

Amyloidosis

Protein misfolding, extracellular deposits, organ injury and diagnosis

Mechanisms • morphology • clinicopathologic correlation

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Learning objectives

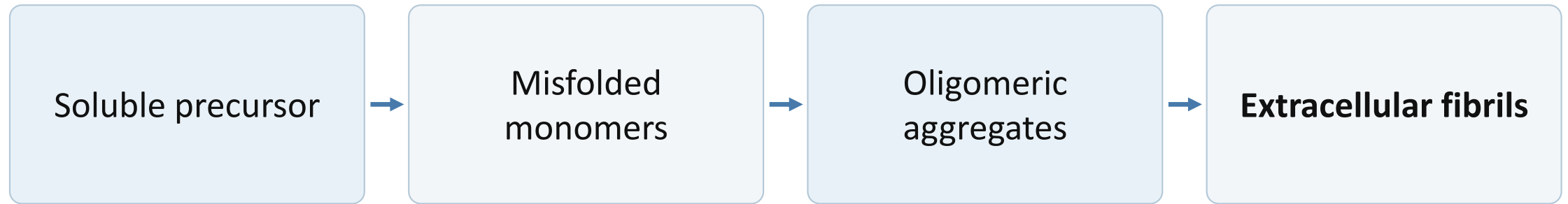
- Define amyloid and explain its shared fibrillar architecture.
- Differentiate AL, ATTR and AA by precursor and mechanism.
- Recognize tissue morphology, diagnostic stains and organ effects.
- Select confirmatory tests and interpret clinicopathologic patterns.

Amyloidosis denotes a family of deposition disorders

Proteins with aggregation propensity form insoluble fibrils.

- Deposits accumulate extracellularly in tissues and organs.
- Progressive accumulation damages tissues and compromises function.
- The same morphologic pattern can arise from distinct precursor proteins.

Molecular route from soluble protein to amyloid



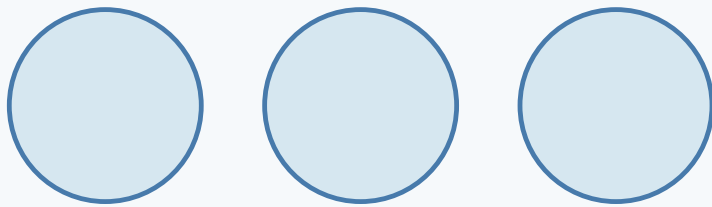
- A soluble precursor becomes unstable or misfolded.
- Monomers associate into oligomers and larger aggregates.
- Insoluble fibrils accumulate in the extracellular compartment.
- The identity of the precursor determines the amyloid type.

“Amyloid” is a historical misnomer

- Early staining behavior was interpreted as resembling starch (amylose).
- The deposits are proteinaceous—not starch.
- Bound proteoglycans and glycosaminoglycans contribute to histochemical behavior.
- Serum amyloid P component is associated with deposits.

The extracellular location drives the lesion

SCHEMATIC — NOT A TISSUE IMAGE



Expanding extracellular amyloid

Extracellular material displaces adjacent cells

- Amyloid appears between cells and adjacent to basement membranes.
- Increasing deposits encroach on neighboring functional tissue.
- Affected cells may atrophy or disappear with progression.

Distribution and burden determine manifestations

Localized

- Restricted to one site
- May form a nodule
- Often discovered locally

Systemic

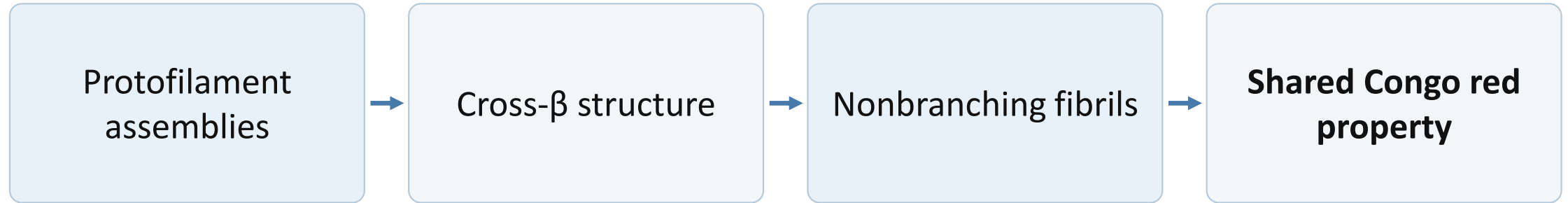
- More than one organ may be involved
- Renal and cardiac disease can dominate
- May be clinically occult early

Shared histology does not imply shared chemistry

More than 40 distinct proteins can form amyloid.

- The deposited proteins have characteristic fibrillar organization.
- Routine light microscopy cannot reliably assign biochemical type.
- Typing is necessary to identify the underlying disease process.

Amyloid fibrils have a characteristic ultrastructure



- Electron microscopy reveals continuous, nonbranching fibrils.
- Fibril diameter is approximately 8–10 nm.

- Protofilaments have a β -pleated sheet arrangement.
- The common conformation helps explain staining similarities.

Amyloid deposits include nonfibrillar components

Fibril core

- Predominant protein fraction
- Amyloidogenic precursor-derived
- Defines biochemical amyloid type

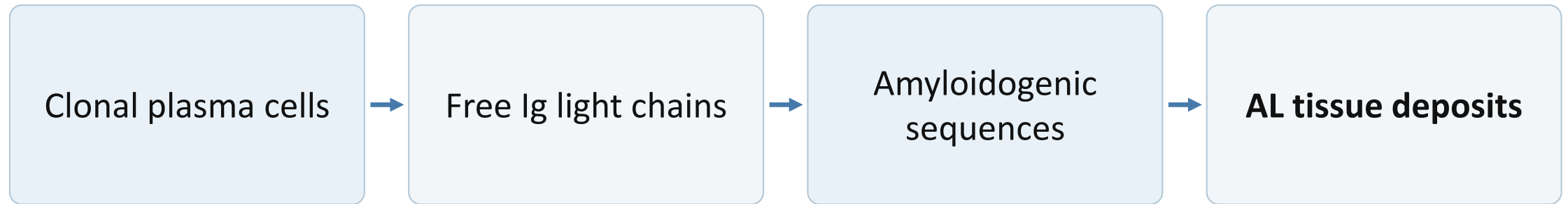
Associated constituents

- Serum amyloid P and glycoproteins
- Proteoglycans/glycosaminoglycans
- Contribute to deposit properties

Three major amyloid types identify different precursors

Type	Precursor	Typical context
AL	Ig light chain	Clonal plasma cell disorder
ATTR	Transthyretin	Aging or inherited TTR variant
AA	Serum amyloid A	Sustained inflammation

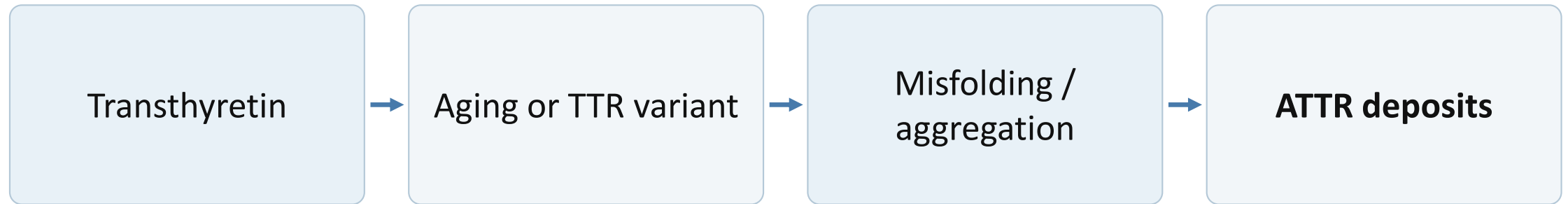
AL identifies immunoglobulin light-chain amyloid



- Amyloid may contain intact light chains or light-chain fragments.
- The precursor is secreted by a monoclonal plasma cell population.

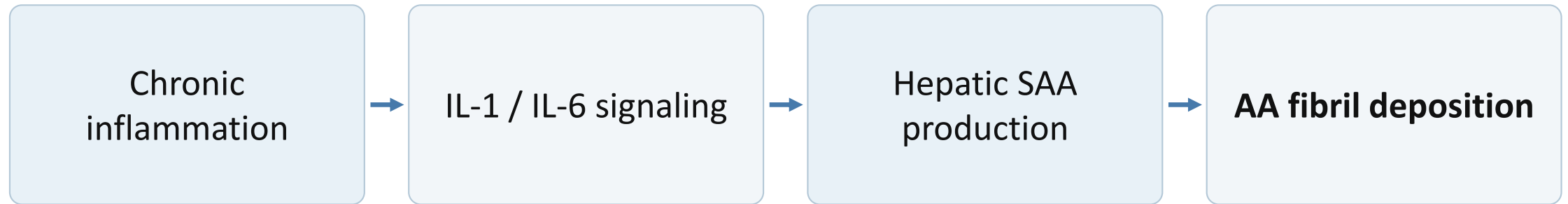
- λ light chains predominate account; κ may also form amyloid.
- AL frequently has a systemic distribution.

ATTR identifies transthyretin-derived amyloid



- Transthyretin transports thyroxine and retinol.
- Wild-type TTR can aggregate with aging.
- Inherited TTR variants can favor protein misfolding.
- Deposits often target heart, peripheral nerves or connective tissues.

AA identifies an inflammation-linked amyloid

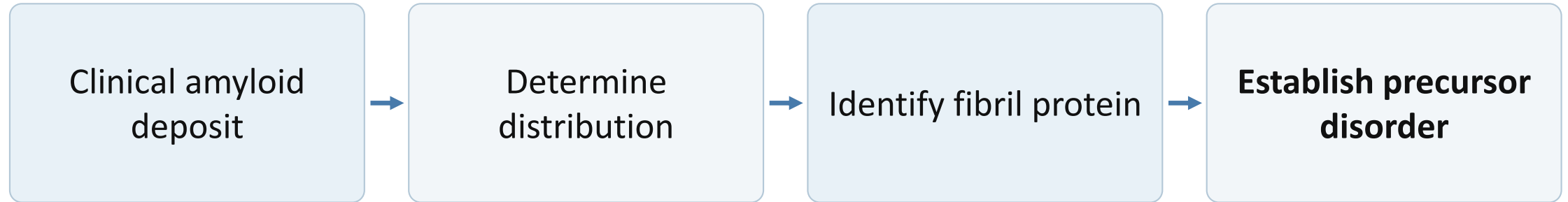


- The AA fibril protein is derived from circulating serum amyloid A.
- Hepatocytes synthesize SAA as an acute-phase reactant.
- SAA production increases in chronic inflammatory states.
- Persistent supply plus altered processing favors AA deposition.

Other proteins also form amyloid

Deposit	Precursor/source	Example
A β	Amyloid precursor protein	Alzheimer disease
A β_2 M	β_2 -microglobulin	Long-term hemodialysis
AIAPP	Islet amyloid polypeptide	Type 2 diabetes
ACal	Calcitonin	Medullary thyroid carcinoma

Classify amyloidosis by distribution and protein type



- Systemic: Amyloidogenic protein or deposits affect multiple organs.
- Localized: Deposits remain in an individual site or organ.

- Hereditary: A molecular predisposition may influence the precursor.
- An etiologic diagnosis requires protein identification and clinical context.

Systemic and localized are separate axes from type

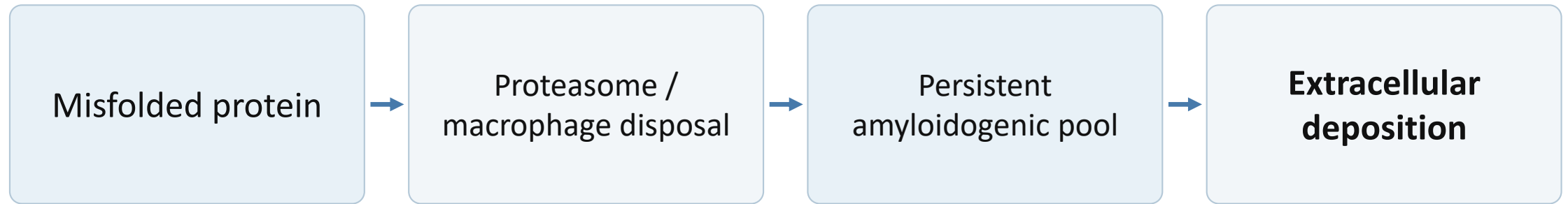
Anatomic classification

- Single site or multiple organs
- Defines extent of involvement
- Guides organ assessment

Biochemical classification

- AL, AA, ATTR, other proteins
- Identifies deposited precursor
- Guides investigation of mechanism

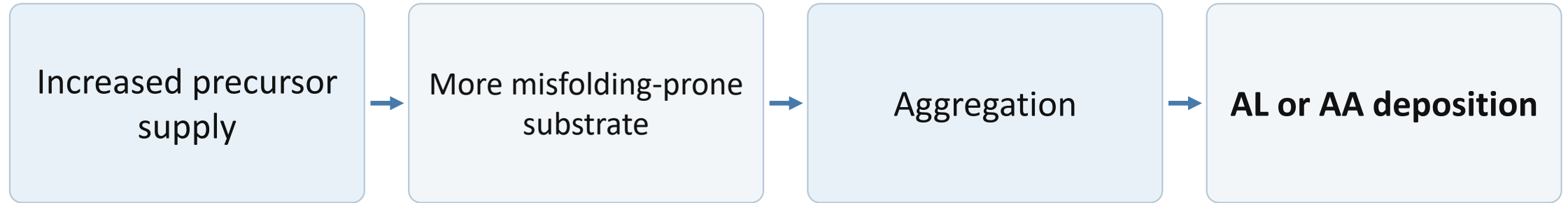
Protein homeostasis ordinarily limits amyloid



- Intracellular misfolded proteins undergo proteasomal degradation.
- Macrophages help clear extracellular misfolded proteins.

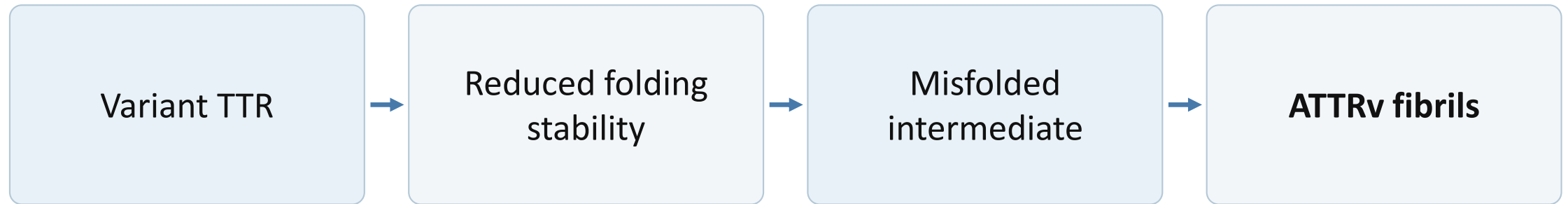
- Failure of these processes allows amyloidogenic material to persist.
- Fibril formation reflects supply, instability and impaired clearance.

Mechanism I: Excess production of a normal precursor



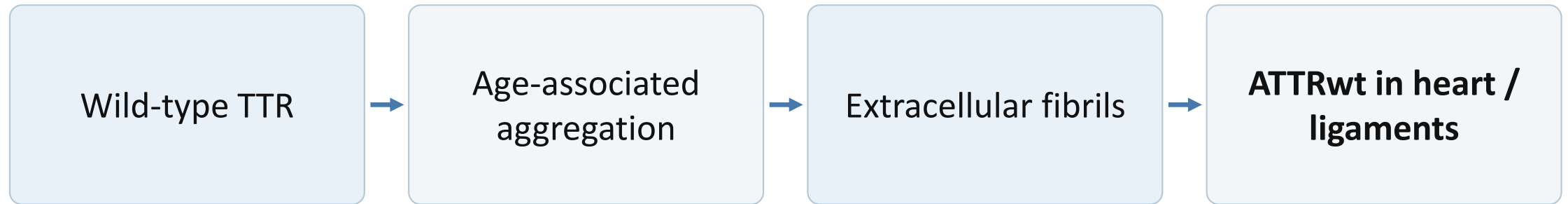
- Some normal proteins can misfold when their concentration rises.
- Clonal plasma cells can supply large quantities of light chain.
- Inflammation can sustain high circulating SAA concentrations.
- Production outpaces effective degradation or clearance.

Mechanism II: Inherited protein instability



- Variants can alter the folding propensity of an otherwise normal protein.
- Variant transthyretin exemplifies genetically mediated amyloidogenesis.
- Different variants may have different organ preferences.
- A mutation does not guarantee identical phenotype in all carriers.

Mechanism III: Aging-associated protein misfolding



- Unmutated transthyretin can form amyloid in older adults.
- The heart is a major site of ATTRwt deposition.

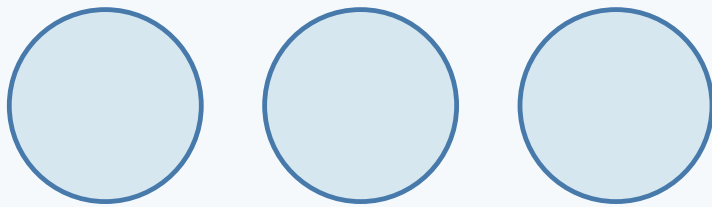
- Connective tissues, including ligaments, can also be affected.
- This is distinct from autosomal dominant variant ATTR.

Amyloid generation has multiple entry points

Mechanism	Driver	Fibril
Clonal production	Abnormal Ig light-chain supply	AL
Inflammatory production	Increased SAA synthesis	AA
Inherited instability	Variant TTR	ATTRv
Age-associated instability	Wild-type TTR aggregation	ATTRwt

Amyloid injures organs by replacing functioning tissue

SCHEMATIC — NOT A TISSUE IMAGE

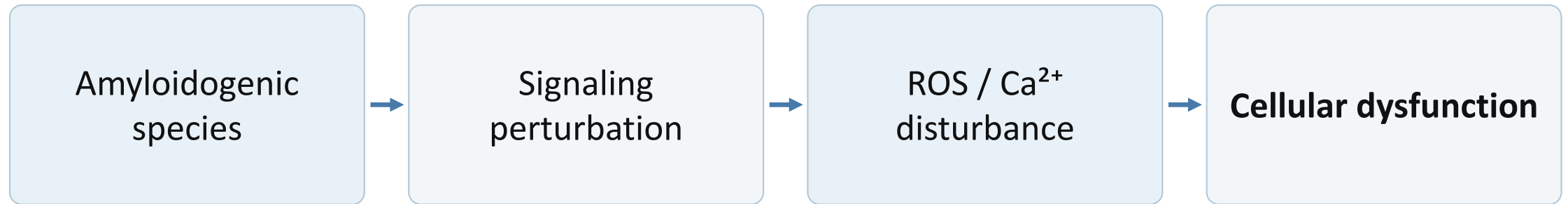


Expanding extracellular amyloid

Extracellular material displaces adjacent cells

- Extracellular deposits distort the local architecture.
- Compression and pressure atrophy diminish viable parenchyma.
- Vascular and basement-membrane deposits impede normal exchange.

Additional cellular effects may contribute to injury



- Some amyloidogenic proteins may alter intracellular signaling.
- Increased reactive oxygen species have been implicated.

- Abnormal calcium homeostasis may compromise cell function.
- These as possible adjuncts to architectural disruption.

Amyloid appears as extracellular hyaline on H&E

What H&E suggests

- Amorphous extracellular material
- Expanding interstitial/basement-membrane deposits
- Compression of neighboring cells

What H&E cannot prove

- Specificity for amyloid
- Amyloid fibril protein identity
- Exclusion of collagen or fibrin

Congo red provides the key tissue stain

Ordinary light

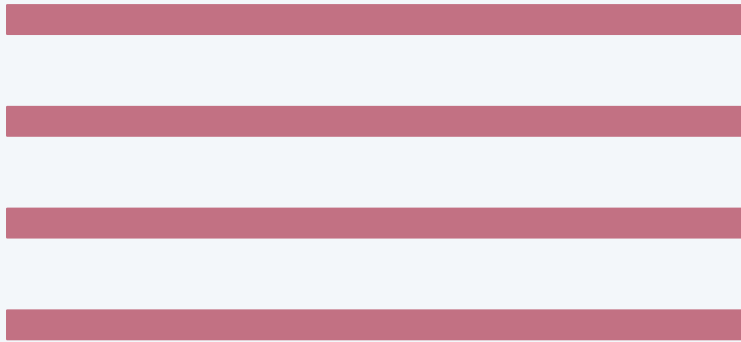
- Pink–red Congo red-positive deposits
- Localizes suspected amyloid
- Interpret with tissue morphology

Polarized light

- Characteristic apple-green birefringence
- Reflects ordered fibrillar conformation
- Shared across amyloid types

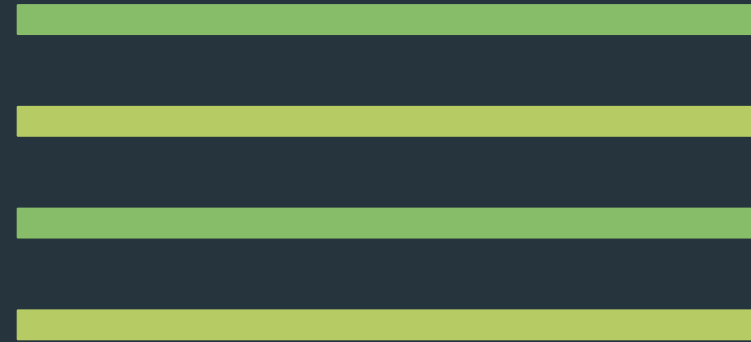
Polarized Congo red reveals birefringence

Ordinary transmitted light



Pink-red deposits

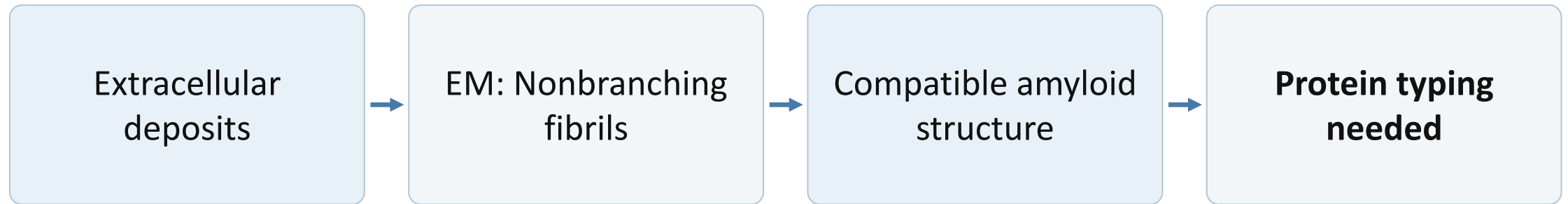
Polarized illumination



Apple-green birefringence

Schematic of optical appearance only; Not a polarized tissue photomicrograph.

Ultrastructure can support amyloid identification



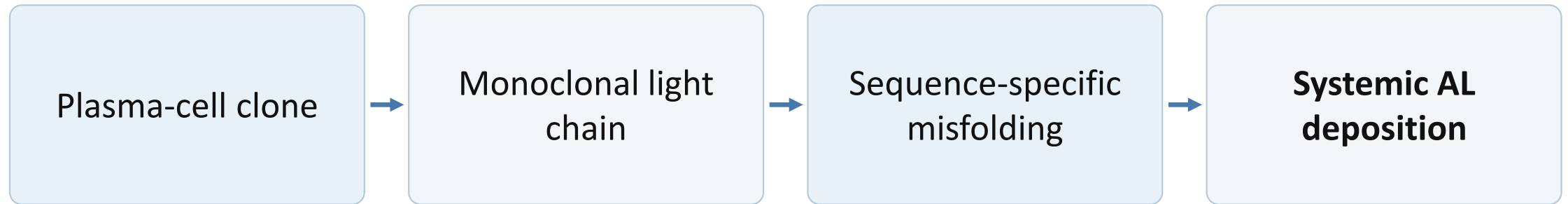
- Electron microscopy shows randomly arranged, fine fibrils.
- The fibrils are nonbranching and approximately 8–10 nm wide.

- This supports an amyloid diagnosis when light microscopy is uncertain.
- Electron microscopy does not by itself identify precursor protein.

Protein typing is different from deposit recognition

Diagnostic question	Approach	Interpretation
Is this amyloid?	Histology + Congo red	Deposit identification
Which protein?	IHC or mass spectrometry	Fibril type
What causes it?	Clinical and laboratory correlation	Underlying disorder

AL originates in a clonal plasma-cell population



- A monoclonal clone produces an immunoglobulin light chain.
- Intrinsic sequence-dependent properties promote amyloid formation.

- Many patients lack overt multiple myeloma.
- Secreted abnormal protein may be the main clinical consequence.

AL amyloidosis is not synonymous with myeloma

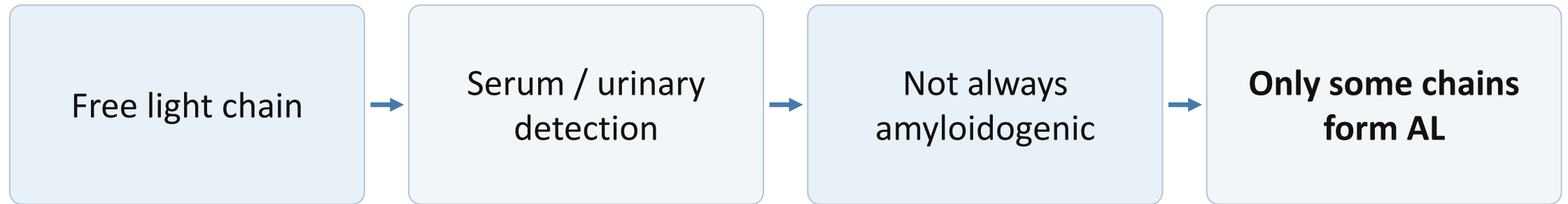
AL with myeloma

- Recognizable plasma-cell tumor
- Light chains may appear in serum/urine
- Amyloid may complicate tumor

AL without overt myeloma

- No classic bulky neoplasm required
- Small clone can produce harmful protein
- Amyloid drives organ disease

Free light chains are clues, not sufficient proof

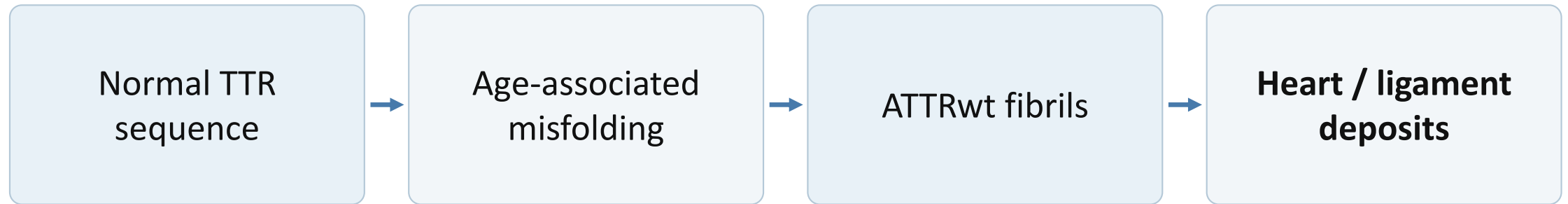


- Clonal cells can release unpaired κ or λ light chains.
- Small light chains may circulate and appear in urine as Bence Jones protein.
- Most myeloma patients with free light chains do not develop amyloid.
- Light-chain sequence influences amyloidogenic propensity.

AL organ involvement cannot be inferred from clone size

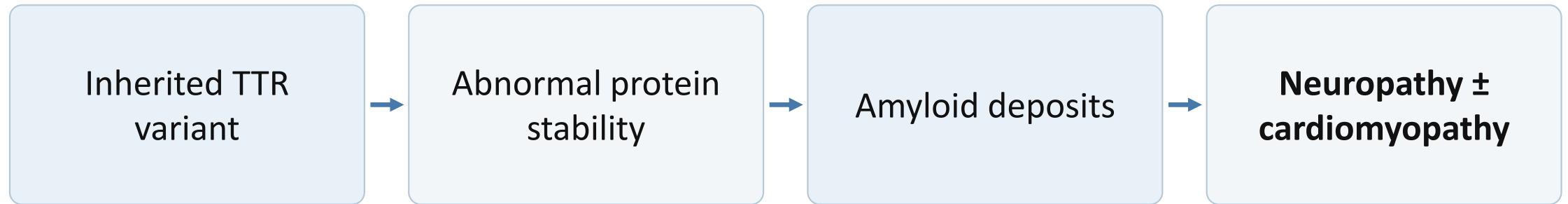
- Organ deposition may dominate the phenotype despite limited marrow disease.
- Heart, kidneys, gastrointestinal tract and nerves may be involved.
- Tongue, skin and respiratory tissues can be affected.
- Assessment must focus on target-organ manifestations.

ATTRwt: Wild-type protein in an aging host



- Wild-type transthyretin can misfold and aggregate.
- Cardiac involvement predominates in the source description.
- Connective-tissue deposits may occur in ligaments.
- Older men as a common affected population.

ATTRv: A heritable protein misfolding disorder



- A pathogenic TTR variant predisposes the protein to aggregation.
- Inheritance is autosomal dominant.
- Peripheral/autonomic neuropathy or cardiac disease may predominate.
- Clinical expression varies considerably among carriers.

Different TTR variants favor different tissues

Neuropathy-predominant ATTRv

- Peripheral nerve deposits
- Autonomic nerve involvement
- Familial amyloid polyneuropathy

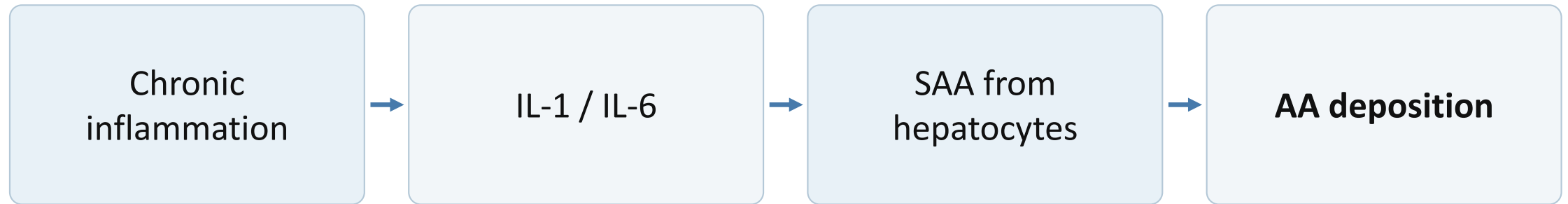
Cardiac-predominant ATTRv

- Myocardial deposition
- Restrictive physiology may follow
- Hereditary cardiac amyloidosis

Wild-type and variant ATTR: Critical distinctions

Feature	ATTRwt	ATTRv
TTR sequence	Wild-type	Variant
Underlying driver	Age-associated misfolding	Inherited sequence change
Typical involvement	Heart; Connective tissues	Heart and/or nerves
Inheritance	Not mendelian TTR mutation	Autosomal dominant

AA follows persistent inflammatory signaling



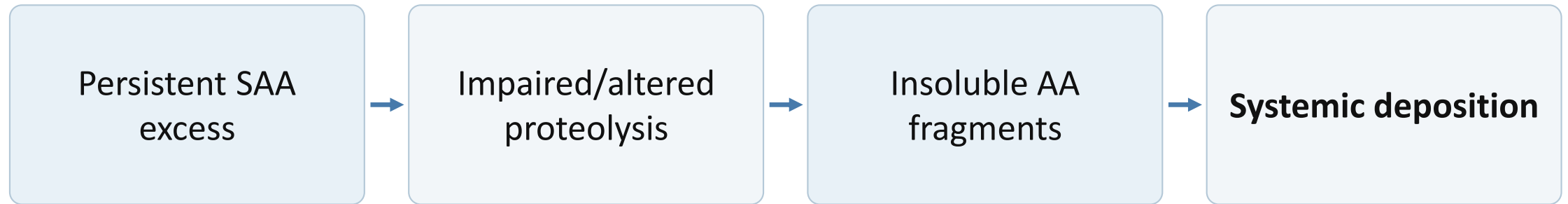
- Macrophage-associated IL-1 and IL-6 stimulate hepatic SAA synthesis.
- Chronic inflammation maintains elevated SAA concentrations.

- Normally SAA is metabolized to soluble products.
- A subset of patients develop insoluble AA fibril deposits.

AA associations reflect chronic inflammatory load

Source of inflammation	Robbins examples
Autoimmune / rheumatic	Rheumatoid arthritis; Ankylosing spondylitis
Inflammatory bowel disease	Crohn disease; Ulcerative colitis
Chronic infections	Tuberculosis; Osteomyelitis; Bronchiectasis
Other settings	Repeated skin infections; Selected tumors

Raised SAA alone does not guarantee AA amyloid



- SAA is normally degraded by macrophage-derived enzymes.
- Excess synthesis may combine with incomplete proteolytic degradation.

- Inherited molecular differences in SAA may alter degradation susceptibility.
- The source presents processing defects as possible explanations.

Treating inflammation changed AA epidemiology

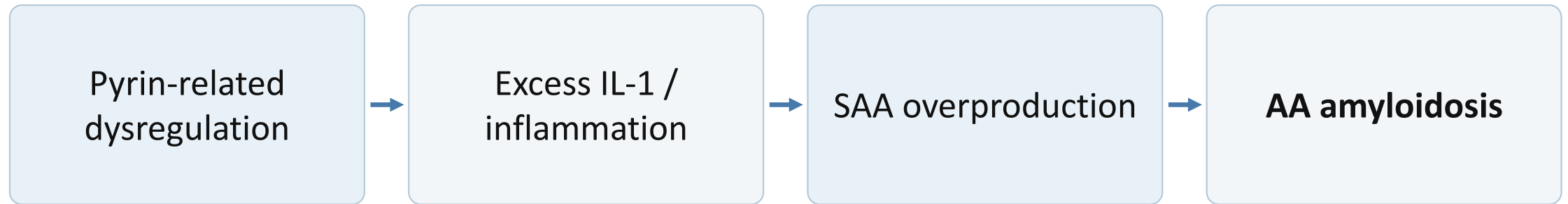
Earlier prominent associations

- Tuberculosis
- Bronchiectasis
- Chronic osteomyelitis

More prominent contemporary settings

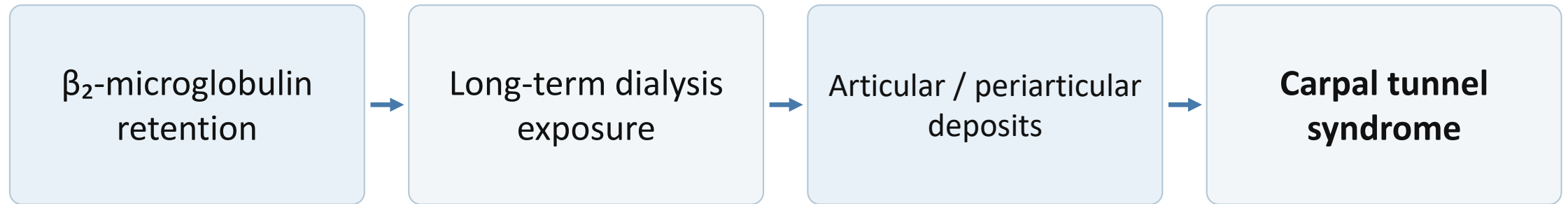
- Rheumatoid arthritis
- Other connective-tissue disorders
- Inflammatory bowel disease

Familial Mediterranean fever can lead to AA



- Familial Mediterranean fever is an autosomal recessive autoinflammatory syndrome.
- Pyrin-associated inflammasome dysregulation drives excess IL-1.
- Recurrent fever and serosal inflammation create persistent inflammatory exposure.
- Systemic deposits are of the AA type, not ATTR.

Dialysis-associated amyloid uses β_2 -microglobulin



- β_2 -microglobulin is a component of MHC class I molecules.
- Long-standing impaired clearance permits circulating accumulation.
- Deposits favor joints, tendons, ligaments and adjacent soft tissues.
- Improved dialysis filters have reduced this complication.

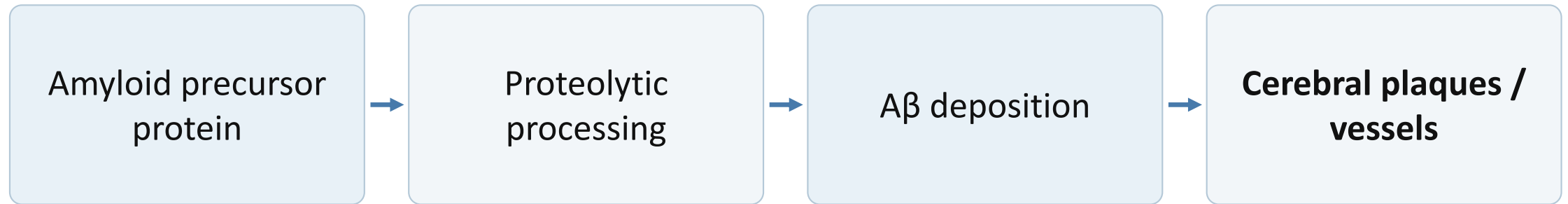
Localized nodular amyloid may resemble a mass

- Deposits can be confined to a single tissue without systemic involvement.
- Examples include lung, larynx, skin, bladder, tongue and periorbital tissue.
- Peripheral plasma cells and lymphocytes may accompany a nodule.
- Some localized deposits are AL-related.

Endocrine amyloid is often localized

Context	Amyloid protein	Role
Medullary thyroid carcinoma	Calcitonin (ACal)	Diagnostic morphology
Type 2 diabetic islets	Islet amyloid polypeptide (AIAPP)	Localized islet deposits
Selected endocrine tumors	Hormone-related / other proteins	Context-dependent deposits

Amyloid- β is a localized cerebral deposition process



- Amyloid- β derives from cleavage of amyloid precursor protein.
- Deposits contribute to plaques in Alzheimer disease.

- Amyloid can also accumulate in cerebral vascular walls.
- This should not be conflated with systemic AL, ATTR or AA disease.

Distribution patterns overlap across amyloid types

AA often involves

- Kidneys
- Liver and spleen
- Lymph nodes; Adrenals; Thyroid

AL often involves

- Heart
- Gastrointestinal and respiratory sites
- Nerves; Skin; Tongue

Gross amyloid appearance is variable

Minimal gross change

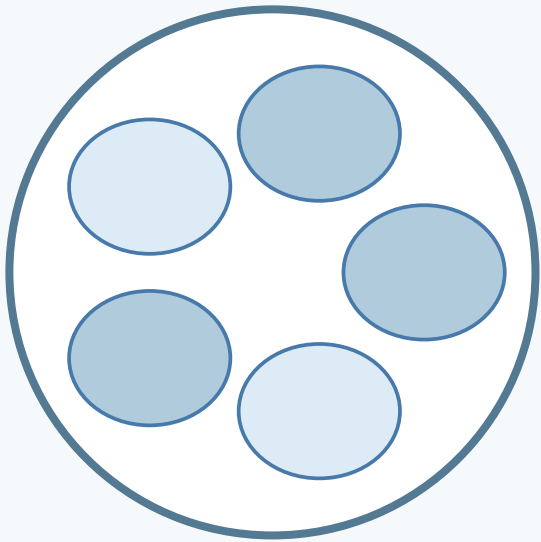
- No reliable enlargement
- Appearance may be inconspicuous
- Tissue diagnosis still possible

Advanced deposition

- Organ enlargement may develop
- Gray, waxy, firm parenchyma
- Function may be impaired

The renal glomerulus is a major amyloid target

SCHEMATIC — NOT A TISSUE IMAGE

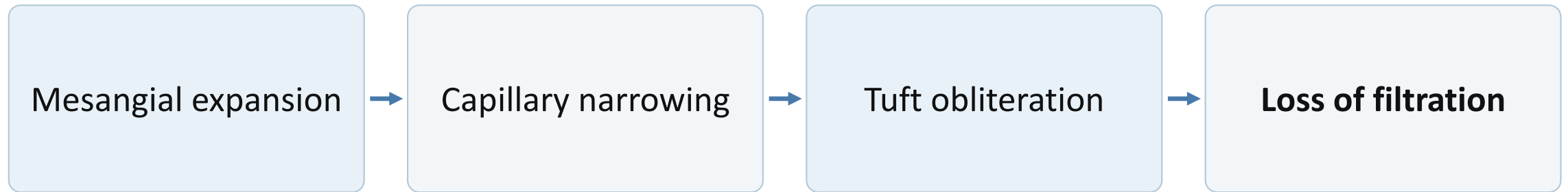


Glomerular tuft

Mesangial expansion and tuft distortion

- Deposits develop in mesangial matrix and capillary basement-membrane regions.
- Peritubular interstitium and small vessels may also be affected.
- Amyloid restricts capillary lumen caliber.

Glomerular amyloidosis progresses structurally



Progressive deposition compromises the structure or function indicated by the final stage.

Renal deposits produce proteinuria and failure

Anatomic lesion

- Mesangial/capillary-wall deposits
- Tuft distortion and impaired capillary function

Clinical consequence

- Proteinuria → nephrotic syndrome
- Progressive kidney failure

The spleen has two classic deposition patterns

Sago spleen

- Predominantly white-pulp follicles
- Tapioca-like granules
- Follicle-centered appearance

Lardaceous spleen

- Predominantly red-pulp framework
- Confluent, map-like deposits
- Wider pulp involvement

Hepatic amyloid begins in the space of Disse

SCHEMATIC — NOT A TISSUE IMAGE



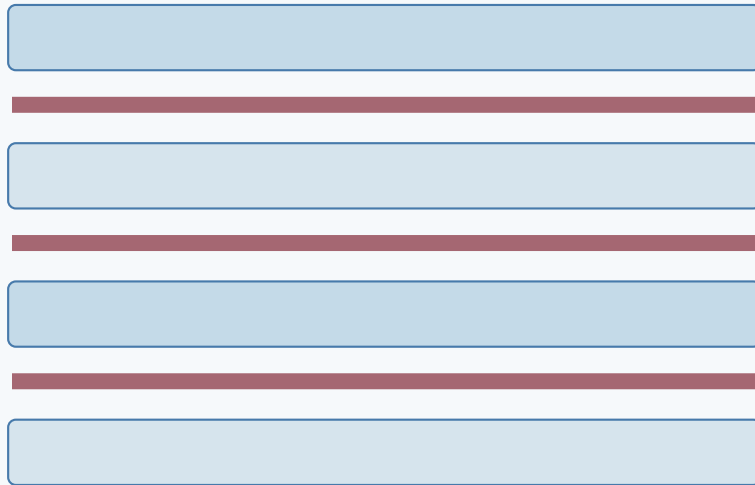
Sinusoidal interface / space of Disse

Deposits accumulate between sinusoid and hepatocytes

- Extracellular deposits begin along sinusoidal interfaces.
- Progression compresses hepatocytes and narrows sinusoidal spaces.
- Vascular involvement can accompany parenchymal disease.

Cardiac amyloid infiltrates between myocytes

SCHEMATIC — NOT A TISSUE IMAGE



Myocyte bands separated by deposits

Interstitial deposits compress myocardium

- Deposits may be subendocardial and interstitial within myocardium.
- Expansion separates and compresses cardiac muscle fibers.
- Subendocardial involvement can compromise the conduction system.

Cardiac injury may be hemodynamic or electrical

Mechanical dysfunction

- Amyloid between myocytes
- Reduced myocardial compliance
- Restrictive cardiomyopathy / heart failure

Electrical dysfunction

- Subendocardial / conduction deposits
- Conduction abnormalities
- Potentially fatal arrhythmias

Gastrointestinal effects depend on deposit location

- Tongue involvement can cause macroglossia and impaired swallowing.
- Stomach or intestinal deposition may lead to malabsorption.
- Diarrhea and digestive disturbances can occur.
- The same organ may harbor deposits without overt symptoms.

Nerves, tendons and ligaments are clinically informative

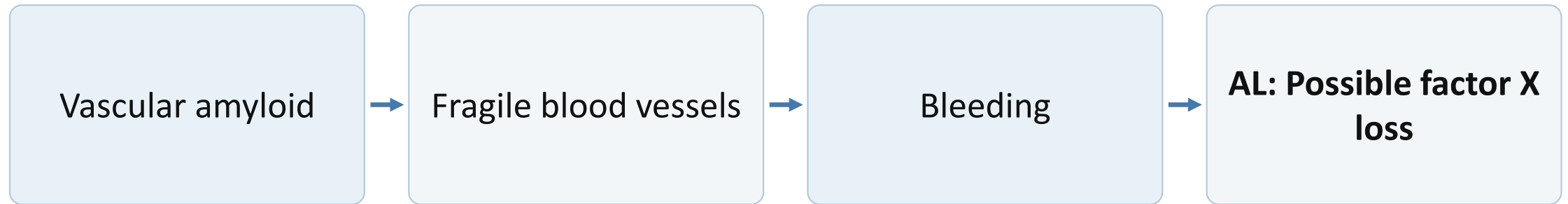
ATTRv neuropathy

- Peripheral and autonomic nerve deposits
- Sensory/autonomic consequences
- Genetically mediated TTR precursor

Dialysis-associated soft-tissue amyloid

- Joints / tendons / ligaments
- Median nerve compression at wrist
- β_2 -microglobulin precursor

Amyloid can produce bleeding by two mechanisms

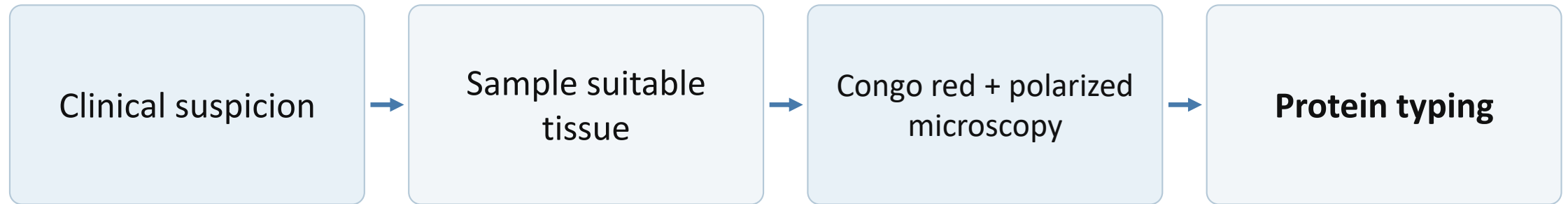


- Vascular-wall deposits increase vessel fragility.
- Bleeding can occur after minor trauma or spontaneously.
- Some AL amyloid binds and inactivates coagulation factor X.
- Anatomic fragility and coagulopathy are distinct contributors.

The initial clinical presentation can be nonspecific

- Fatigue or weakness may precede organ-specific recognition.
- Weight loss, lightheadedness and syncope can occur.
- Later manifestations often arise from renal, cardiac or gastrointestinal injury.
- Clinical recognition requires connecting symptoms to possible tissue deposits.

Tissue confirmation is central to diagnosis



- Diagnosis depends on histologic demonstration of amyloid deposits.
- An affected-organ biopsy may be selected when clinically indicated.

- Rectal or gingival biopsies are described for systemic evaluation.
- Sampling strategy depends on suspected site and procedural considerations.

Abdominal fat sampling offers a less invasive site

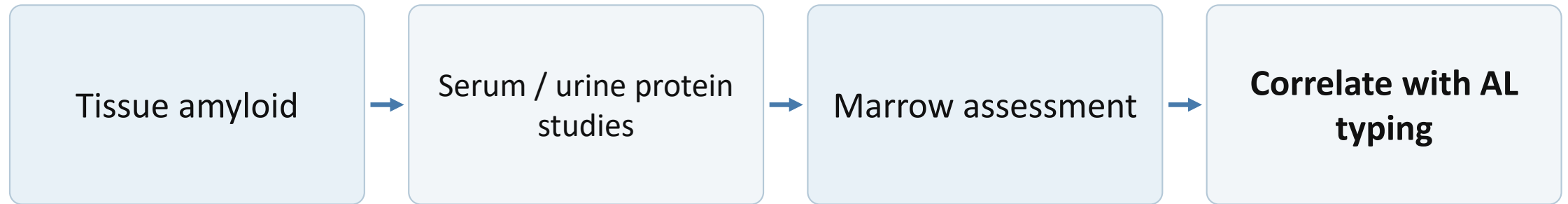
Positive aspirate

- Demonstrates Congo red-positive material
- Supports systemic involvement
- Requires fibril typing

Negative aspirate

- Does not reliably exclude amyloid
- May require another biopsy site
- Interpret with clinical suspicion

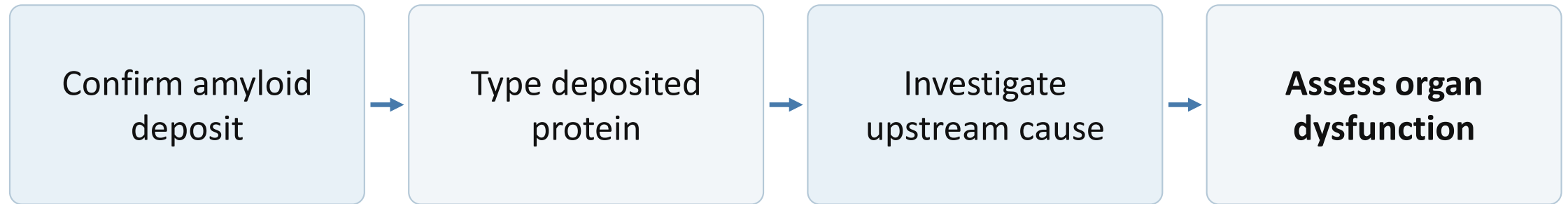
Suspected AL requires monoclonal protein evaluation



- Examine serum and urine for a monoclonal immunoglobulin/light chain.
- Protein electrophoresis and immunologic methods are discussed.

- Bone marrow examination may reveal monoclonal plasma cells.
- A clone supports the mechanism but does not substitute for amyloid typing.

A diagnostic workflow links deposit and mechanism



- First establish amyloid in a suitable specimen.
- Determine biochemical fibril type using available typing methods.
- Investigate corresponding precursor source or inherited/inflammatory driver.
- Assess organs damaged by deposition.

Do not assign amyloid type from organ distribution

Unsafe shortcut

- “Heart disease means ATTR”
- “Myeloma means biopsy must be AL”
- “Kidney disease proves AA”

Defensible interpretation

- Recognize Congo red-positive deposit
- Type amyloid protein in tissue
- Integrate pathology with plasma-cell and TTR evaluation

Interpreting biopsy material: Diagnostic pitfalls

Potential pitfall	Corrective step
H&E “hyaline” assumed amyloid	Use Congo red and polarized examination
Congo red assumed to define type	Perform fibril typing
Negative small sample taken as exclusion	Consider tissue/site adequacy
Organ pattern substituted for chemistry	Integrate typing and cause

Clinical example: Proteinuria plus plasma-cell clone

CLINICAL SCENARIO

- A patient develops progressive proteinuria and biopsy-proven amyloid.
- A monoclonal light chain is subsequently identified.
- AL becomes an important mechanistic hypothesis.
- Confirm the deposited amyloid type before attributing disease to the clone.

What two links establish the causal diagnosis?

Tissue amyloid identification + fibril typing, then evidence of a corresponding plasma-cell source.

Clinical example: Inflammation plus renal amyloid

CLINICAL SCENARIO

- A patient with chronic inflammatory arthritis develops nephrotic syndrome.
- Renal histology demonstrates Congo red-positive deposits.
- Persistent SAA production makes AA mechanistically plausible.
- The fibril protein must still be identified.

What mechanism unites the systemic disease and renal lesion?

Inflammation-driven SAA elevation, followed by AA formation and glomerular deposition.

Clinical example: Familial neuropathy with amyloid

CLINICAL SCENARIO

- A family has progressive peripheral and autonomic neuropathy.
- Biopsy confirms amyloid deposition.
- Inherited ATTRv is a major differential when family history supports it.
- Protein typing and inherited TTR context resolve the mechanism.

Which precursor and inheritance pattern fit the vignette?

Variant transthyretin; Autosomal dominant.

Clinical example: Older adult with stiff heart

CLINICAL SCENARIO

- An older patient develops a restrictive cardiomyopathy phenotype.
- Cardiac amyloid is identified during diagnostic assessment.
- ATTRwt is a possible cause, but AL and variant ATTR remain considerations.
- Protein typing prevents classification by age alone.

Why is the diagnosis not simply “senile cardiac amyloid”?

The clinical phenotype overlaps AL, ATTRwt and ATTRv; Biochemical type must be established.

Clinical example: Dialysis and median nerve compression

CLINICAL SCENARIO

- A patient on prolonged dialysis develops symptoms of carpal tunnel syndrome.
- Amyloid deposition within periarticular soft tissue is identified.
- β_2 -microglobulin retention provides a mechanistic explanation.
- This differs from AL, AA and ATTR precursors.

What deposited protein best links dialysis and carpal tunnel syndrome?

β_2 -microglobulin ($A\beta_2M$).

Prognosis is shaped by organ injury and amyloid type

- Generalized amyloidosis can lead to severe organ dysfunction and death.
- AL disease, especially myeloma-associated AL, as high risk.
- The course of AA disease depends partly on control of its inflammatory driver.
- Disease subtype and organ involvement are more informative than the label alone.

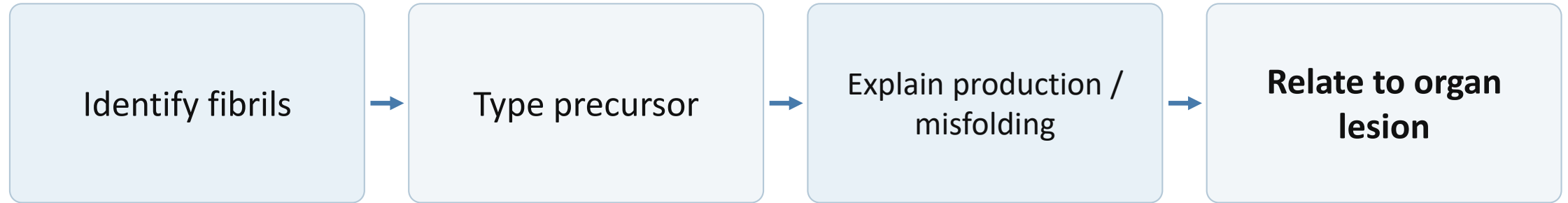
Treatment logic follows the precursor mechanism

Type	Upstream process	Mechanistic treatment objective
AL	Clonal light-chain production	Reduce amyloidogenic light-chain source
AA	Inflammation → SAA synthesis	Suppress ongoing inflammatory drive
ATTR	Transthyretin misfolding	Limit aggregation of TTR

Clinical outcomes follow the involved structure

Primary site	Structural consequence	Manifestation
Kidney	Glomerular tuft loss	Proteinuria / failure
Heart	Myocyte compression; Conduction injury	Heart failure / arrhythmia
GI tract / tongue	Parenchymal and interstitial infiltration	Malabsorption / macroglossia
Blood vessels	Wall fragility	Bleeding

Synthesize precursor, deposit and phenotype



- Identical Congo red behavior can reflect distinct precursor proteins.
- Mechanism may involve protein excess, instability or incomplete degradation.

- Extracellular accumulation perturbs tissue architecture.
- Protein typing and systemic evaluation are complementary—not interchangeable.

Five high-yield conclusions

- Amyloidosis is a protein-folding and deposition disorder, not one protein disease.
- Extracellular cross- β fibrils explain characteristic Congo red birefringence.
- AL, ATTR and AA arise from different precursor pathways.
- Renal and cardiac lesions can cause major morbidity and mortality.
- Confirm tissue amyloid, type the protein and establish the clinical cause.

Reference and source boundaries

- Primary: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), Chapter 6, pp. 230–234.
- Read with the amyloidosis sections on properties, biochemistry, classification, morphology and clinical features.
- The supplied Markdown was used for content; original chapter PDF and reusable specimen images were not provided.
- All constructed tissue/flow schematics in this deck are educational illustrations, not diagnostic images.