

AL Amyloidosis

Immunoglobulin light-chain misfolding, systemic deposits and
clinicopathologic diagnosis

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Learning objectives

- Define AL amyloid and identify its plasma-cell source.
- Explain why some monoclonal light chains become extracellular fibrils.
- Recognize the shared morphology, organ injury and Congo red reaction.
- Integrate tissue amyloid, fibril typing and evidence of a clonal source.

The defining clinicopathologic question

An adult has progressive proteinuria, cardiac dysfunction and a circulating monoclonal immunoglobulin.

Which finding establishes amyloidosis—and which additional result establishes that it is AL?

A circulating monoclonal protein alone does not identify deposited amyloid.

Amyloidosis denotes a group, not one protein

Shared finding

- Extracellular fibrillar protein deposits
- Similar tissue appearance and Congo red behavior

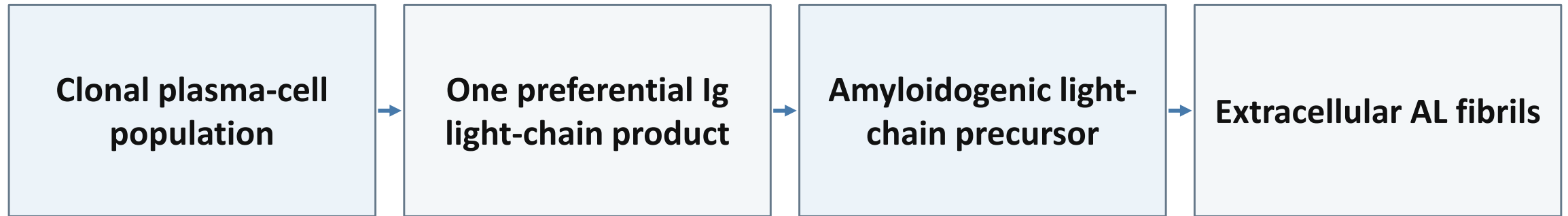
Critical difference

- AL: Immunoglobulin light chain
- AA: SAA-derived; ATTR: Transthyretin-derived

What the abbreviation AL denotes

- A = amyloid; L = immunoglobulin light chain.
- Fibril constituents may be intact light chains, amino-terminal fragments or both.
- AL arises from light chains secreted by a monoclonal plasma-cell population.

A restricted light-chain clone



- The pathogenic product—not necessarily a bulky tumor—is central to AL disease.

The light-chain classes: λ and κ

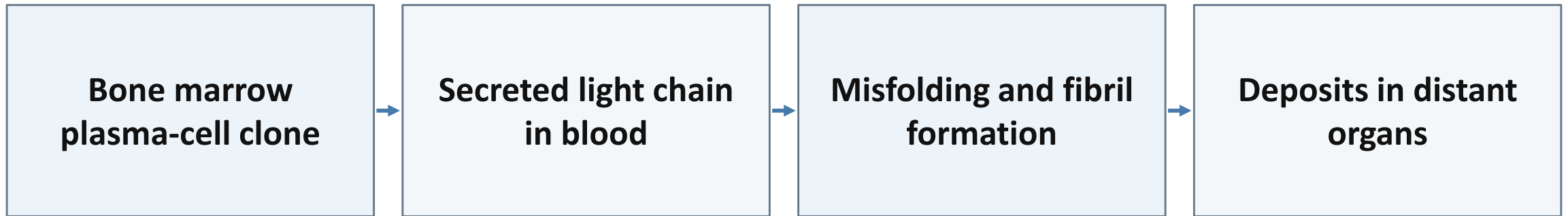
λ (lambda)

- Most AL proteins analyzed are λ -derived.
- This is a tendency, not a requirement.

κ (kappa)

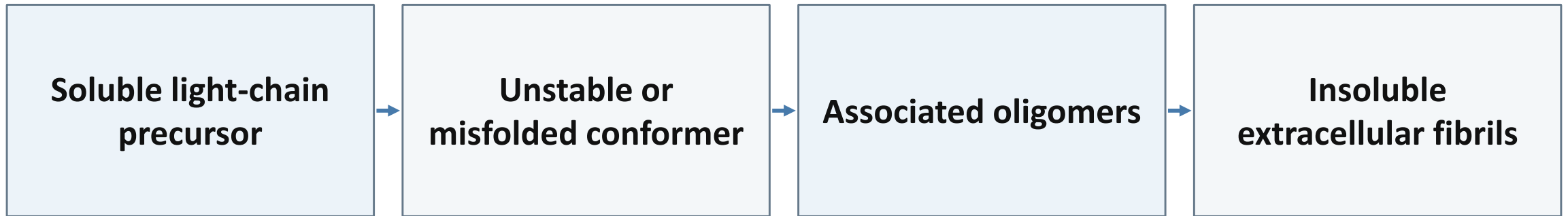
- κ light chains and fragments can also form amyloid.
- Typing must determine the actual deposited product.

Systemic disease begins at a cellular source



- AL amyloidosis is usually systemic because its precursor circulates.

Proteins cross the threshold into aggregation



- The normal soluble form and the deposited fibril share a protein origin, not a folding state.

Why a plasma-cell clone matters

- Normal plasma cells generate immunoglobulin proteins.
- A monoclonal population repeatedly secretes a restricted product.
- A disease-specific light-chain sequence can impart a high tendency to misfold.
- Even a modest clone may therefore cause severe tissue pathology.

Monoclonal protein production is not equivalent to amyloid

Monoclonal protein

- Identifies a restricted Ig-producing population.
- May be found in serum or urine.

Tissue amyloid

- Demonstrates extracellular insoluble fibrils.
- Must be detected in tissue and then biochemically typed.

AL often lacks overt multiple myeloma

- Most persons with AL amyloid do not have classic multiple myeloma.
- Many have a modest increase in marrow plasma cells.
- Abnormal protein production may dominate without tumor masses.
- “Primary amyloidosis” is the older name, not evidence of a nonclonal disease.

Myeloma-associated AL is an important subset

- Systemic AL amyloidosis to 5%–15% of individuals with multiple myeloma.
- Myeloma plasma cells may produce an M protein and free unpaired light chains.
- AL pathology depends on the amyloidogenic properties of those light chains.

A source-based epidemiologic anchor

AL burden in the United States

- Approximately 2,000–3,000 new AL cases annually.
- Interpret this as a textbook-reported estimate.

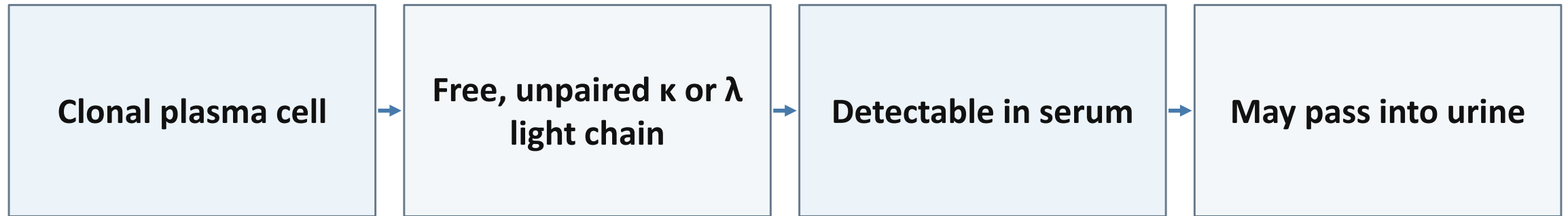
Relationship to myeloma

- AL in 5%–15% of persons with myeloma.
- Most AL patients lack classic myeloma.

The M-protein spike: What it represents

- An M spike reflects abnormal production of a restricted immunoglobulin by plasma cells.
- It provides evidence of monoclonality in the appropriate clinical context.
- It neither proves a tissue deposit nor assigns that deposit to the AL type.

Free immunoglobulin light chains



- Circulating and urinary light chains are part of the clonal-protein investigation.

Bence Jones protein is a clinical clue

- Bence Jones proteins are free, unpaired immunoglobulin light chains.
- Their relatively small molecular size permits urinary excretion.
- Finding them supports a plasma-cell product—but does not itself establish amyloid deposition.

Why most free light chains do not become amyloid

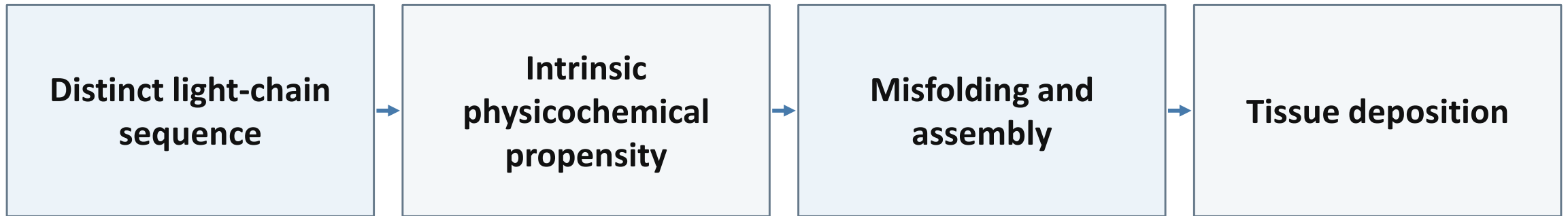
Free light chains in myeloma

- May be abundant in serum and urine.
- Most affected individuals do not develop amyloidosis.

Amyloidogenic light chains

- A specific sequence can favor folding instability and aggregation.
- Deposition depends on protein quality as well as quantity.

Amino-acid sequence shapes amyloidogenicity



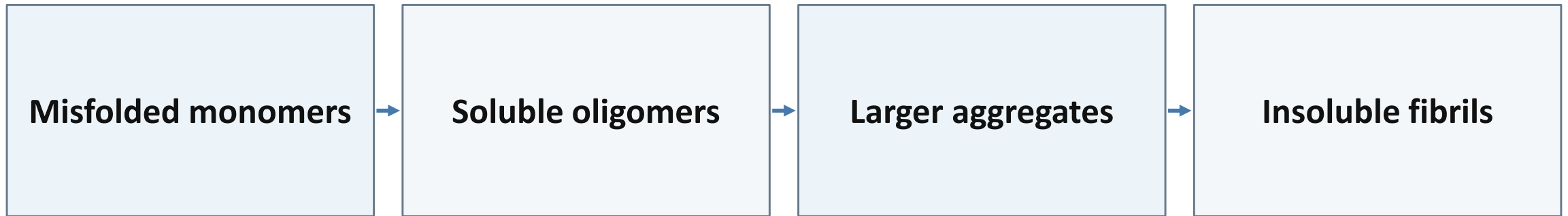
- The source identifies sequence dependence as a principal explanation for why amyloidogenicity varies.

Protein quality control usually limits deposition



- Proteasomes and macrophages normally remove misfolded material; Persistence favors deposition.

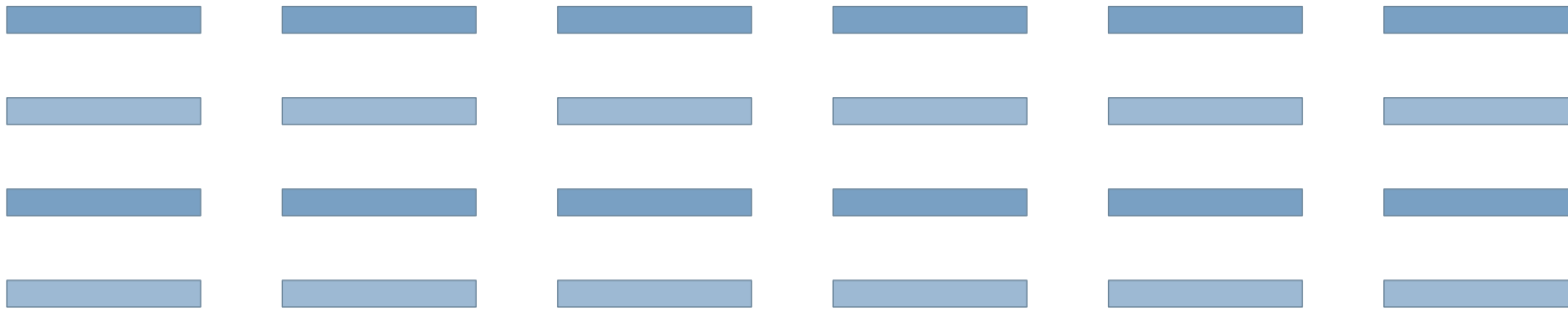
Oligomers are precursors to mature fibrils



- Progressive self-association converts a soluble precursor into persistent deposits.

Cross- β structure explains shared staining

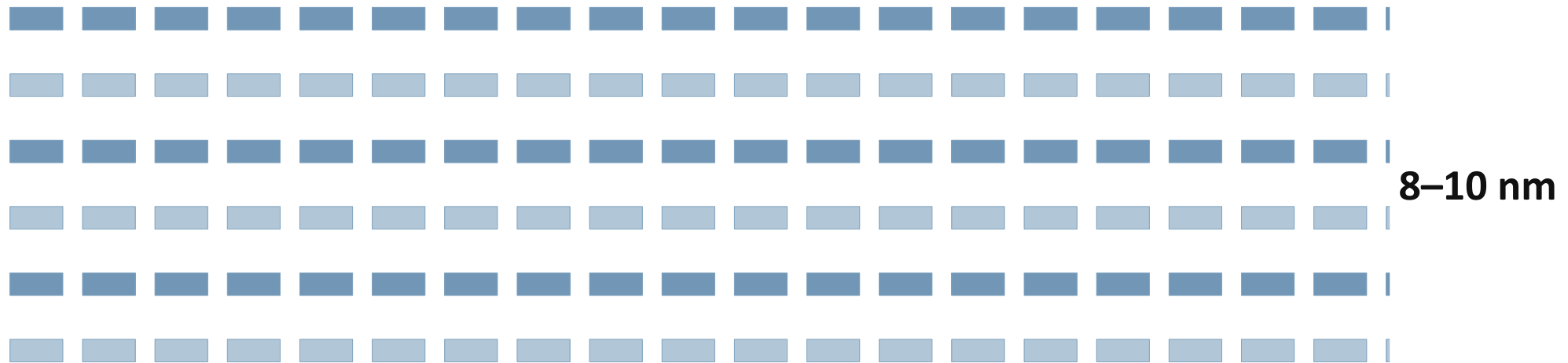
Schematic: Stacked β -sheet segments



- Amyloid fibrils have a β -pleated organization irrespective of precursor protein.
- This common conformation underlies the characteristic Congo red optical reaction.

Ultrastructure: Nonbranching fibrils

Schematic: Parallel nonbranching fibrils



- Electron microscopy demonstrates continuous, nonbranching fibrils.
- Robbins gives an approximate fibril diameter of 8–10 nm.
- Ultrastructure identifies amyloid morphology, not its specific precursor.

Amyloid deposits contain accessory molecules

- Fibrils are associated with serum amyloid P component and extracellular matrix constituents.
- Proteoglycans and glycosaminoglycans bind to deposits.
- Amyloid as approximately 95% fibril protein and 5% SAP/other glycoproteins.

Systemic versus localized deposition

Systemic AL

- Clonal precursor enters the circulation.
- Several distant organs may accumulate AL amyloid.

Localized AL-related deposits

- A nodular deposit may be confined to one site.
- Some localized deposits contain AL and adjacent lymphoplasmacytic infiltrates.

AL has tendencies, not a diagnostic organ map

Heart

Infiltrative cardiomyopathy

Kidney

Glomerular proteinuria

Gastrointestinal tract

Digestion and absorption

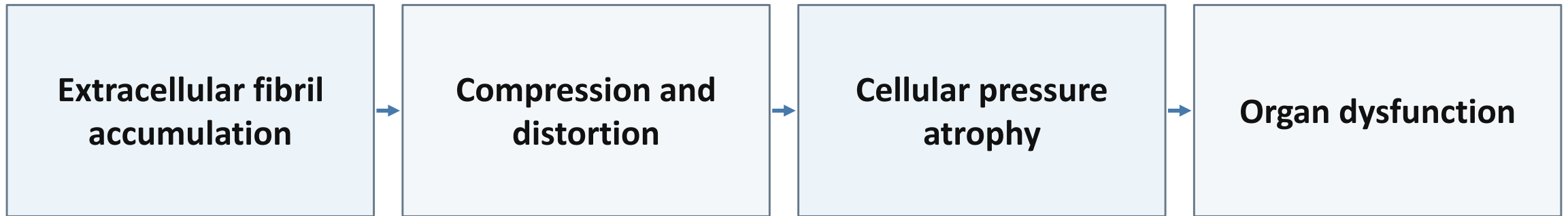
Peripheral nerves

Neuropathic involvement

Tongue and skin

Soft-tissue deposition

Deposits impair function through tissue architecture



- Deposits injure tissues predominantly without eliciting a marked inflammatory response.

Gross pathology may be surprisingly subtle

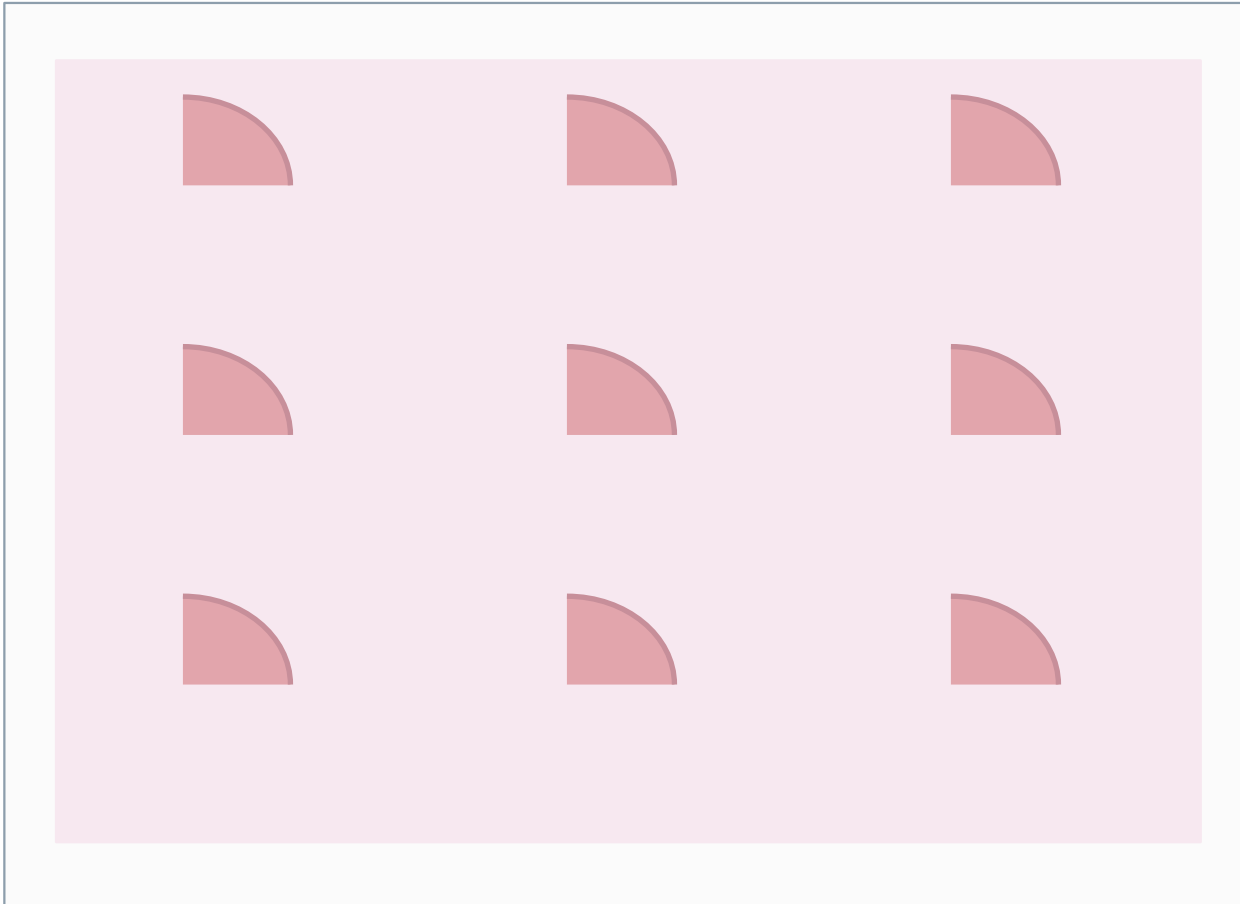
Minimal deposits

- Tissue can appear unremarkable macroscopically.
- Microscopy remains decisive.

Extensive deposits

- An organ may enlarge and become gray, firm and waxy.
- Gross appearance alone does not establish amyloid type.

H&E: Amorphous extracellular eosinophilia



Schematic: H&E appearance

- Amyloid appears as amorphous, eosinophilic, hyaline material between cells.
- The finding is suggestive but is not specific among hyaline extracellular substances.

Why H&E alone is insufficient

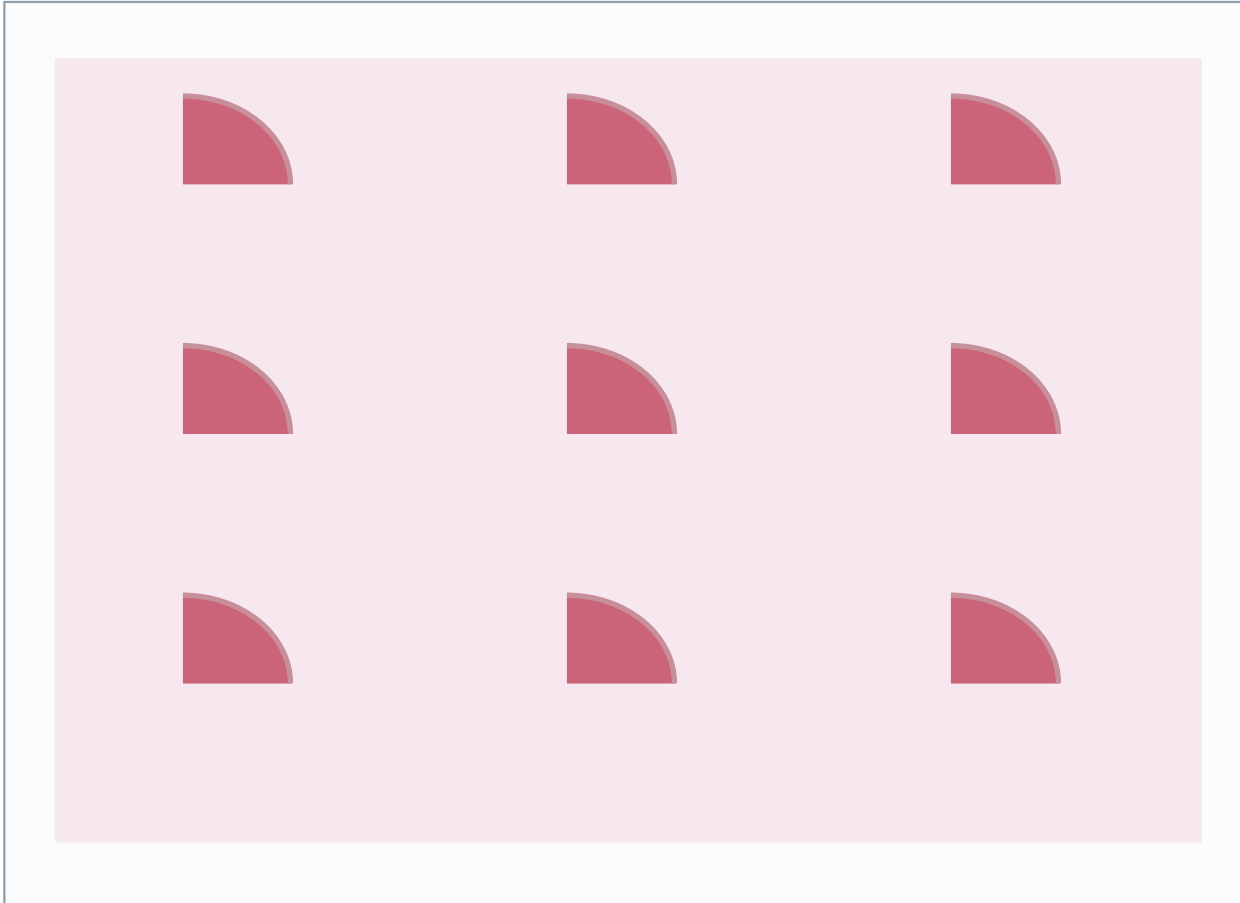
H&E appearance

- Pink, amorphous, extracellular material.
- Suggestive in the appropriate distribution.

Potential mimics

- Collagen and fibrin may also appear hyaline.
- Special staining confirms that the material has amyloid properties.

Congo red under ordinary light



Schematic: Congo red staining

- Congo red imparts a pink-to-red hue to amyloid deposits.
- The deposited protein still requires proper optical confirmation and subsequent typing.

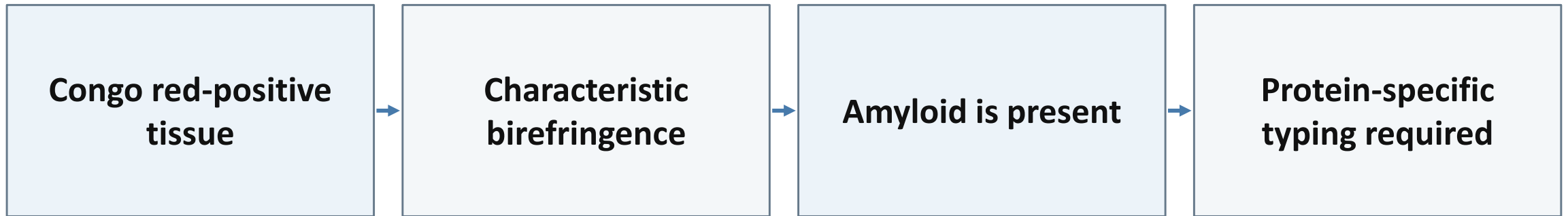
Congo red with polarized microscopy



Schematic: Crossed polarizers

- Amyloid shows characteristic apple-green (or yellow-green) birefringence after Congo red staining.
- This is a property shared by different amyloid proteins.

Congo red identifies amyloid—not AL



- An amyloid-positive specimen does not answer whether the deposit is AL, AA or ATTR.

Typing determines the precursor protein

Immunohistochemistry

- Specific stains can help distinguish AL, AA and TTR amyloid.
- Interpret within the clinical and morphologic context.

Mass spectrometry

- Protein identification for all amyloid types.
- Available in specialized centers.

Electron microscopy complements Congo red

Light/polarized microscopy

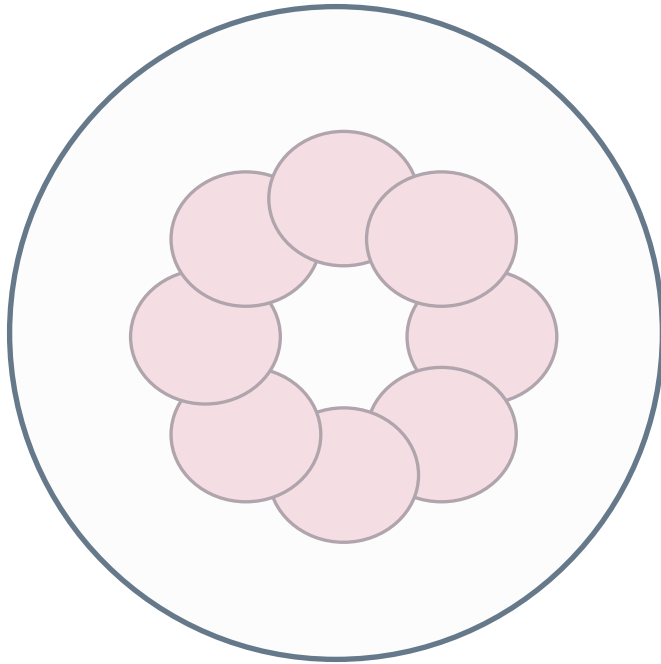
- Congo red positivity and birefringence demonstrate the defining optical pattern.

Electron microscopy

- Nonoriented, thin, unbranched fibrils provide structural support.
- EM does not by itself type the fibril precursor.

Early glomerular deposition

Schematic: Early glomerular change

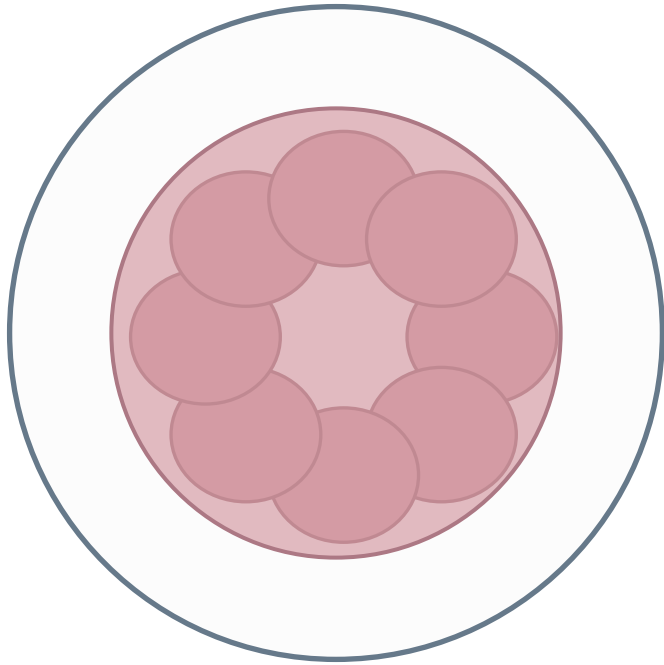


- Mesangial matrix expansion is an early manifestation.
- Uneven thickening of glomerular capillary basement membranes accompanies deposits.

Illustration only — not a glomerular micrograph

Progressive glomerular destruction

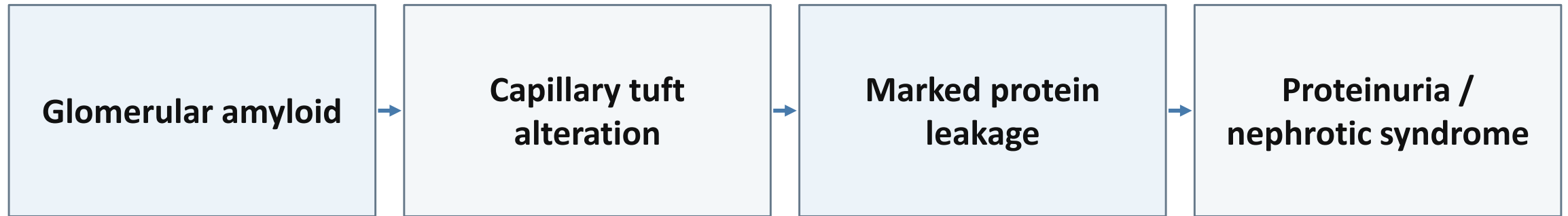
Schematic: Advanced glomerular change



- Deposits progressively narrow and distort glomerular capillary loops.
- Confluent deposits can nearly obliterate the capillary tuft.

Illustration only — not a glomerular micrograph

Kidney: Structure explains the proteinuria



- Continued glomerular destruction may ultimately cause kidney failure and uremia.

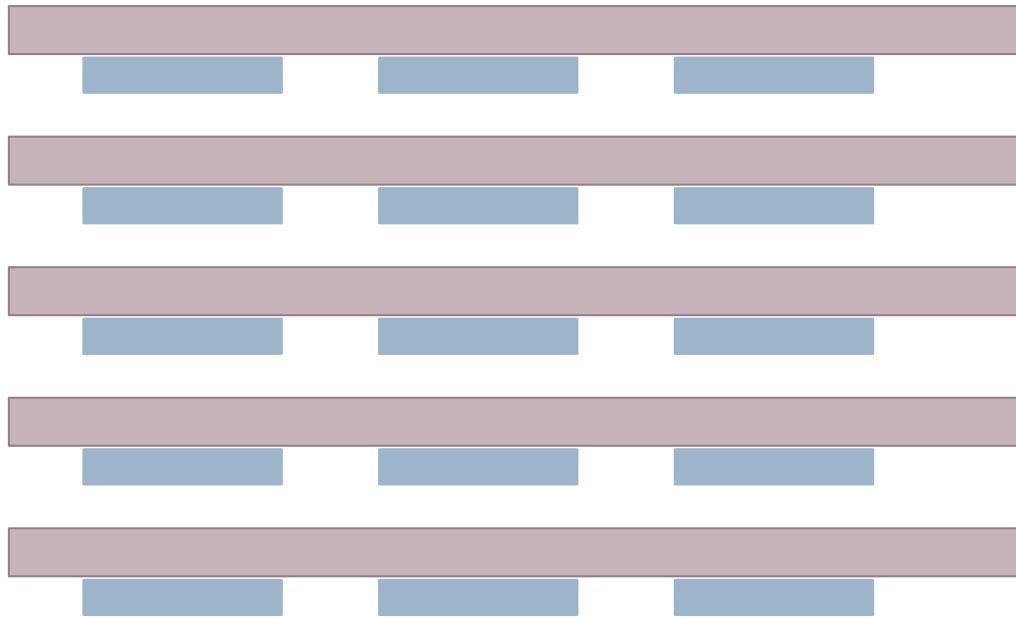
Renal vessels contribute to ischemic injury



- A kidney with amyloidosis need not always be enlarged.

The myocardial interstitium is a major target

Schematic: Myocardial amyloid infiltration



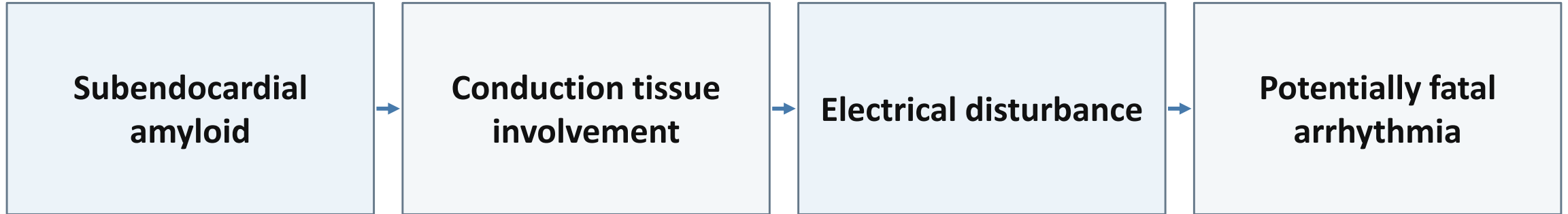
Muscle-fiber bundles

Deposits between fibers

Schematic — not a histologic specimen

- Amyloid accumulates between cardiac muscle fibers and may begin subendocardially.
- Expanded deposits compress myocytes and impair myocardial function.

Subendocardial deposition affects conduction



- Cardiac danger is not limited to the mechanical effects of interstitial infiltration.

Clinical cardiac phenotype

Mechanical consequences

- Insidious heart failure; Restrictive cardiomyopathy may develop.
- A grossly unremarkable heart does not exclude disease.

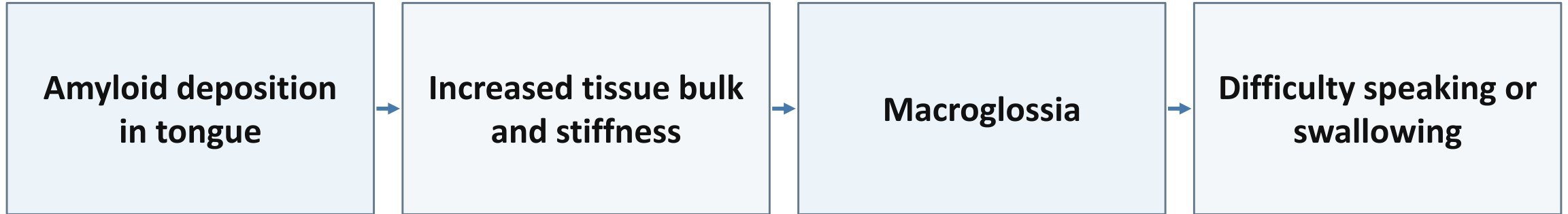
Electrical consequences

- Conduction abnormalities and arrhythmias.
- These may be immediately life-threatening.

Gastrointestinal disease may be heterogeneous

- Stomach and intestinal deposits can cause malabsorption and diarrhea.
- Disturbed digestion may accompany extensive infiltration.
- Other patients with gastrointestinal deposits can remain asymptomatic.

Macroglossia is a useful tissue clue

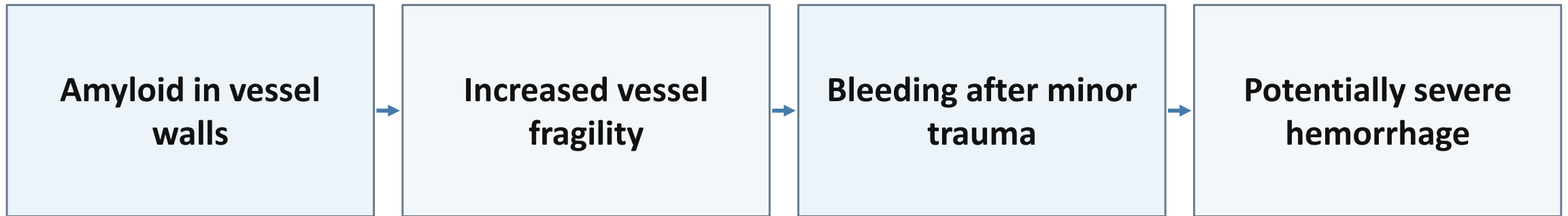


- This clinical sign reflects local extracellular accumulation, not cellular proliferation.

Peripheral-nerve involvement in the differential

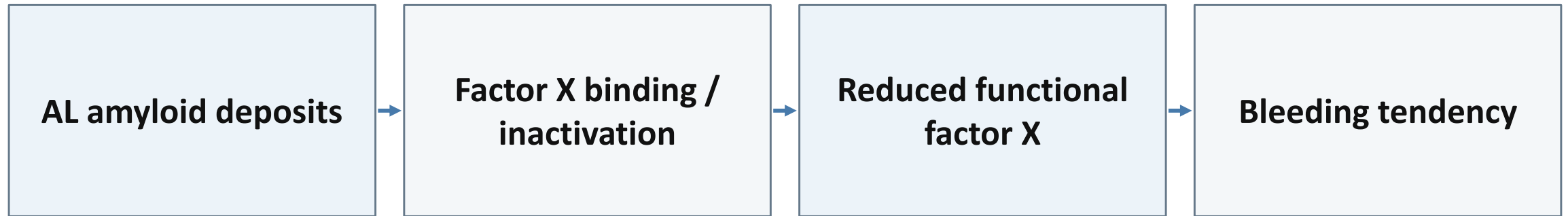
- Peripheral nerves are among the sites more often involved in plasma-cell–associated amyloid.
- Peripheral and autonomic neuropathy are not unique to AL; Some hereditary ATTR syndromes also affect nerves.
- Protein typing is required before attributing a neuropathic phenotype to AL.

Vascular deposition predisposes to bleeding



- Clinical bleeding may arise from tissue fragility even without a specific coagulation-factor defect.

An additional AL-specific bleeding mechanism



- Factor X inactivation occurs in some AL cases—not universally.

Histologic confirmation depends on tissue

- The disease diagnosis requires demonstration of amyloid in a specimen.
- The affected kidney may be biopsied when renal involvement dominates.
- Other potential tissues include rectal or gingival biopsies and abdominal fat aspirate.

Fat aspirate: Interpret a negative result correctly

Positive Congo red finding

- Supports a systemic amyloid diagnosis in an appropriate specimen.
- The precursor still needs to be typed.

Negative fat aspirate

- Does not rule out amyloidosis.
- Robbins characterizes the test as specific but insensitive.

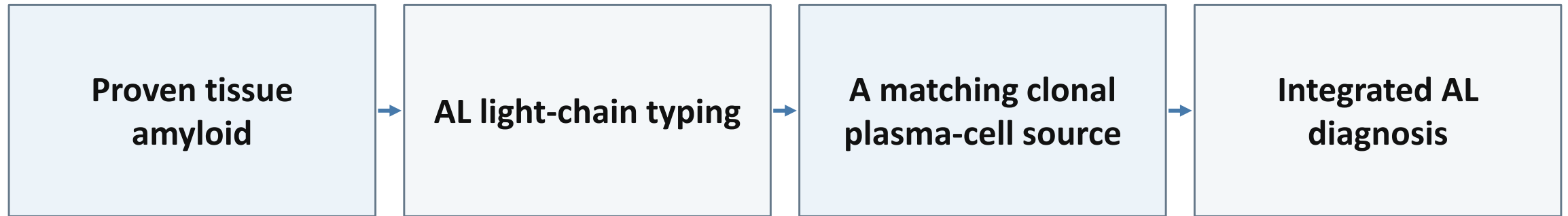
Look for a circulating clonal product

- Robbins recommends serum and urine protein electrophoresis and immunoelectrophoresis for suspected AL.
- A monoclonal immunoglobulin or free light chain suggests a clonal source.
- Interpret protein studies alongside tissue identification, not as a substitute.

Bone marrow: A small clone can be consequential

- Marrow evaluation often reveals monoclonal plasmacytosis in suspected AL.
- An overt myeloma phenotype is not required for systemic AL disease.
- The plasma-cell burden and burden of organ deposits are distinct clinical dimensions.

Three linked observations establish the mechanism



- Avoid assigning amyloid type solely from a monoclonal protein detected in blood.

Plasma-cell clonality does not type the deposit

What clonality answers

- Is there a restricted immunoglobulin-producing population?
- Source investigation: Serum, urine and marrow.

What amyloid typing answers

- Which precursor forms the actual tissue fibrils?
- Deposit investigation: Specific tissue-based methods.

The main biochemical alternatives

Feature	AL	AA	ATTR
Fibril precursor	Ig light chain	SAA-derived	Transthyretin
Typical source	Plasma-cell clone	Inflammatory acute-phase response	Wild-type or variant TTR
Interpretive caution	Clone $\neq$ tissue typing	Organ site not definitive	Cardiac phenotype overlaps

Localized AL-related amyloid is a separate pattern

Systemic AL

- Circulating light chain reaches multiple organs.
- Clinical effects reflect multiorgan deposits.

Localized deposits

- Some nodular masses contain AL-derived material.
- Local lymphocytes/plasma cells may surround the deposit.

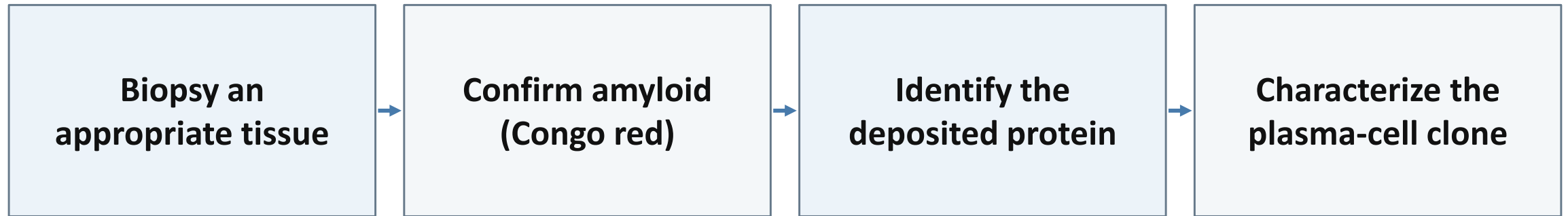
First application: Kidney–heart presentation

A patient develops nephrotic-range proteinuria and progressive heart failure; Serum studies show a restricted light-chain product.

What is the most defensible next diagnostic sequence?

Prioritize tissue confirmation and amyloid-protein typing rather than naming AL from the serum result.

Application: Evidence-based resolution



- Only integrated findings support assigning systemic AL amyloidosis.

Second application: Amyloid without myeloma

Biopsy-confirmed AL deposits are present, but marrow shows only a modest expansion of monoclonal plasma cells; There is no overt tumor mass.

Does this exclude a pathogenic plasma-cell disorder?

No. A small clone may be clinically defined by its amyloidogenic protein product.

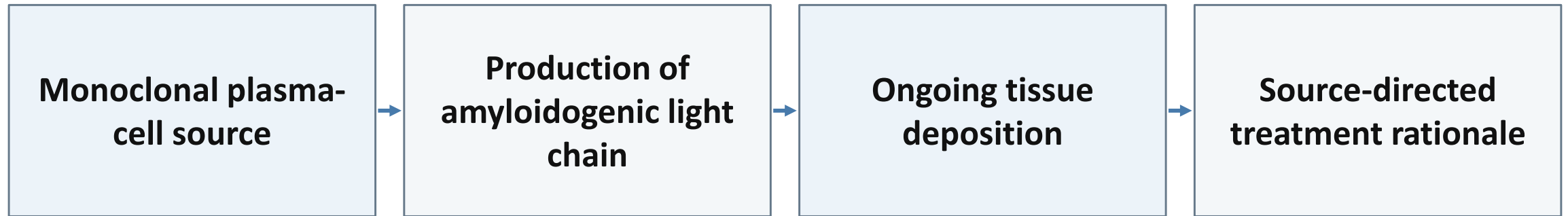
A nonbulky clone may still cause major disease

- AL is driven by the abnormal secreted protein rather than an obligatory mass-forming malignancy.
- Organ injury arises where light chains deposit and alter tissue architecture.
- A small marrow clone and extensive organ dysfunction are therefore compatible.

Prognosis follows systemic organ injury

- Generalized amyloidosis as potentially life-threatening.
- An overall median survival of about 2 years after AL diagnosis.
- That number is a textbook summary, not an individualized prognosis or a newly verified contemporary treatment-era estimate.

Therapeutic logic follows precursor biology

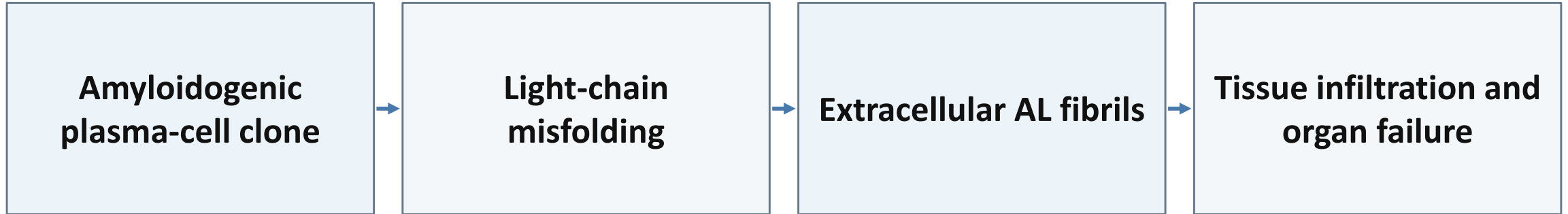


- Improved treatment options for plasma-cell disorders and emerging anti-misfolding approaches, without specifying a regimen here.

Major diagnostic errors to avoid

- Do not equate an M spike or urinary light chain with tissue-proven amyloid.
- Do not infer AL from renal or cardiac organ distribution alone.
- Do not mistake Congo red positivity for precursor-specific typing.
- Do not exclude AL merely because classic myeloma is absent.

Integrated take-home model



- Establish the deposit, type the protein and investigate the clonal source.

Primary reference and interpretation limits

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 6, Amyloidosis, pp. 230–235.
- Core AL section begins on p. 231; tissue morphology, diagnosis and clinical effects are described on pp. 233–235.
- The supplied Markdown conversion includes interleaved figure text; no original chapter PDF or reusable authentic microscopy asset was supplied.
- All microscopic drawings in this lecture are labeled schematics and are not diagnostic photomicrographs.