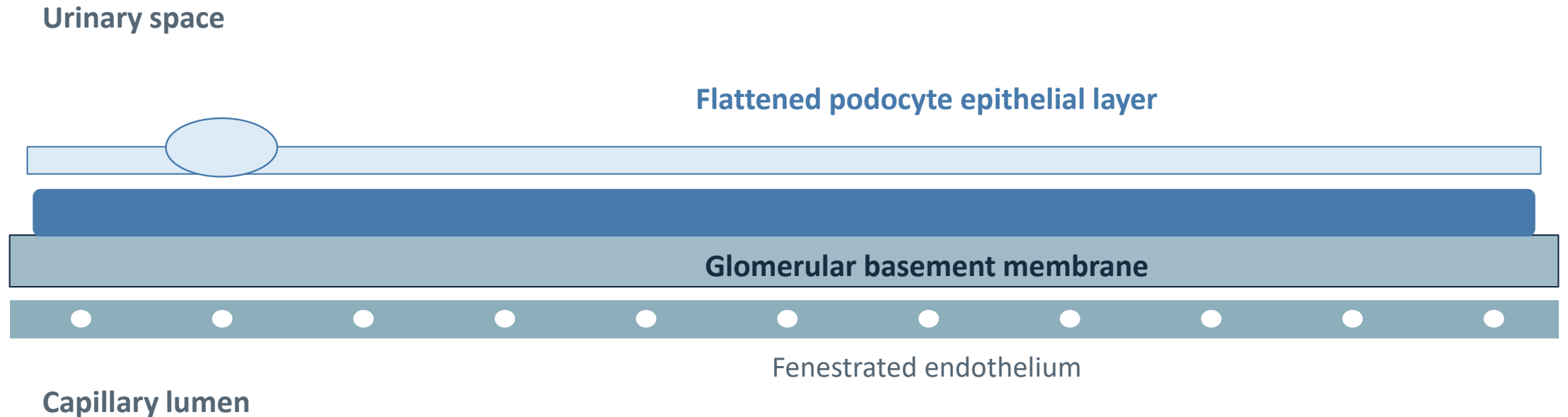
The glomerular basement membrane generally retains normal ultrastructure.

No characteristic basement-membrane thickening or duplication is expected.

This contrasts with disorders defined by basement membrane remodeling.

The primary diagnostic lesion resides on the podocyte side of the barrier.

Electron microscopy: Diffuse effacement



Schematic: Not diagnostic tissue imagery

The principal ultrastructural abnormality is diffuse flattening of podocyte processes. • The distribution is extensive rather than a few isolated altered sites. • Loss of slit diaphragms commonly accompanies the effacement.

Electron microscopy: Disappearance of slits

Intervening slit diaphragms are reduced or absent in affected segments.

Flattened epithelium covers much of the outer GBM surface.

This architecture offers a structural correlate of protein permeability change.

Foot-process alteration is reversible in many steroid-responsive patients.

Electron microscopy: No dense deposits

No glomerular electron-dense immune-complex deposits are expected.

Their absence helps distinguish MCD from membranous nephropathy.

“No dense deposits” is compatible with podocyte-bound antibodies.

Absence of deposits must be read together with the clinical and LM pattern.

Immunofluorescence can be negative

Routine immunofluorescence may show no convincing immune deposition.

This historically supported a non-immune-complex interpretation.

Negative staining should not override clear diffuse foot-process effacement.

MCD cannot be identified from immunofluorescence alone.

Subtle podocyte IgG can be present

Delicate diffuse, global fine granular IgG in some biopsies.

The signal follows podocyte surfaces rather than forming bulky GBM deposits.

IgG signal may colocalize with clustered nephrin.

This finding is distinct from classic capillary-wall immune-complex deposition.

Complement negativity matters

The subtle podocyte-associated IgG pattern lacks accompanying complement reactivity.

This differs from several immune-complex glomerulopathies.

A negative complement pattern does not prove an anti-nephrin mechanism.

Microscopy is interpreted as an integrated pattern, not a single-marker test.

An integrated biopsy interpretation

LM: Minimal alterations

No significant proliferation
or sclerosis

IF: None / fine podocyte IgG

Complement-negative; No
classic deposits

EM: Diffuse effacement

Normal GBM and absence of
dense deposits

Interpret all modalities together; No single finding alone is sufficient.

MCD versus membranous nephropathy

Feature	Minimal change disease	Membranous nephropathy
Light microscopy	Often normal	Diffuse capillary-wall thickening
Immunofluorescence	Negative or fine podocyte IgG	Granular capillary-wall IgG/C3
Electron microscopy	Diffuse effacement; no deposits	Subepithelial dense deposits
Major injury	Podocyte architecture	Immune deposits on epithelial GBM side

MCD versus focal segmental glomerulosclerosis

Feature	MCD	Primary FSGS
Light microscopy	Glomeruli essentially normal	Focal segmental sclerosis
Electron microscopy	Diffuse effacement	Diffuse podocyte injury; may be podocyte loss
Clinical course	Usually steroid responsive	Lower steroid responsiveness
Renal risk	Typically excellent prognosis	Progressive CKD more likely

Why FSGS can initially resemble MCD

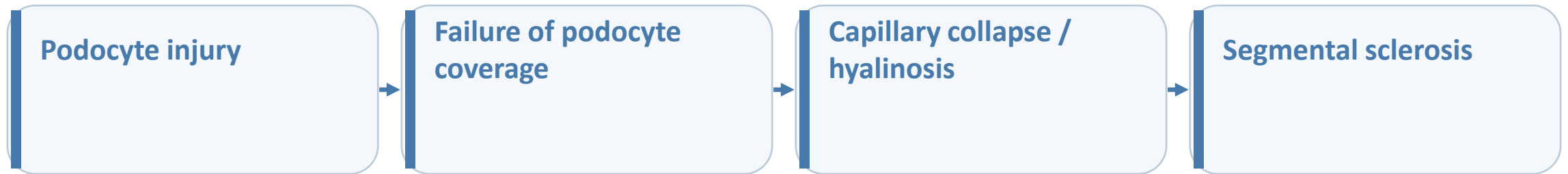
Primary FSGS can also present with diffuse podocyte injury.

Only some glomeruli show sclerosis, and only part of each affected tuft is scarred.

A limited biopsy can underrepresent focal segmental lesions.

Progression or nonresponse to treatment warrants reassessment of this differential.

Podocyte loss marks the path toward sclerosis



FSGS mechanism is downstream podocyte loss, in contrast to reversible MCD

MCD versus diabetic glomerular disease

Feature	MCD	Diabetic nephropathy
Light microscopy	Typically normal tuft	Architectural basement membrane/mesangial changes
Electron microscopy	Diffuse foot-process effacement	Chronic diabetic barrier remodeling + effacement
Clinical setting	Often abrupt nephrotic syndrome	Diabetes with renal disease context
Interpretation	Effacement + normal LM	Effacement alone is nonspecific

Why effacement alone does not diagnose MCD

Membranous glomerulopathy can cause extensive foot-process effacement.

Diabetic nephropathy can also cause epithelial simplification.

Associated GBM or tuft alterations redirect the diagnosis.

The combination of normal light microscopy and diffuse effacement is decisive.

Clinical presentation is often sudden

The presenting syndrome usually reflects heavy urinary albumin loss.

Edema can be the dominant visible finding.

A preceding respiratory infection may be reported, particularly in children.

The apparent severity of proteinuria contrasts with preserved renal function.

Selective albuminuria: Clinical interpretation

Highly selective proteinuria means albumin predominates among lost proteins.

This is characteristic of classic MCD.

Selective protein loss is consistent with podocyte-selectivity injury.

Selectivity alone is not a stand-alone histologic diagnosis.

Renal function often remains stable

Marked albuminuria does not necessarily imply reduced filtration rate.

Most patients maintain relatively stable renal function at presentation.

Severe nephrotic manifestations can occur without destructive glomerular inflammation.

An atypical decrease in kidney function should prompt broader evaluation.

Hematuria and hypertension are usually absent

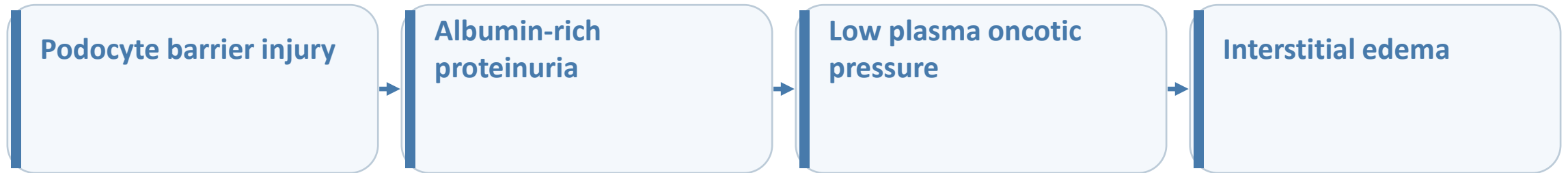
Classic MCD does not usually manifest prominent hematuria.

Hypertension is typically absent presentation.

The clinical picture therefore differs from nephritic syndromes.

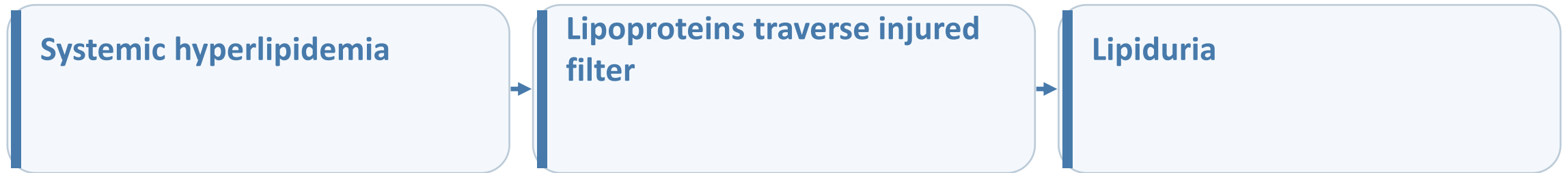
When these features dominate, alternate or overlapping pathology deserves attention.

How glomerular leakage produces edema



Renal sodium and water retention may additionally amplify edema.

How MCD produces lipiduria



Parallel tissue effect: Proximal tubular uptake → cytoplasmic lipid accumulation.

Clinical associations in adults

Hodgkin lymphoma

Other lymphomas / leukemias

NSAID exposure

Infection or vaccination

Corticosteroid response is characteristic

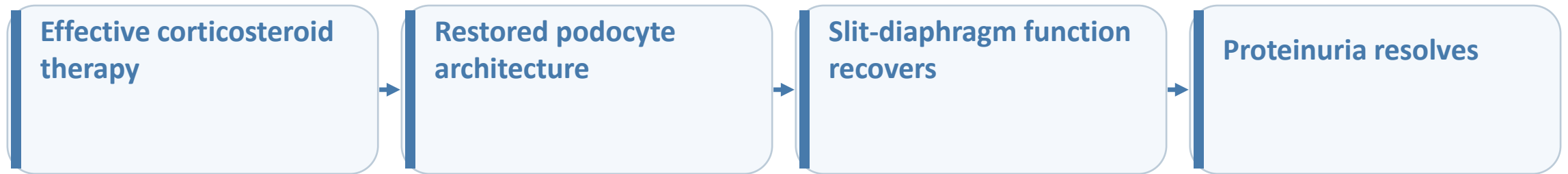
A dramatic decline in proteinuria with corticosteroids is a hallmark.

Rapid response in more than 90% of children.

Clinical remission often parallels resolution of podocyte abnormalities.

Response supports the diagnosis but is not a substitute for appropriate evaluation.

Remission parallels podocyte repair



MCD morphologic response and disappearance of antibodies in many patients

Recurrence does not negate the diagnosis

A substantial proportion of patients experience recurrent proteinuria.

Episodes can follow apparently complete earlier remissions.

Clinical care therefore monitors the pattern over time.

Relapse is distinct from sustained irreversible sclerosis.

Steroid dependence and resistance

Some cases become steroid dependent after an initial response.

Some patients are steroid resistant or develop resistance during their course.

These patterns alter management and diagnostic reassessment.

A subset may evolve toward a focal segmental sclerosing phenotype.

The link with FSGS has clinical implications

MCD-like process

Predominantly reversible podocyte simplification.

Sclerosing progression

Podocyte loss with tuft denudation and segmental scarring.

Compare the underlying morphologic mechanisms.

Adults tend to respond more slowly

Adult minimal change disease may require a longer interval to respond.

A slower response does not imply inevitable long-term deterioration.

An excellent long-term prognosis in adults as well.

Associated drugs or neoplasms require appropriate contextual review.

B-cell depletion: An important therapeutic clue

Steroid-dependent or frequently relapsing disease has responded to B-cell-depleting therapy.

This therapeutic observation supports interest in humoral immune mechanisms.

It does not establish anti-nephrin antibodies in every patient.

Treatment selection lies beyond the scope of histopathologic classification.

Long-term prognosis is generally excellent

Most children recover without progressive renal dysfunction.

Steroid-dependent disease can resolve around puberty.

Adults also often have excellent long-term renal outcomes.

Relapse burden and a possible transition to FSGS remain key qualifications.

Case: A child with edema and albuminuria

Clinical vignette

A 4-year-old develops periorbital edema after a respiratory infection. Urine contains abundant albumin; Serum albumin is reduced. Kidney filtration is preserved, and hematuria is absent.

What syndrome is present?

Which glomerular cellular compartment is most likely injured?

Case reasoning: Predict the renal biopsy

Light microscopy

No major glomerular abnormalities

Immunofluorescence

Negative or fine podocyte IgG

Electron microscopy

Diffuse foot-process effacement; No deposits

Interpret all modalities together; No single finding alone is sufficient.

Case: Adult nephrotic syndrome with NSAIDs

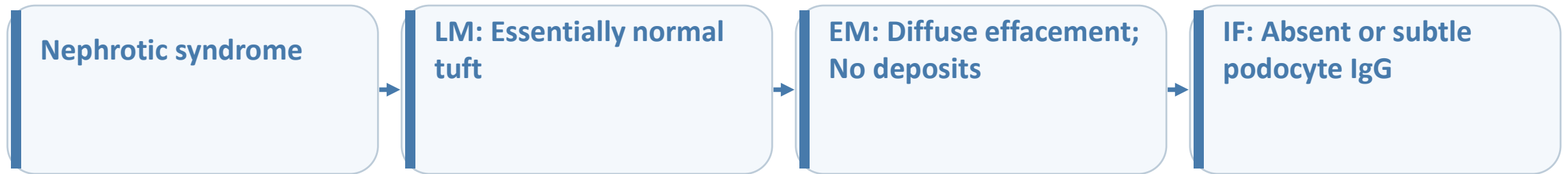
Clinical vignette

An adult develops nephrotic syndrome while receiving nonsteroidal anti-inflammatory therapy. Glomerular light microscopy is essentially normal; Electron microscopy shows diffuse podocyte effacement.

Which medication association is relevant?

What concurrent findings would make FSGS or membranous nephropathy more likely?

Decision pathway: Three microscopy modalities



Conceptual diagnostic integration; Not a substitute for complete renal workup

Core distinctions in one view

Diagnostic axis	MCD interpretation	Common pitfall
Light microscopy	Little or no structural abnormality	Assuming normal LM excludes disease
Electron microscopy	Diffuse effacement; normal GBM	Calling effacement itself specific
Immunofluorescence	Often negative; subtle podocyte IgG	Assuming every IgG signal means deposits
Clinical behavior	Typically highly steroid responsive	Equating relapse with poor renal prognosis

Critical concepts for recall

The pathologic hallmark lies in podocyte ultrastructure, not glomerular hypercellularity.

Anti-nephrin antibodies provide a compelling but non-universal pathogenic hypothesis.

MCD usually has selective proteinuria, stable renal function, and steroid responsiveness.

Follow-up must recognize relapse, steroid dependence, and potential FSGS evolution.

References and visual provenance

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. Chapter 20, The Kidney, pp. 815–816, 827–831.

Primary focus: “Minimal Change Disease (Diffuse Podocytopathy With Minimal Changes).”

Figures in this presentation are original PowerPoint schematics—not diagnostic tissue images.

For authentic LM/EM/IF examples, consult Fig. 20.11 in the original textbook.