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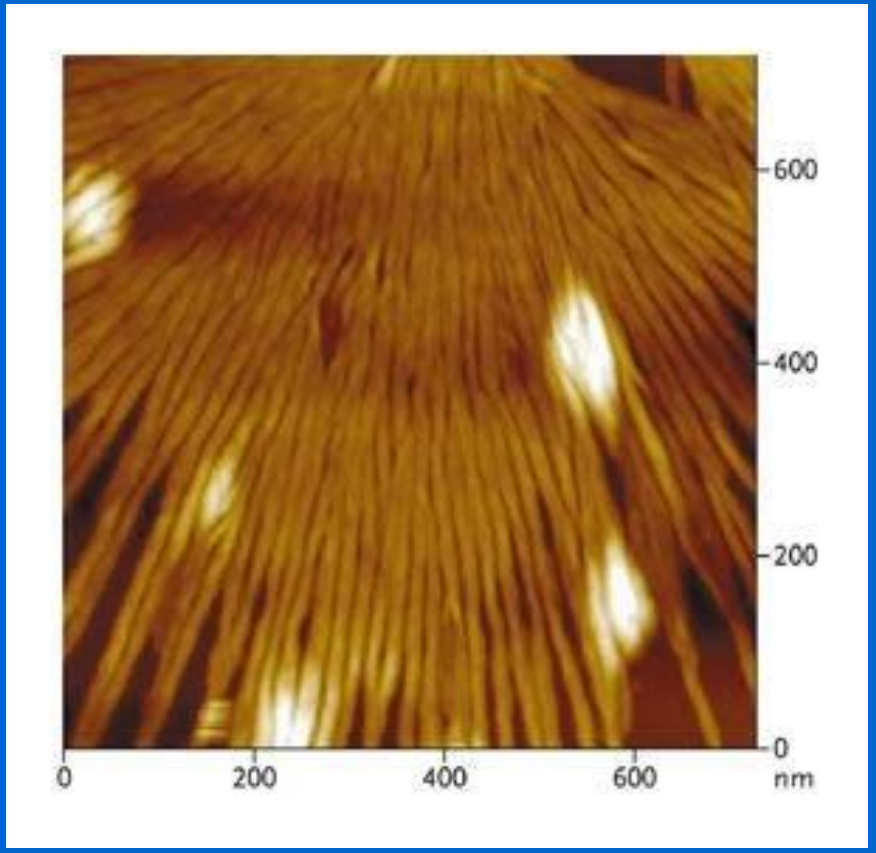
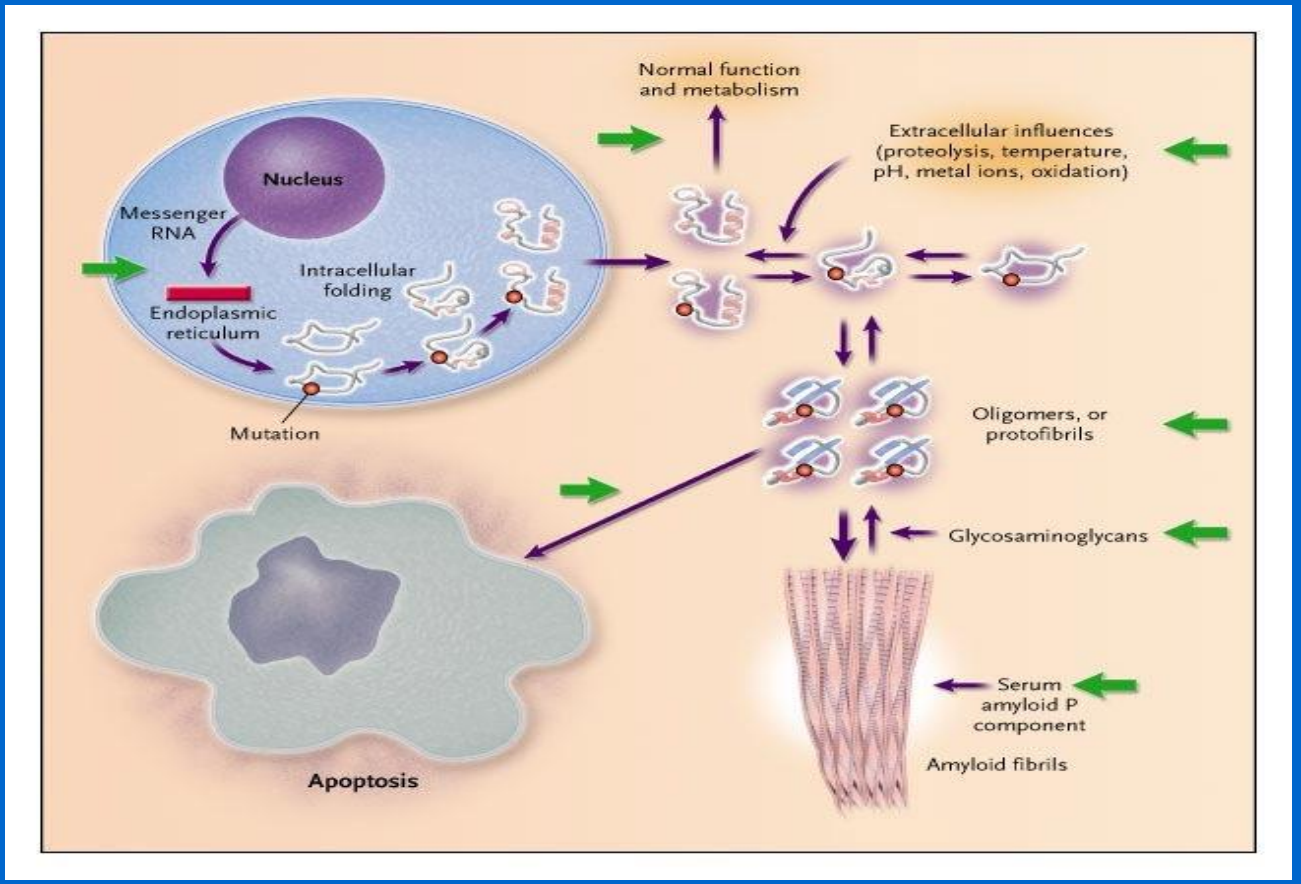
Amyloid is formed by the aggregation of monomeric protein precursors into fibrils by a common nucleation growth mechanism. oligomers that do not go on to form fibrils, may still be cytotoxic



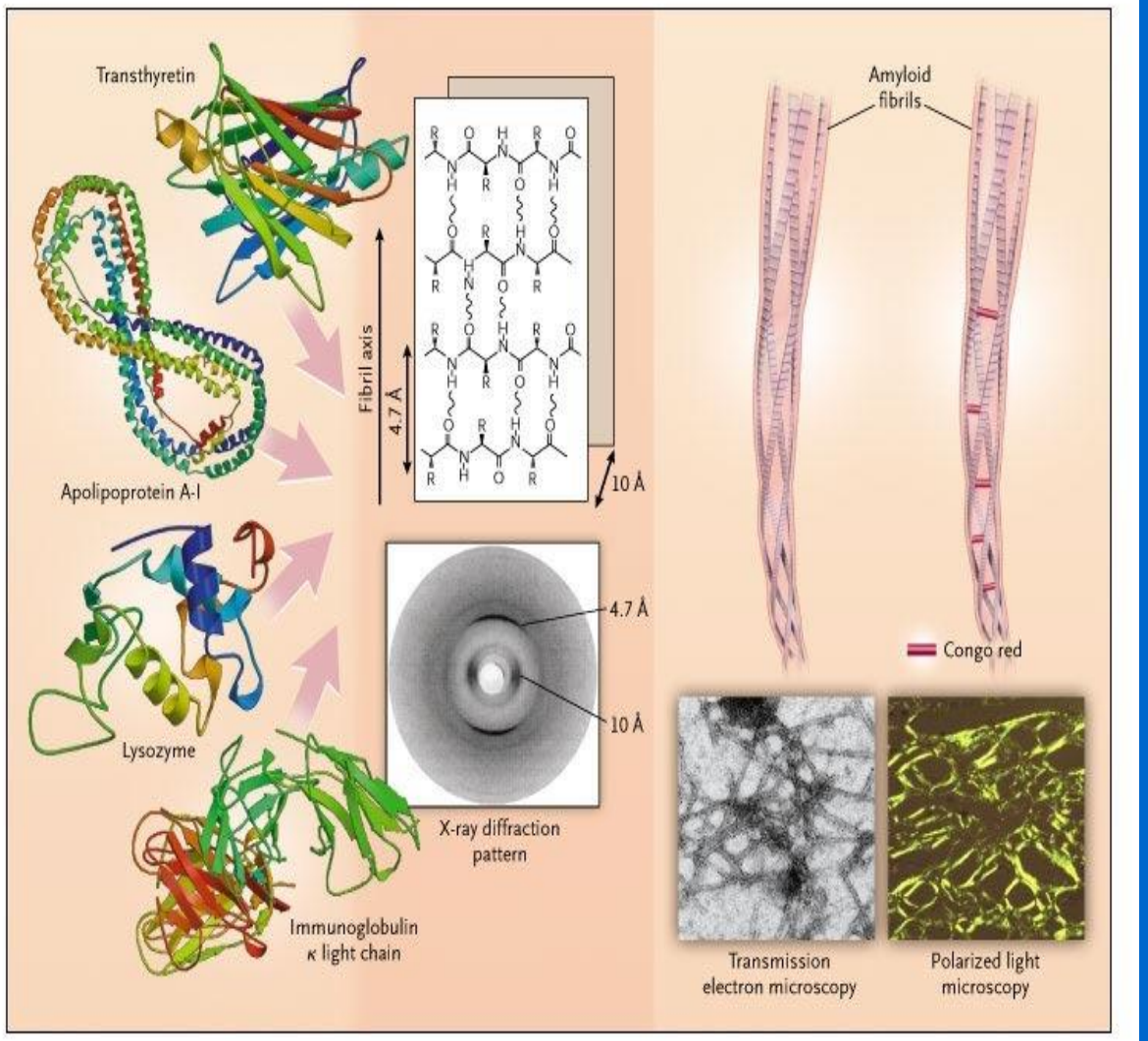
Fibrils of a familial form of apolipoprotein A-I amyloidosis. The image was obtained by atomic-force microscopy;. The scan size was 720 nm, with a Z range of 14 nm

- These are “typically composed of a felt-like array of 7.5- to 10-nm wide rigid, linear, non branching, aggregated fibrils of indefinite length.” One amyloid fibril is made of two twisted 3-nm–wide laments, each having a regular antiparallel -pleated sheet configuration; the –sheets are perpendicular to the lament axis.

- amyloid may result from a “one-dimensional crystallization.” Formation of an ordered nucleus, followed by a thermodynamically favorable addition of monomers leading to elongation of the fibrils

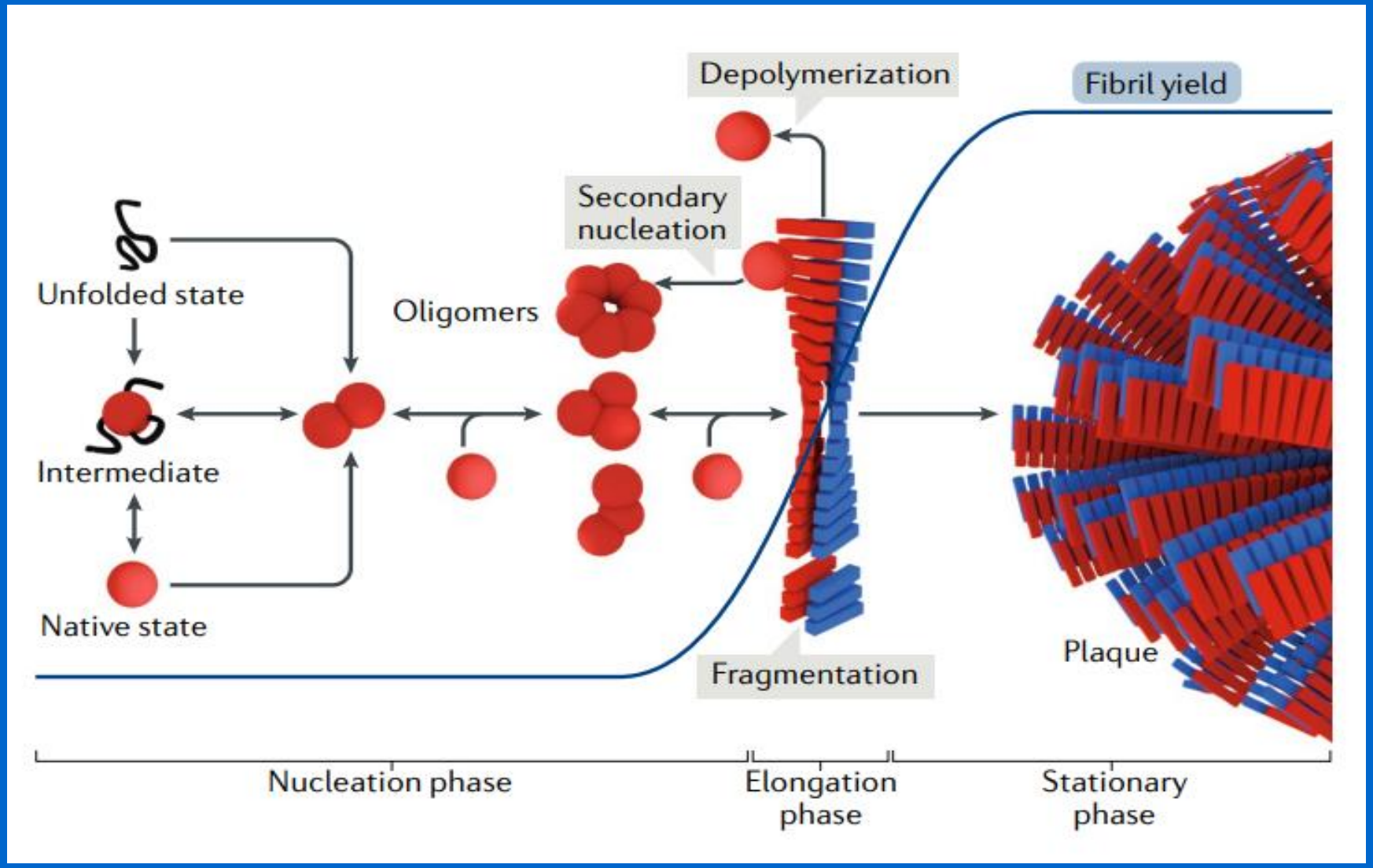


Normal polypeptides are normally metabolized. The partially folded polypeptides can generate misfolded molecules, which have a high propensity to self-aggregate..



Contiguous β-sheet polypeptide chains constitute a proto filament. As shown on the right, several (four to six) proto filaments are wound around one another to form an amyloid fibril, with a distinct diameter of 7.5 to 10 nm visible on transmission electron microscopy (×100,000). This regular ultrastructure, conferring a diagnostic optical property to amyloid such as apple-green birefringence under polarized light microscopy

Schematic of amyloid formation

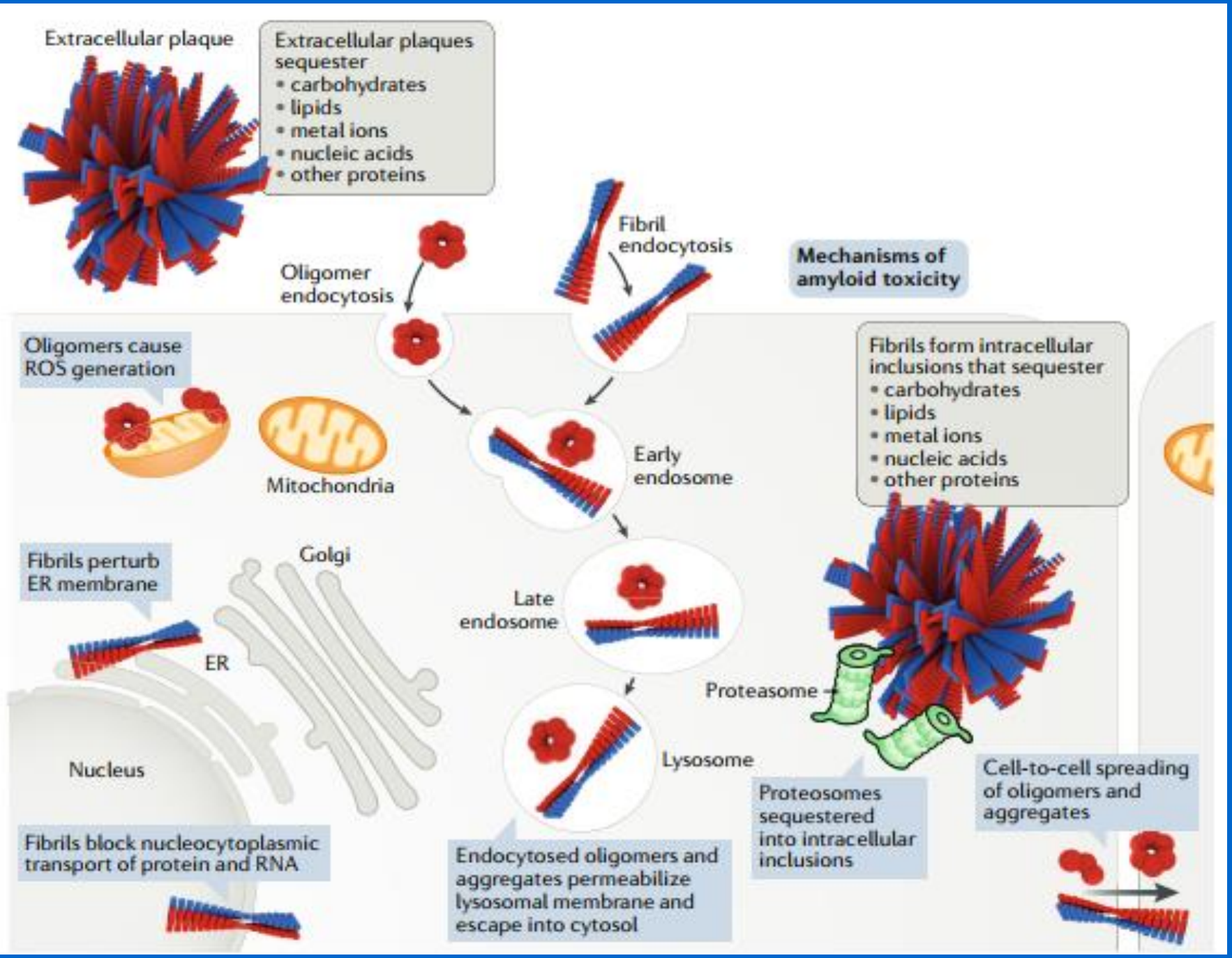


At some point during self-assembly, each precursor undergoes a structural transformation to form β-strand rich secondary structure, irrespective of its initial fold and resulting in exponential fibril growth.

Cytotoxicity of amyloid deposits

amyloid-associated cytotoxicity include proteasomal degradation, impairment of autophagy, perturbation of mitochondrial function, reactive oxygen species (ROS), sequestration of other proteins and disruption of mitochondria, endoplasmic reticulum (ER), lysosomes .

Emerging evidence has shown that intracellular inclusions of amyloid can interfere with cellular physiology, for example, by disrupting transport of proteins and RNA and by sequestering chaperones and proteasomes.


Extracellular plaque
Extracellular plaques sequester
• carbohydrates
• lipids
• metal ions
• nucleic acids
• other proteins
Fibril endocytosis
Oligomer endocytosis
Mechanisms of amyloid toxicity
Oligomers cause ROS generation
Mitochondria
Early endosome
Fibrils form intracellular inclusions that sequester
• carbohydrates
• lipids
• metal ions
• nucleic acids
• other proteins
Fibrils perturb ER membrane
Golgi
ER
Late endosome
Proteasome
Nucleus
Lysosome
Fibrils block nucleocytoplasmic transport of protein and RNA
Endocytosed oligomers and aggregates permeabilize lysosomal membrane and escape into cytosol
Proteosomes sequestered into intracellular inclusions
Cell-to-cell spreading of oligomers and aggregates

difference in fibril characteristics may in part explain why amyloid fibril load does not always correlate with the severity of disease, as the biological effects and clinical symptoms may depend fibril polymorphs.

Amyloid formation is a dynamic process, with monomers and oligomers in rapid exchange with each Other. Oligomers can also be generated directly, by loss of monomers

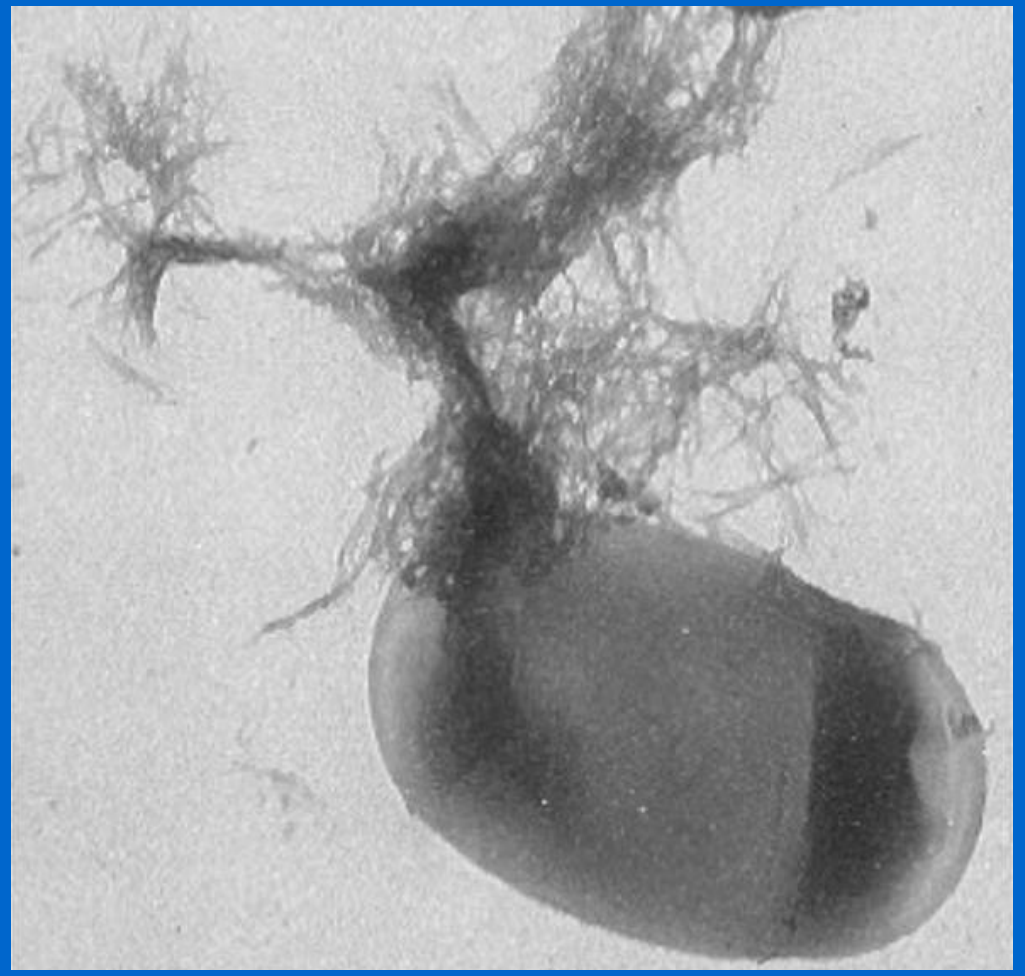
The protein concentration in cells is finely tuned, with tight coupling of the rates of synthesis and degradation to keep the solubility limit. overproduction of a protein can trigger aggregation of susceptible proteins that are at the cusp of their solubility in the cell.

The Functional Amyloid Curli Protects Escherichia coli against Complement-Mediated Bactericidal Activity

bacterial amyloid curli is a virulence factor acts in bacterial adherence and ,formation of biofilms. binding of E. bindimg (C1q) and inhibition of the classical complement pathway.

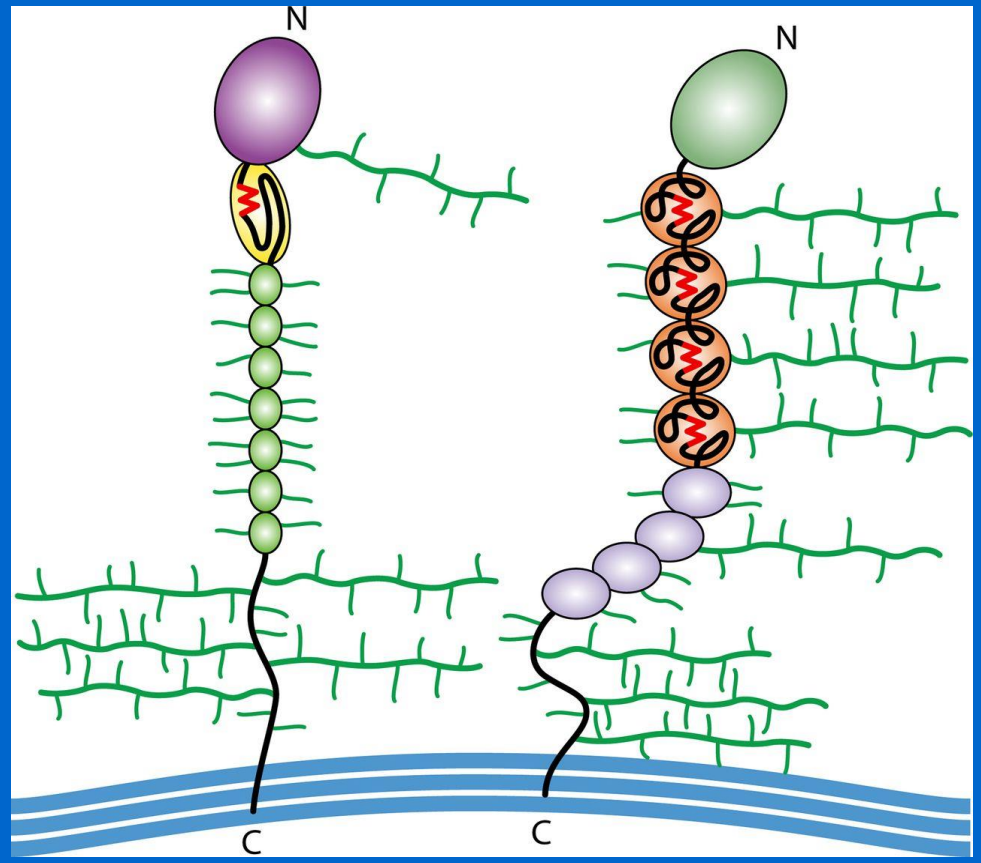
Biesecker SG, Ç. The Functional Amyloid Curli Protects Escherichia coli against Complement-Mediated Bactericidal Activity. Biomolecules. 2018 Jan 24;8(1):5..

extracellular bacterial proteins form functional amyloids with roles in biofilm formation of Escherichia coli, Bacillus subtilis, Staphylococcus aureus, Streptococcus mutans, and Pseudomonas aeruginosa



Amyloid-Like β-Aggregates as Force-Sensitive Switches in Fungal Biofilms and Infections

sequences in fungal adhesins can form amyloids and can facilitate amyloid and amyloid-like could aggregation activity and biofilm formation. Thus, promote fungal growth.



Lipke PN,. Amyloid-Like β-Aggregates as Force-Sensitive Switches in Fungal Biofilms and Infections. Microbiol Mol Biol Rev. 2017 Nov 29;82(1)

The precursor protein in AA amyloid is SAA, an apolipoprotein acute-phase reactant produced predominately by hepatocytes,but also by macrophages, endothelial cells, and smooth muscle cells. under the influence of proinflammatory cytokines, such as TNF-a, IL-1b, and IL-6

Table 1. Amyloid Proteins and Their Precursors.*

Amyloid Protein	Precursor	Distribution	Type	Syndrome or Involved Tissues
Aβ	Aβ protein precursor	Localized Localized	Acquired Hereditary	Sporadic Alzheimer's disease, aging Prototypical hereditary cerebral amyloid angiopathy, Dutch type
APrP	Prion protein	Localized Localized	Acquired Hereditary	Sporadic (iatrogenic) CJD, new variant CJD (alimentary?) Familial CJD, GSSD, FFI
ABri	ABri protein precursor	Localized or systemic?	Hereditary	British familial dementia
ACys	Cystatin C	Systemic	Hereditary	Icelandic hereditary cerebral amyloid angiopathy
Aβ2M	Beta$_2$-microglobulin	Systemic	Acquired	Chronic hemodialysis
AL	Immunoglobulin light chain	Systemic or localized	Acquired	Primary amyloidosis, myeloma-associated
AA	Serum amyloid A	Systemic	Acquired	Secondary amyloidosis, reactive to chronic infection or inflammation including hereditary periodic fever (FMF, TRAPS, HIDS, FCU, and MWS)
ATTR	Transthyretin	Systemic Systemic	Hereditary Acquired	Prototypical FAP Senile heart, vessels
AApoAI	Apolipoprotein A-I	Systemic	Hereditary	Liver, kidney, heart
AApoAII	Apolipoprotein A-II	Systemic	Hereditary	Kidney, heart
AGel	Gelsolin	Systemic	Hereditary	Finnish hereditary amyloidosis
ALys	Lysozyme	Systemic	Hereditary	Kidney, liver, spleen
AFib	Fibrinogen Aα chain	Systemic	Hereditary	Kidney

* Data were adapted from Westermark et al.[1] The following proteins may also cause amyloidosis: immunoglobulin heavy chain, calcitonin, islet-amyloid polypeptide, atrial natriuretic factor, prolactin, insulin, lactadherin, keratoepithelin, and Danish amyloid protein (which comes from the same gene as ABri and has an identical N-terminal sequence). CJD denotes Creutzfeldt–Jakob disease, GSSD Gerstmann–Sträussler–Scheinker disease, FFI fatal familial insomnia, FMF familial Mediterranean fever, TRAPS tumor necrosis factor receptor–associated periodic syndrome, HIDS hyper-IgD syndrome, FCU familial cold urticaria, MWS Muckle–Wells syndrome, and FAP familial amyloidotic polyneuropathy.

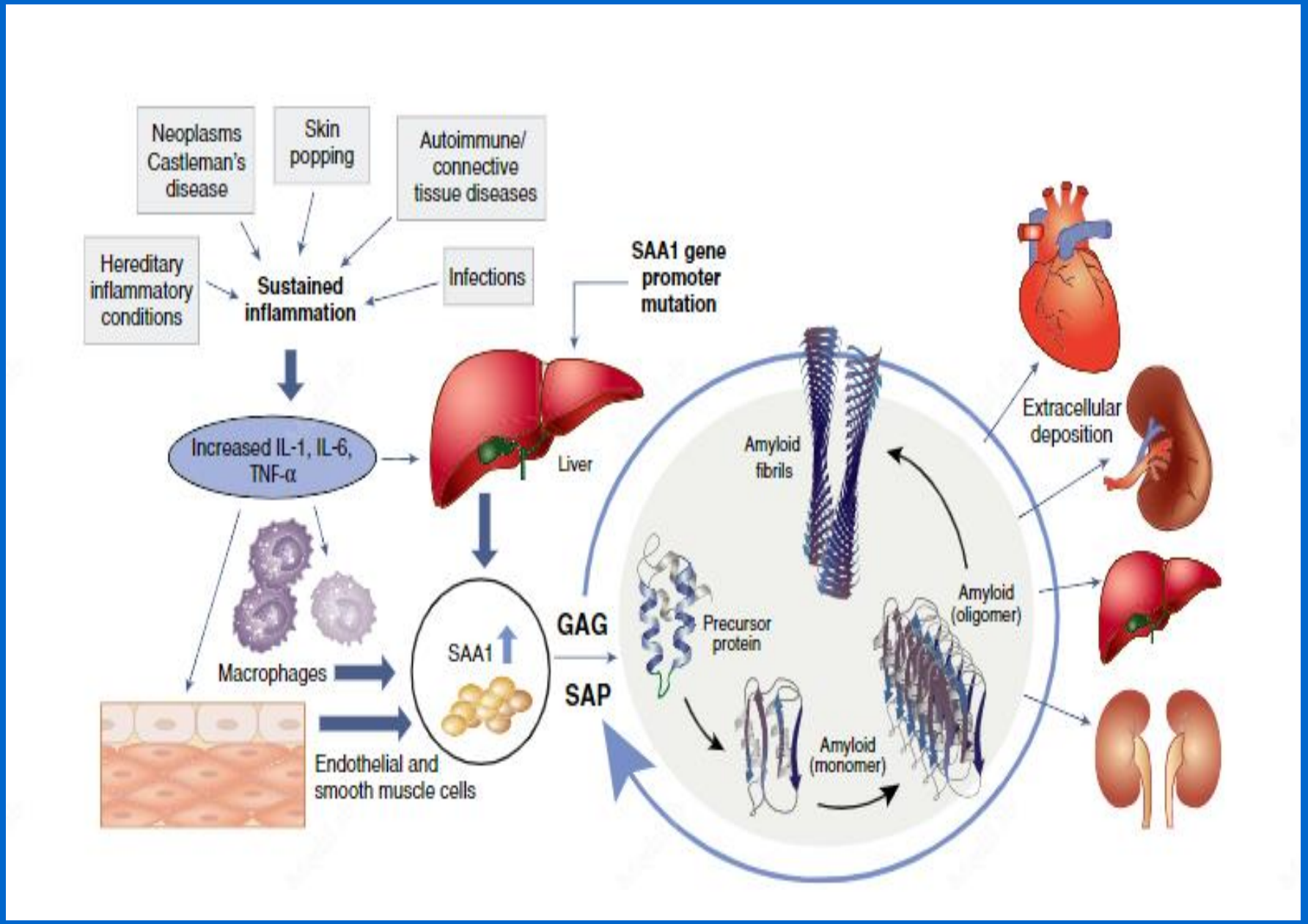
A. AL
B. AA
C. Heredity

SAA possesses multiple functions, as opsonin, and inducing expression of matrix metalloproteinase and angiogenesis, promoting tumor metastasis. SAA may also play a role in maintenance of normal body weight and protection from hepatic steatosis.

Aggregation of SAA into amyloid fibrils only occurs when a critical concentration has been reached, and persists for a prolonged period. Proteolytic cleavage of SAA1 from a 122–amino acid peptide to a 76–amino acid residue by metalloproteases is a crucial step for amyloid formation.

- Interactions with glycosaminoglycan (GAGs) and serum amyloid P component (SAP)promote aggregation and lead to the formation of amyloid.

- In addition to GAGs, apolipoprotein A1,apolipoprotein A4, and apolipoprotein E are essential for fibrillo genesis


Neoplasms
Castleman's
disease
Skin
popping
Autoimmune/
connective
tissue diseases
Hereditary
inflammatory
conditions
Sustained
inflammation
Infections
SAA1 gene
promoter
mutation
Increased IL-1, IL-6,
TNF-α
Liver
Macrophages
SAA1
GAG
SAP
Endothelial and
smooth muscle cells
Amyloid
fibrils
Precursor
protein
Amyloid
(oligomer)
Amyloid
(monomer)
Extracellular
deposition

AA amyloidosis causes a greater degree of kidney dysfunction than AL and is more likely to affect younger individuals. In 80% to 90% of cases of AA, the kidneys are involved with kidney dysfunction and nephrotic syndrome

There is also a predominantly tubular form of AA present with a bland sediment and little proteinuria, but they may show signs of distal tubular dysfunction, such as nephrogenic DI , there have been reports of Fanconi syndrome and renal tubular acidosis, but these are usually in association with nephrotic syndrome

tissue biopsy is recommended to confirm the presence of amyloid. Potential sites include abdominal fat and minor salivary glands. More invasive sites like kidney, rectal tissue, or the GI tract, when more accessible sites are negative

The SAP scintigraphy is a tool that can be used to detect and quantify amyloid deposits.

highly purified SAP radiolabeled with the isotope of123 I localizes amyloid deposits and quantifies the amount of amyloid deposited.

It has a sensitivity of 100% with systemic amyloidosis, but cannot type the amyloid.

The measurement of SAA levels can be used to estimate the amount of amyloid genesis.

Elevated level>10 mg/L is associated with increased risk of developing AA, but it is not enough to make the diagnosis.

Amyloid burden , kidney prognosis, and the risk of death are highly correlated with the level.

Treatment is to address the infection or chronic inflammation. Traditionally disease-modifying antirheumatic drugs (DMARDs) such as colchicine, steroids, and cyclophosphamide, have had some success.

Colchicine, HAS inhibitory effects on mmicrotubule assembly, celladhesion, and inflammasome activation, remains the stan-dard of care for FMF development of amyloidosis. it reduces the occurrence of kidney disease,

Miridesap depleted circulating SAP in an open-label study and reduced SAP content in affected organs.

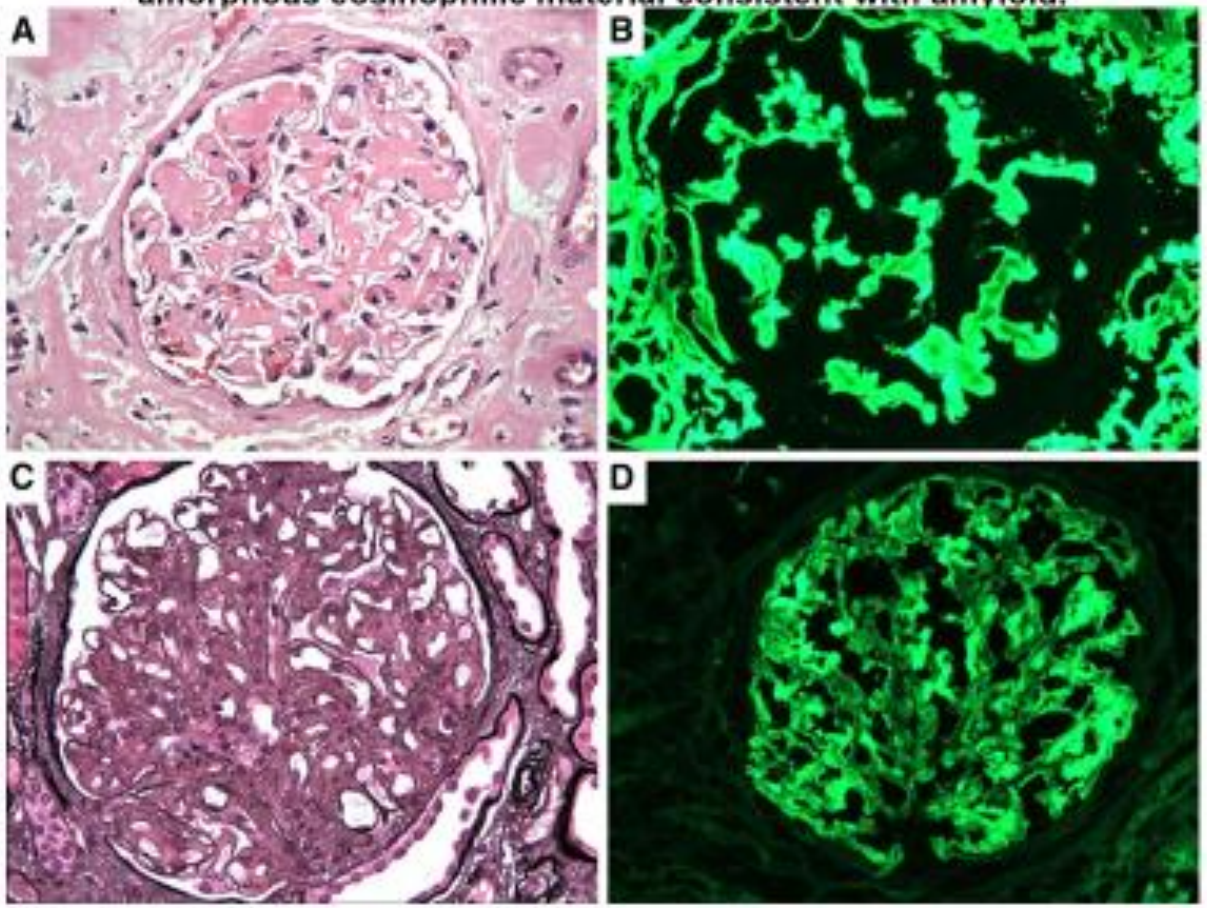
Dezamizumab, a fully humanized monoclonal IgG1 anti-SAP antibody, was administered to 23 adult subjects after they received 3 cycles of miridesap, and it triggered immuno-therapeutic clearance of amyloid deposited in tissue.

Anti-cytokine therapy is another tyherapiutic wondow used in AA amyloidosis

When AA progress to ESKD , survival on dialysis is poor, with cardiac involvement being a strong predictor of death within the first year of dialysis. AA amyloidosis also can recur after KT.

Systemic Light chain (AL) amyloidosis is a monoclonal plasma cell proliferative disorder characterized by deposition of amyloidogenic monoclonal light chain fragments causing organ dysfunction.

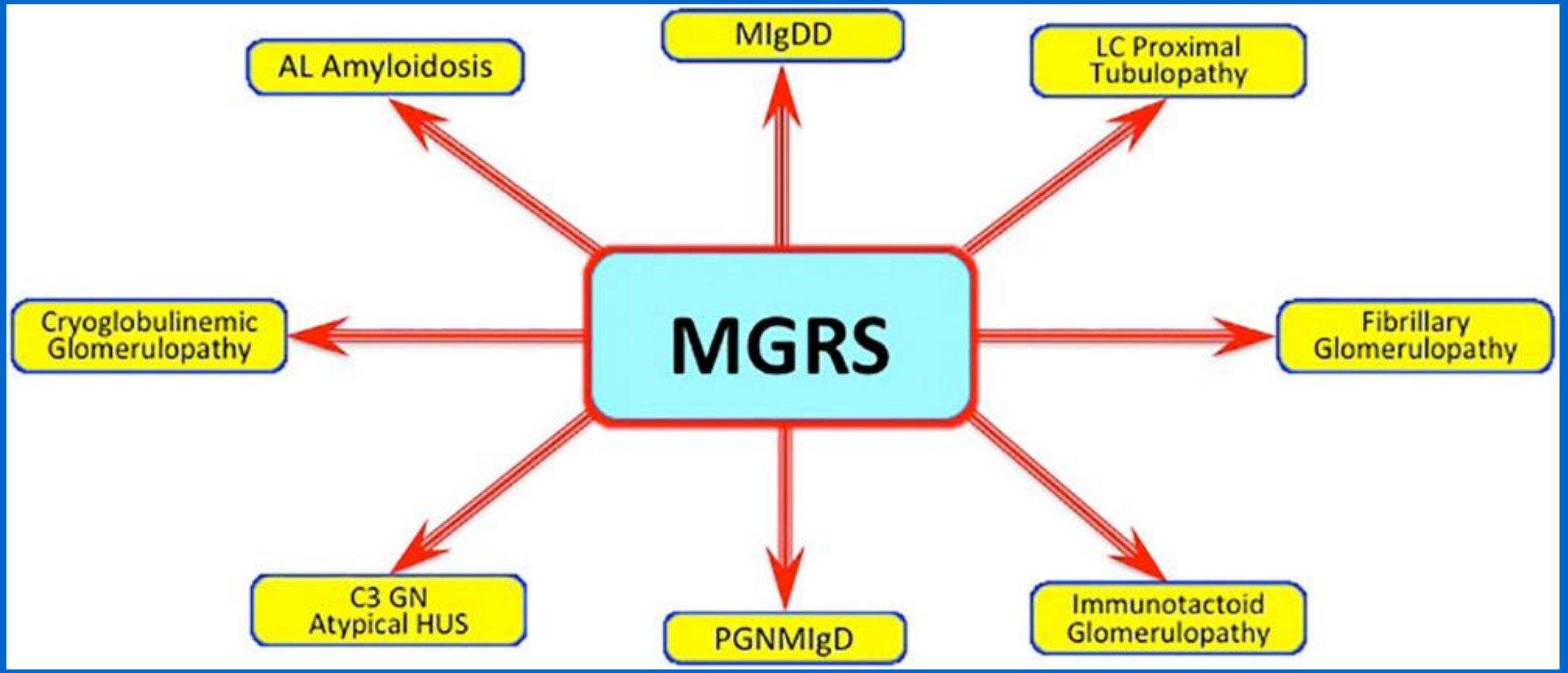
Light microscopy and immunofluorescence findings in light chain amyloidosis and fibrillary GN. (A) Hematoxylin and eosin (H&E) shows a glomerulus with prominent mesangial infiltration by amorphous eosinophilic material consistent with amyloid.



Shveta S. Motwani et al. CJASN 2016;11:2260-2272

CJASN

AL amyloidosis, light/heavy–chain deposition disease Cryoglobulinemic Waldenstrom macroglobulinemic glomerulopathy, Immunotactoid glomerulopathy, Fibrillary glomerulopathy, Proliferative GN with monoclonal Ig deposits, C3 glomerulopathy with monoclonal gammopathy, Tubulointerstitial disease


MGRS
AL Amyloidosis
MIgDD
LC Proximal Tubulopathy
Cryoglobulinemic Glomerulopathy
Fibrillary Glomerulopathy
C3 GN Atypical HUS
PGNMIgD
Immunotactoid Glomerulopathy

- The precursor protein in AL amyloidosis is a monoclonal FLC or fragment secreted by clonal plasma cell it include the amino terminus of the light chain, and particularly, the variable component of free light chain subtype 6 as the most common precursor protein that forms amyloid fibrils.

- Mesangial cells, in the presence of pathogenic FLCs, behave phenotypically like macrophages and are active participants in the generation of amyloid fibrils .After endocytosis by mesangial cells, FLCs are processed by lysosomes and undergo incomplete proteolysis to form amyloid fibrils.

- Paraproteins or monoclonal proteins (M proteins) are classically defined as either monoclonal Igs or light chains (rarely heavy chains),The source of these M proteins can be malignant clone plasma cells, like (MM), or a plasmacytoma, lymphoproliferative disorders (cll), B and T cell lymphomas, and Waldenstrom macroglobulinemia), or a MGUS, which is characterized by a lower clonal cell burden, less paraprotein production, and absence of end organ injury.

- Amyloid fibrils have a tendency to deposit within the glomeruli, vessel walls, interstitial, and less commonly, tubular basement membrane. conformational changes of FLCs could make the constant domain of k-light or LCs inaccessible to antisera, causing a false negative result on IF.
- laser capture microdissection followed by mass spectrometry circumvents this potential limitation of IF.

- HCDD is a less common cause of glomerular disease relative to LCDD. Deposits in HCDD are composed of truncated heavy–chain fragments without associated light chains. gamma-Heavy chain is the predominant heavy–chain class detected, specifically the Gamma3-subtype. However, cases of a-HCDD, mu-HCDD, and delta-HCDD have also been reported. In contrast to LCDD, glomerular C3 deposition and hypocomplementemia have been observed in HCDD. First heavy constant domain deletion is present in all cases of gamma-HCDD and leads to premature secretion of free heavy chains into circulation before assembly with light chains to form intact Igs.

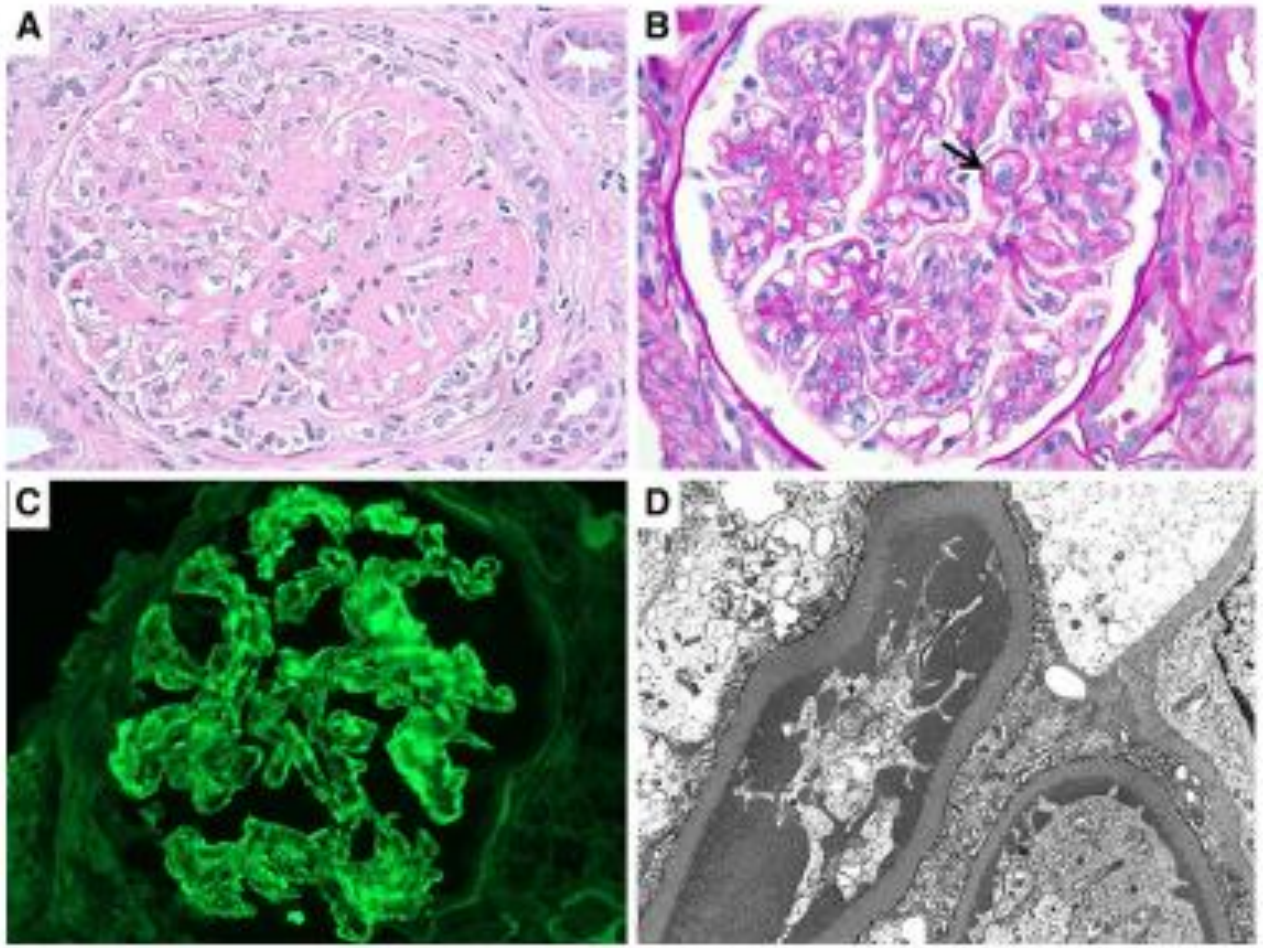
- In contrast to AL amyloidosis, mesangial cells in LCDD assume a myofibroblastic phenotype causing upregulation of the endoplasmic reticulum .This leads to increased mesangial matrix production. Mesangial cells incubated with FLCs from patients with LCDD have increased expression of collagen type 4 and tenascin-C, which promote nodule formation, and increased TGF-b expression, which drives matrix expansion.

- Patients with MIDD typically present with proteinuria, renal impairment, and hypertension.
- A monoclonal M spike was detected in 86% of patients by serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP) and immunofixation, and all patients with MIDD had an abnormal serum free light chain ratio

- C3 glomerulopathy that results from deregulation of the alternative complement pathway .The term C3 glomerulopathy comprises C3GN and dense deposit disease (DDD)

- an association between C3 glomerulopathy . Monoclonal l-light chains can activate AP by acting as an autoantibody against complement factor H (CFH)

Histopathologic features of proliferative GN with monoclonal IgG deposits (PGNMID).



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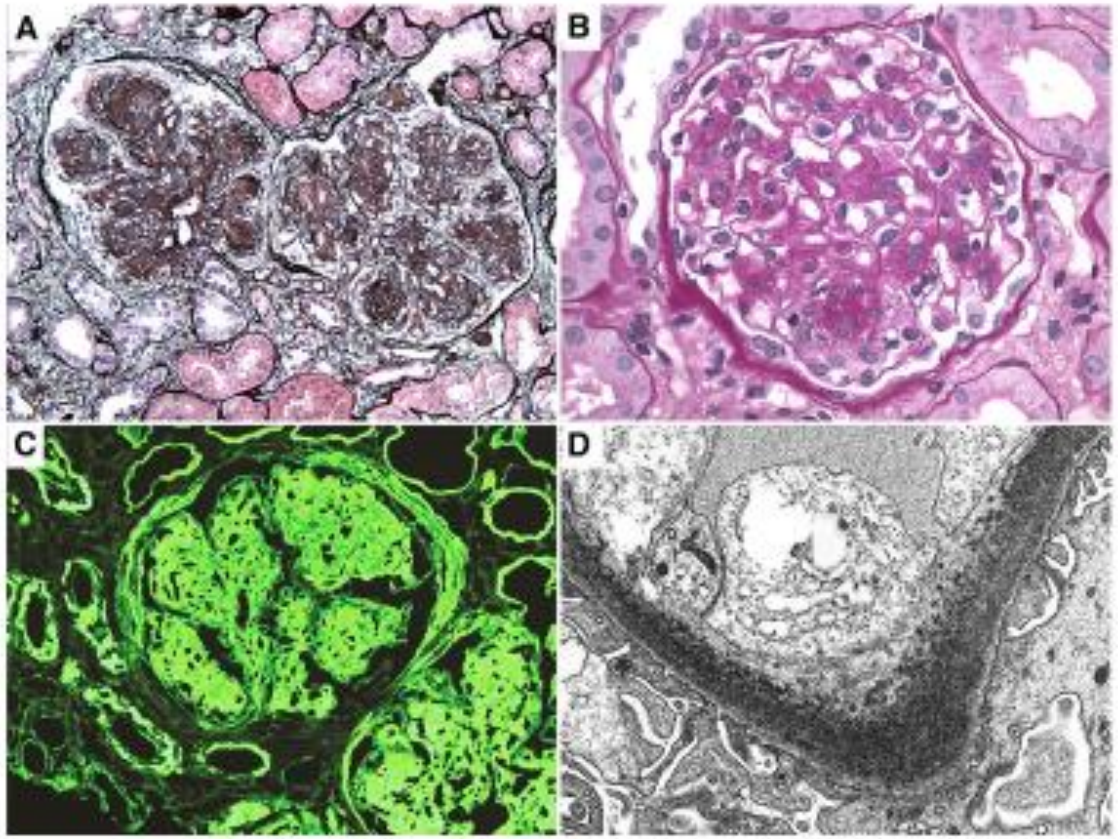
Histopathology of monoclonal Ig deposition disease (MIDD).



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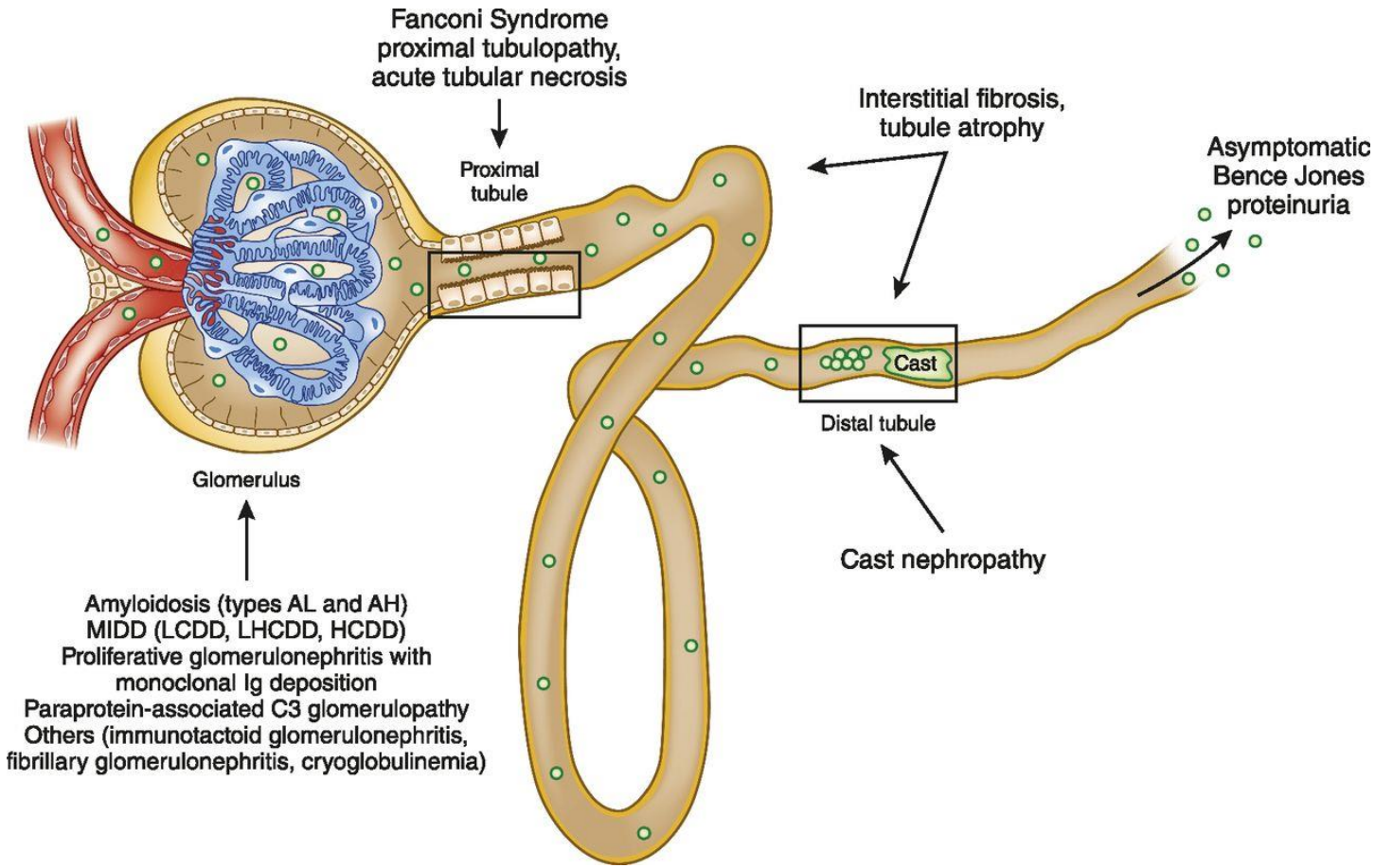
Patterns of nephron injury associated with paraproteins.



Mona Doshi et al. CJASN 2016;11:2288-2294

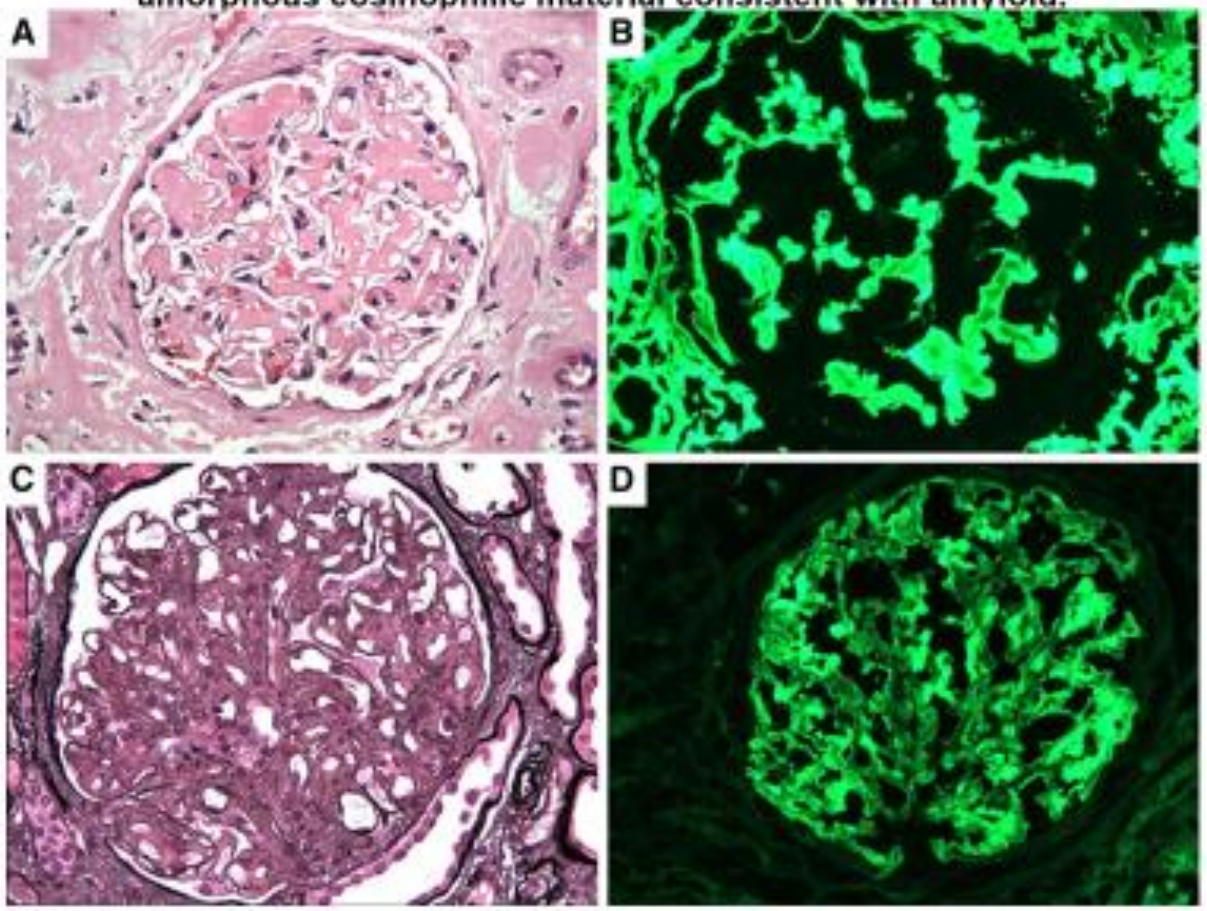
CJASN

- FGN is a rare disorder defined by the glomerular deposition of randomly oriented Congo red–negative fibrils typically 16–24 nm in diameter. Although most cases of FGN are idiopathic, associations with paraprotein disease have been documented
- 23% had an associated malignancy that was diagnosed 15 years before to 10 years after the onset of kidney disease. More than one half of those malignancies were MM or leukemia.
- autoimmune disorders, hepatitis C, or immune thrombocytopenic purpura, In comparison with ITG, the majority of patients with FGN do not have disease associated with MG.

- ITG, also referred to as GN with organized microtubular monoclonal Ig deposits ,is defined by the glomerular deposition of microtubules that have distinct hollow centers,which can range in size from 10 to 90 nm ,Because the deposits in ITG can appear similar to those in cryoglobulinemia and lupus nephritis ,these entities must be ruled out before a diagnosis of ITG can be made. ITG is approximately 10-fold rarer than FGN, occurring in 0.06% of all native kidney biopsies

- the glom … and in contrast … iction. LMD/MS … bE and high spe … t help distingui …

Light microscopy and immunofluorescence findings in light chain amyloidosis and fibrillary GN. (A) Hematoxylin and eosin (H&E) shows a glomerulus with prominent mesangial infiltration by amorphous eosinophilic material consistent with amyloid.



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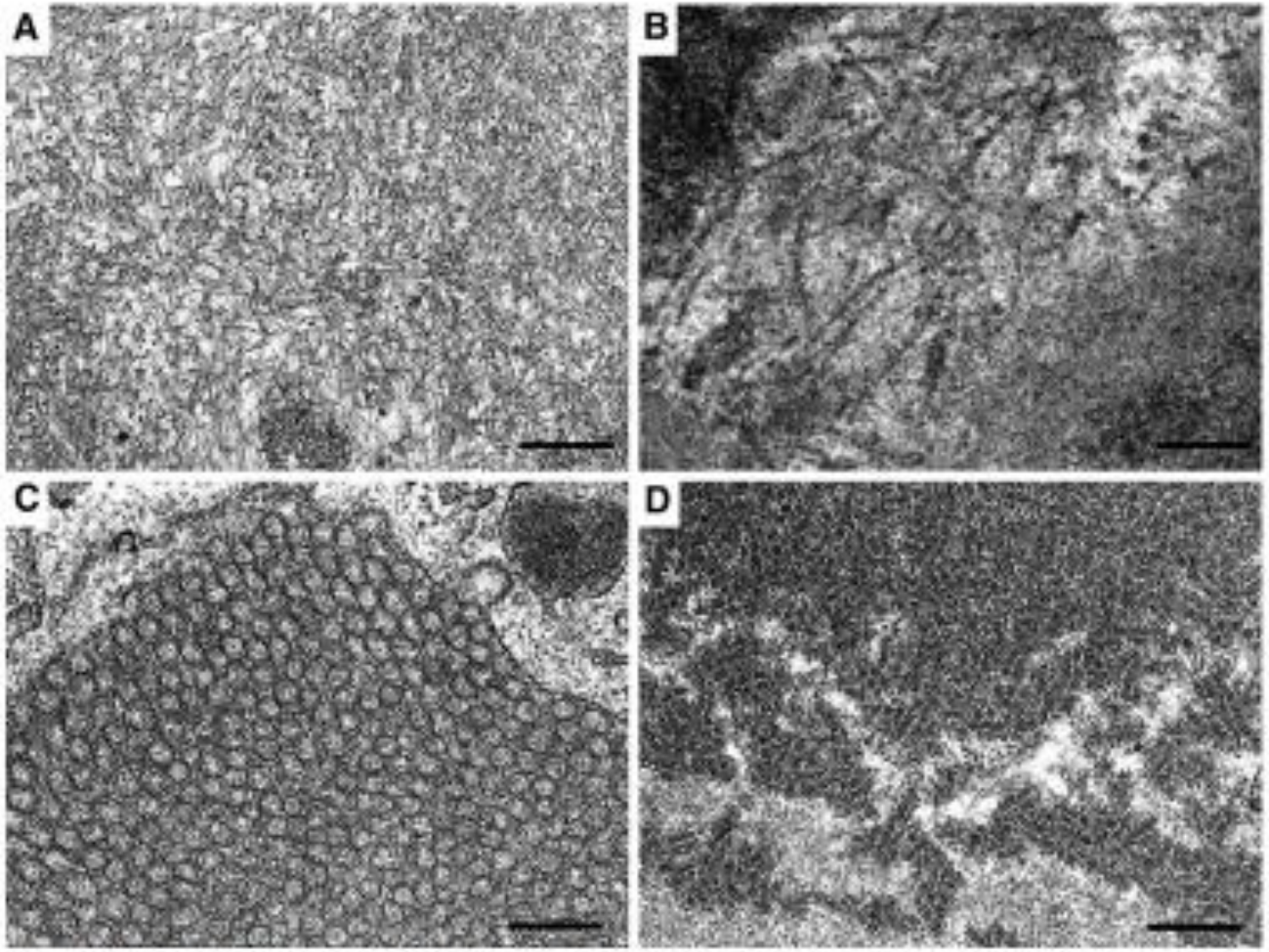
Comparison of electron microscopy findings in paraproteins with organized fibrillar deposits.



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- Cryoglobulins are reversibly precipitate at temperatures less than 37°C. The precipitation results in symptoms that are seen in vasculitis: rash, ischemia, ulcers, joint pains, fatigue, and GN .The pathogenesis of cryoglobulin-induced injury involves two main mechanisms, hyperviscosity and immune complex deposition, that activate complement and induce vascular inflammation.
- Cryoglobulinemic GN occurs in 24% of patients with cryoglobulinemia and can occur with all three types of cryoglobulins, although it is more commonly seen with type in the setting of hepatitis C virus infection.

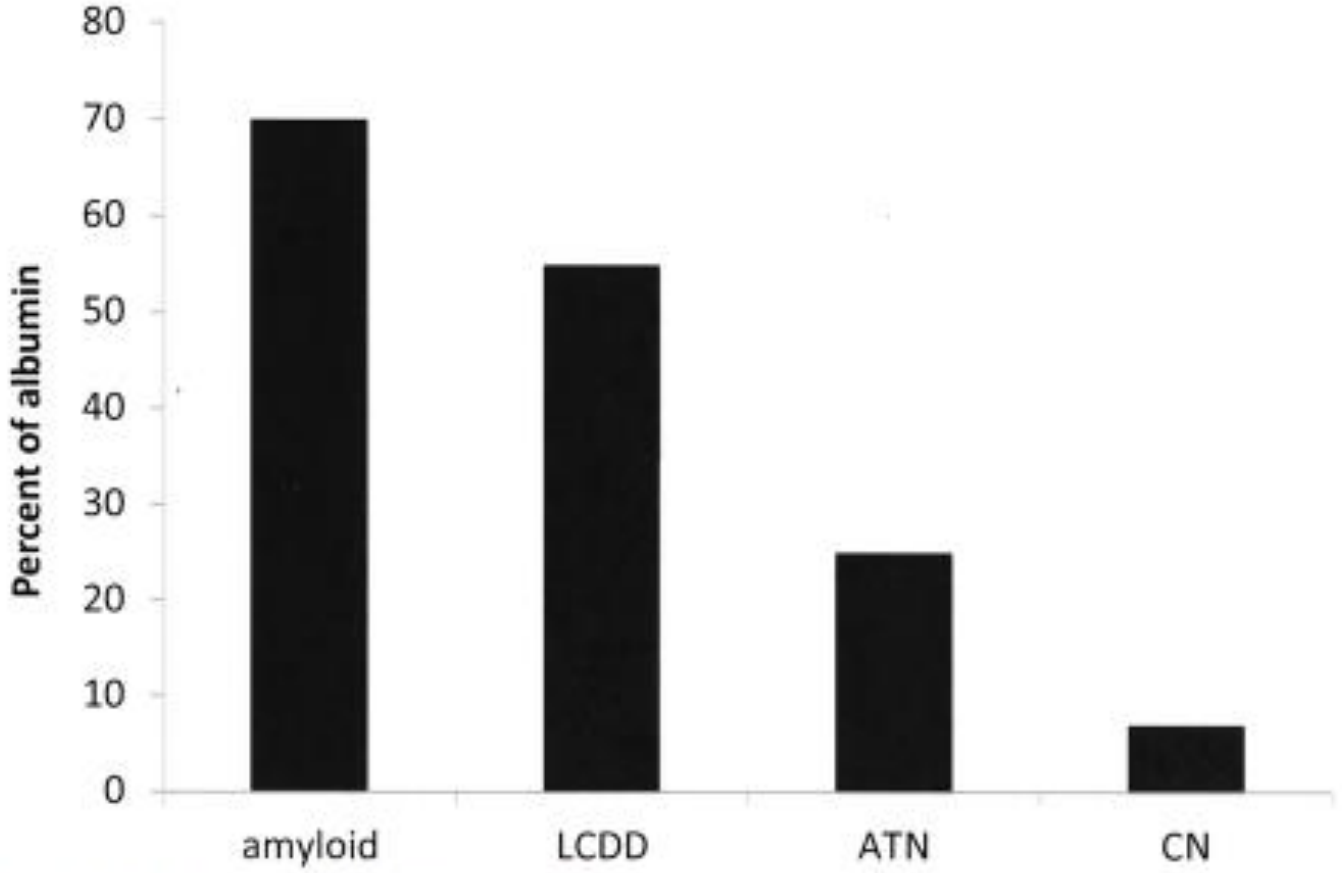
glomerular crystals predominantly in podocytes and proximal tubular cells. crystalglobulin-induced nephropathy results from accumulation and precipitation of light chain crystals that are extracellular but within the glomerular microvasculature.

Skin ulcers and purpuric lesions are common in crystalglobulinemia because of precipitation of monoclonal proteins in the cutaneous vasculature

Inhibition of ADAMTS13 by autoantibodies, and hyperviscosity may be another pathogenetic mechanism.

Other patients with myeloma-associated TMA have been observed in the setting of concurrent k-LCDD ,hematopoietic stem cell transplantation ,and chemotherapeutic agents, such as bortezomib and carfilzomib .In addition, there has been one reported patient with TMA with MGUS and an unpublished case report of renal-limited TMA in the setting of smoldering myeloma.

Percentage of urinary protein that is albumin in the four main types of paraprotein–related kidney dysfunction.



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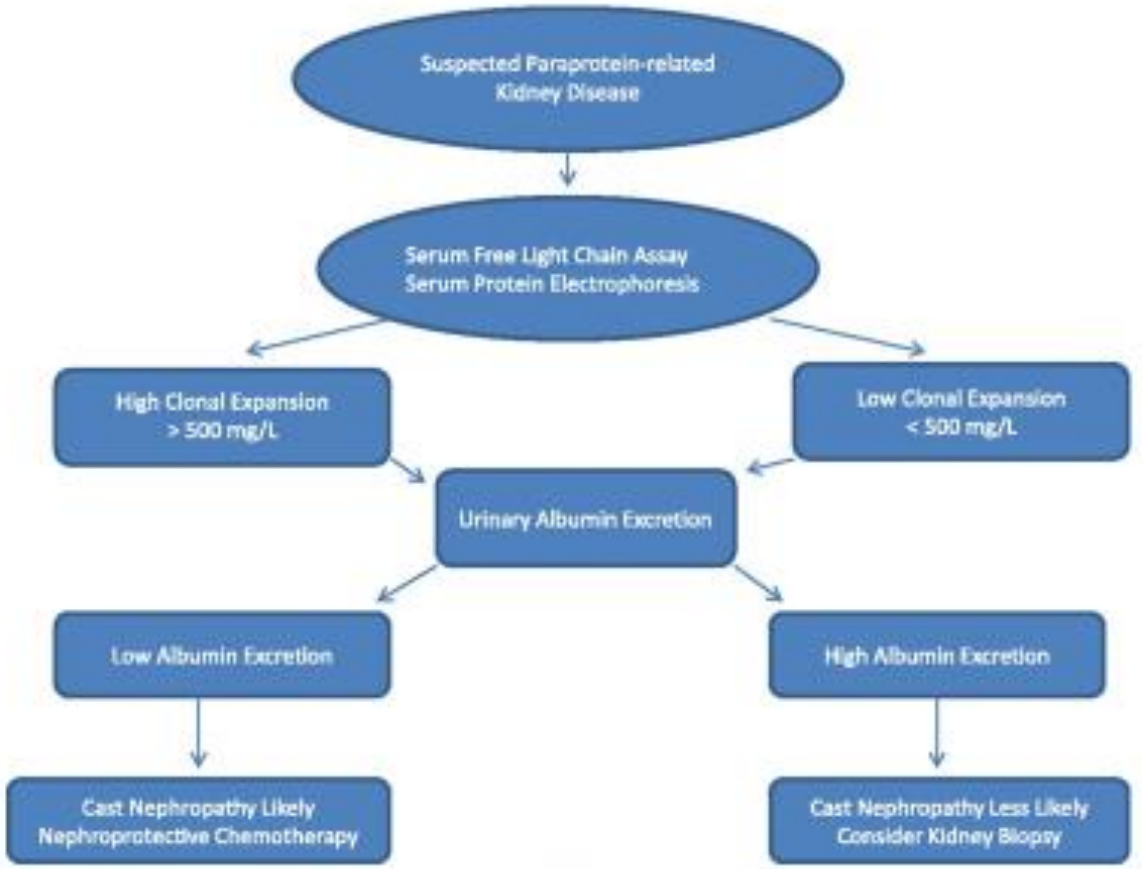
CJASN

Simplified algorithm for evaluation of suspected paraprotein–related kidney dysfunction.



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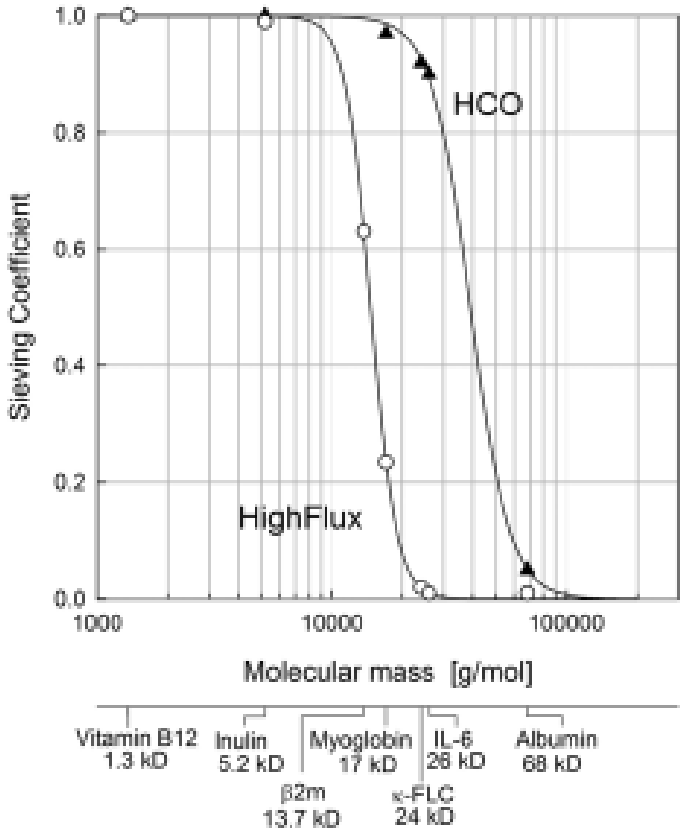
CJASN

- The benefit of HCO-HD over current chemotherapeutic regimens is uncertain. What is clear is that bortezomibbased chemotherapy is highly effective in reversing kidney failure in a significant percentage of patients
- Among 90 patients randomized to HCO-HD or high-flux dialysis, HCO-HD was not associated with greater recovery of kidney function but was associated with an increased rate of infectious complications

Comparison of sieving coefficients of high-flux and high-cutoff (HCO) membranes. κ-FLC, κ-free light chain.



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CJASN

- In addition to HCO-HD and TPE, other extracorporeal techniques have been used to reduce serum FLC concentrations through a combination of convection and membrane adsorption
- Clinical experience with these techniques is quite limited and confined to case series with very few patients. These methods should be considered experimental

- Bortezomib-based regimens are currently favored because of their safe use in patients with renal impairment, including those on dialysis
- Overall hematologic response determined by the differenc betweeninvolved and uninvolved serum free light chains (dFLCs), a recently validated parameter for monitoring disease response in MA post-treatment dFLC of 40 g/L was identified as an independent predictive factor of renal response

Current first line induction therapy is daratumumab combined with bortezomib, cyclophosphamide and dexamethasone.

Autologous stem cell transplantation after high dose melphalan therapy (HCT) should be considered for eligible patients.

kidneys and heart are most frequently affected organs, followed by gastrointestinal tract and peripheral nervous system. A tissue biopsy stained with Congo red demonstrating amyloid deposits diagnosis followed by a confirmatory typing by mass spectroscopy.

- Because significant renal dysfunction often excludes patients from consideration for an HSCT, it is imperative that cast nephropathy be treated early with agents that rapidly reduce FLC concentrations. Nevertheless, recent studies have shown that HSCT may be safe and effective in patients with renal failure.

Eligibility criteria for HCT in AL systemic amyloidosis patients

Age >18 years old, with a “physiologic age” <70

Evidence of clonal plasma cell dyscrasia at least 1 major vital organ involvement (solitary amyloid deposition in the bone marrow or soft tissue involvement is not included)

No more than 2 vital organs significantly involved (Heart, autonomic nervous system, kidney, liver)

ECOG performance status of ≤ 2 (exceptions are considered if the peripheral neuropathy is contributing to the advanced ECOG status)

A room air blood oxygen saturation ≥95%, with a DLCO >50%
Supine systolic blood pressure ≥90 mmHg
Absence of orthostatic hypotension that is refractory to medical therapy

Left ventricular ejection fraction ≥40%, with a NYHA class <III
Absence of decompensated heart failure

Absence of decompensated heart failure

Absence of symptomatic or medically refractory atrial or ventricular arrhythmias

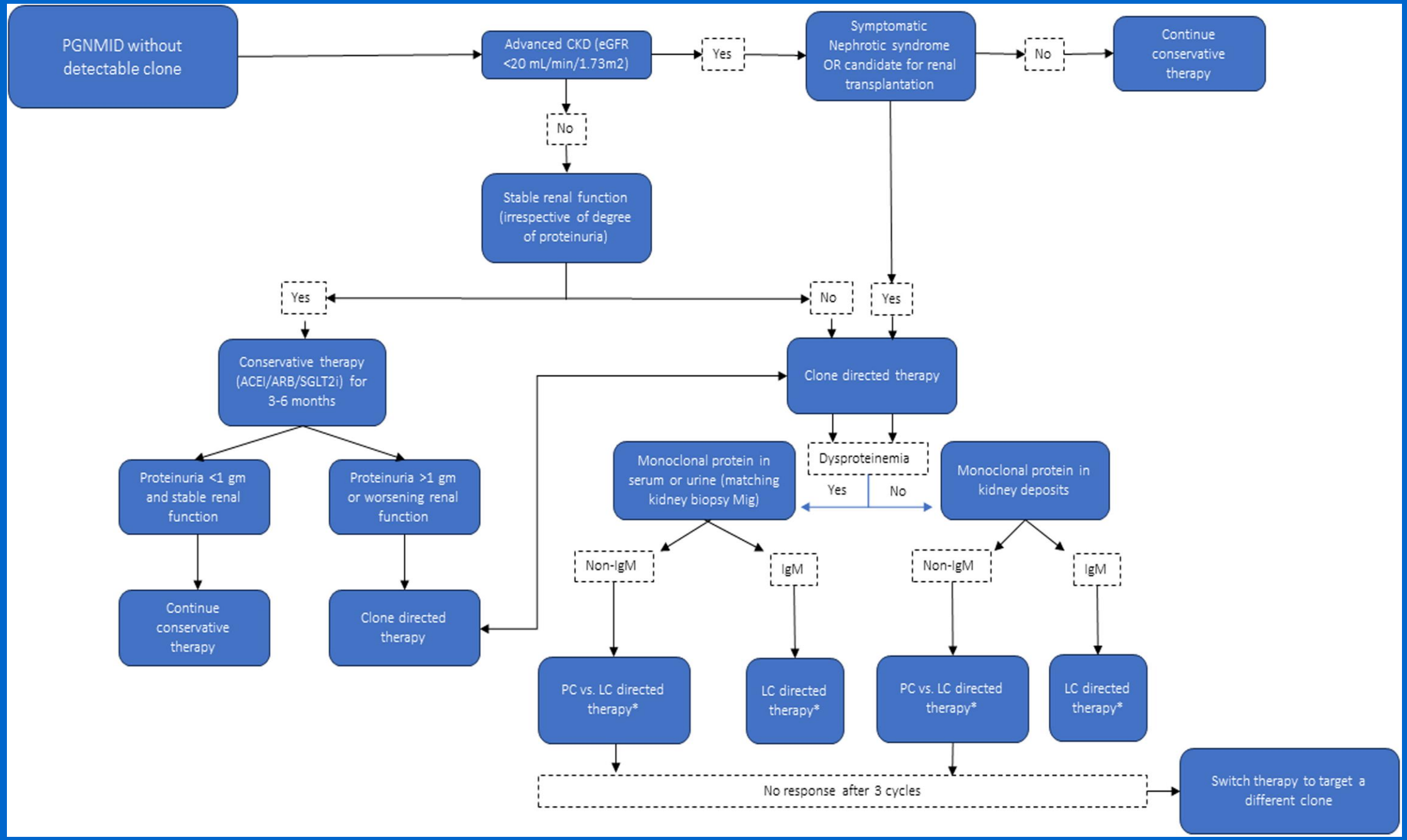
Absence of symptomatic or medically refractory pleural effusions

Absence of significant gastrointestinal tract involvement with active or increased risk of bleeding

Conjugated bilirubin <2 mg/dL ,NTproBNP <5000 pg/mL Troponin I <0.1 ng/mL, Troponin T <60 ng/ML, eGFR >30 mL/min/m2*

Absence of severe factor X deficiency (defined as factor X levels <25%)

MGRS-related renal disorders, proliferative glomerulonephritis with monoclonal Immunoglobulin deposits (PGNMIDs) is distinctively associated with the inability to identify nephropathic clone.


PGNMID without detectable clone
Advanced CKD (eGFR <20 mL/min/1.73m2)
Yes
Symptomatic Nephrotic syndrome OR candidate for renal transplantation
No
Continue conservative therapy
No
Stable renal function (irrespective of degree of proteinuria)
Yes
No
Yes
Conservative therapy (ACEI/ARB/SGLT2i) for 3-6 months
Clone directed therapy
Proteinuria <1 gm and stable renal function
Proteinuria >1 gm or worsening renal function
Monoclonal protein in serum or urine (matching kidney biopsy Mig)
Dysproteinemia
Yes
No
Monoclonal protein in kidney deposits
Continue conservative therapy
Clone directed therapy
Non-IgM
IgM
Non-IgM
IgM
PC vs. LC directed therapy*
LC directed therapy*
PC vs. LC directed therapy*
LC directed therapy*
No response after 3 cycles
Switch therapy to target a different clone

Hereditary transthyretin (ATTRv) amyloidosis is a rare and autosomal dominant disorder associated with mutations in the transthyretin gene. sensory, motor, and autonomic neuropathy, as well as gastrointestinal, ocular, cardiac, renal involvements.

ATTRv amyloidosis progresses slowly or moderately and several therapeutic options are available now, ,to capture the early signs and Family members of patients with ATTRv amyloidosis often have pathogenic mutations in the TTR gene and are at risk ,

More than 140 different mutations in the TTR gene have been reported ,and the primary symptoms of ATTRv amyloidosis may vary depending on the genetic mutations involved .The most common mutation associated with the onset of ATTRv amyloidosis is Val30Met

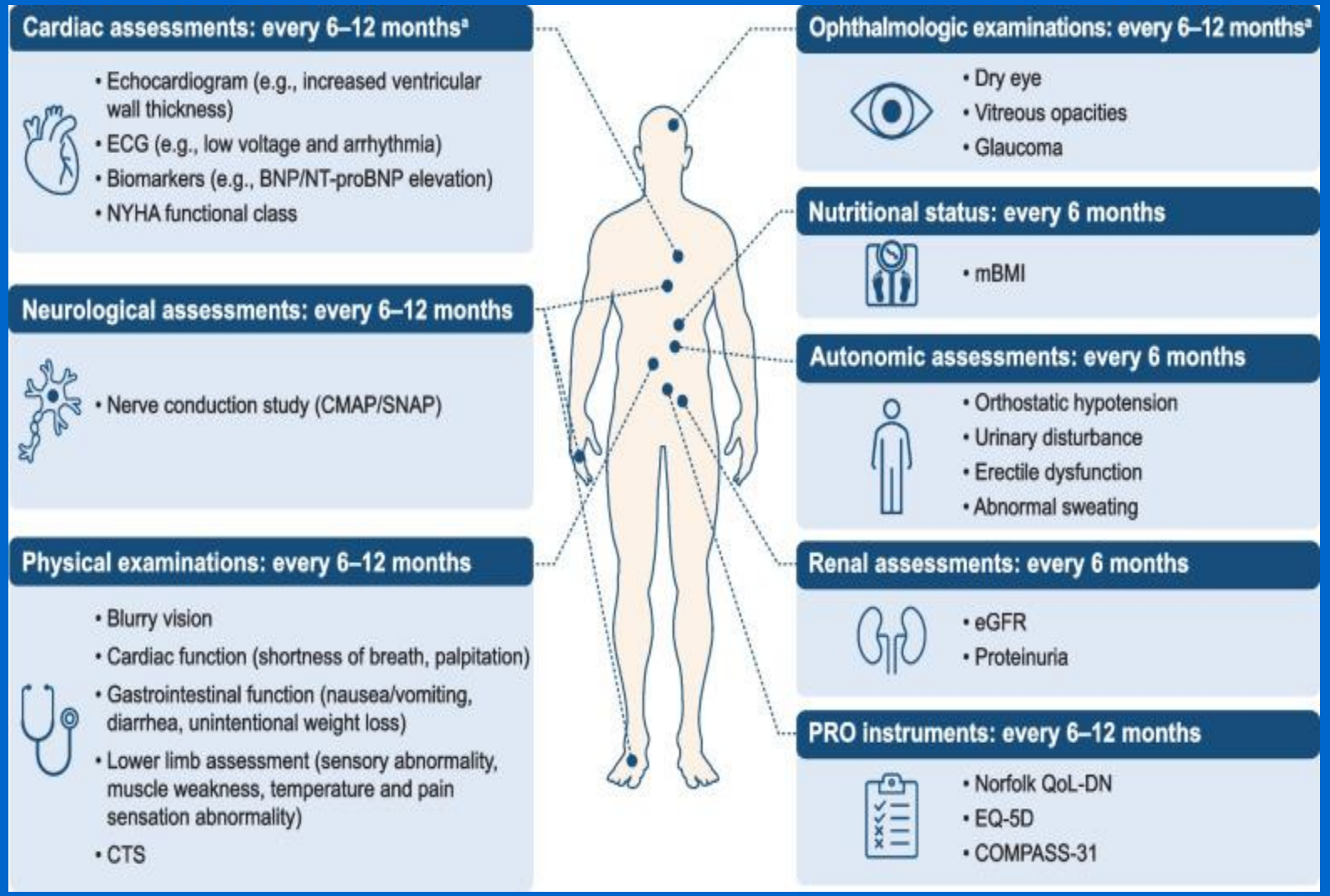
carrying mutation can be categorized into early-onset disease (age < 50 years), more common in the endemic areas, and late-onset disease (age ≥ 50 years.The penetrance of the Val30Met mutation is high in early-onset disease.

Because transthyretin is mainly produced in the liver, liver transplantation has been the standard treatment for ATTRv amyloidosis. However, the number of liver transplantation cases for ATTRv amyloidosis has declined in the past several years owing to the introduction of pharmacotherapeutic agents.

- Disease-modifying treatments (DMTs) such as tafamidis meglumine (transthyretin stabilizer), patisiran, vutrisiran (small-interfering RNA), and inotersen (antisense oligonucleotide) have been approved for the treatment of ATTRv amyloidosis

- 360 patients with ATTR cardiac amyloidosis who were randomly assigned to receive patisiran or placebo.[7] Treatment with patisiran, an siRNA, resulted in a rapid, sustained reduction in serum transthyretin levels.

practical tests and examinations for monitoring ATTRv amyloidosis progression



Prognosis and Biomarkers in AL and particularly early mortality are largely dependent on the pattern and degree of end-organ-damage by the amyloidogenic FLC. Cardiac involvement is the critical determinant of survival.

Deposition of fibrils and direct toxicity of the clonal free light chains in the myocardium leads to increased wall stress, mostly in the left ventricle, the activation of p38-MAPkinase pathway, and induction of proBNP in the cardiac myocytes., proBNP, is a 108-amino acid propeptide, is cleaved into active (BNP) and a leader sequence is NT-proBNP.

NT-pro BNP has emerged as a very sensitive marker of cardiac failure which is elevated in the asymptomatic stages of left ventricular dysfunction

High-risk cytogenetics seen in MM (t(4;14), t(14;16), and del17) are not common in AL. More complex karyotype clones, however, and presence of del17 have an impact on outcome .Gain of 1q21 is an independent adverse prognostic factor in AL patients