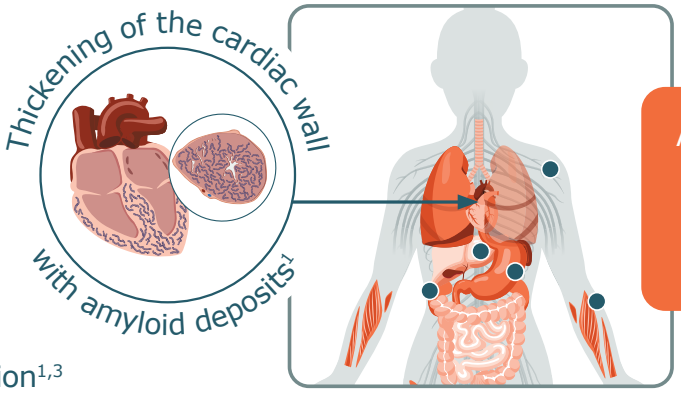
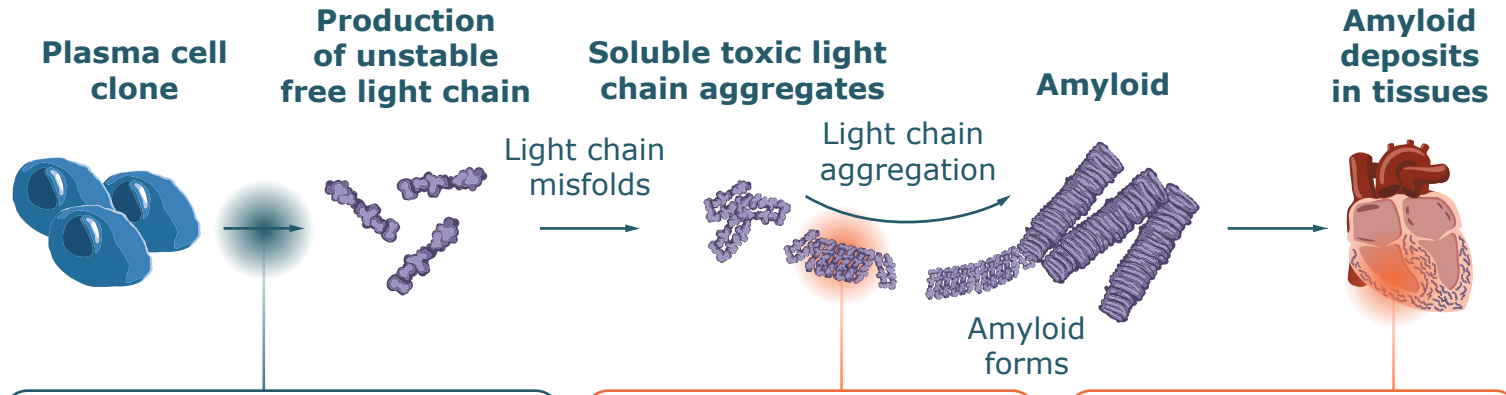
Amyloid Light Chain (AL) Amyloidosis

Is a Rare Disease Involving Deposition of Misfolded Protein in Vital Organs[1]

- AL amyloidosis is a rare, progressive, and typically fatal disease affecting about 10 people per every million[2]
- Approximately 70-80% of patients with AL amyloidosis have cardiac involvement[1]
- Newly diagnosed individuals with AL amyloidosis with cardiac involvement have an elevated risk of death, primarily due to cardiac dysfunction[1,3]



Current Therapies Do Not Target Light Chain Aggregates or Deposited Amyloid[1]



Eliminate or suppress the plasma cell clone and decrease light chain production[1]

Basis of current treatments

Target toxic soluble light chain aggregates[1,5]

Remove AL amyloid deposits from organs/tissues[1,6]

Continuing pathogenic mechanisms not addressed by current treatments[1,6]

- **Cardiac response is limited with current therapies**,[7] likely due to persistence of toxic soluble light chains and/or amyloid deposits that continue to impair organs[8,9]
- **Despite improvements in standard of care, high early mortality rates persist in patients with AL amyloidosis with significant cardiac involvement[10-12]**
  - In recent studies, 23-35% of patients with AL amyloidosis with significant cardiac involvement* treated with daratumumab-based regimens died within 6 months[10-12]
- Patients with AL amyloidosis with significant cardiac involvement are at high risk for early death,[3,13] reinforcing survival as the ultimate goal of therapy[14]

*Data from EU Modified Mayo 2004 Stage IIIa/IIIb patients who received daratumumab-based regimens.

1. Sanchorawala V. *N Engl J Med.* 2024;390:2295-2307; **2.** Kumar S, et al. *Orphanet J Rare Dis.* 2022;17:278; **3.** Barrett CD, et al. *JACC Heart Fail.* 2019;7:958-966; **4.** Milani P, et al. *Amyloid*. 2024;31:220-225; **5.** Renz M, et al. *Amyloid*. 2016;23:168-177; **6.** Wechalekar AD, et al. *JACC CardioOncol.* 2022;4:427-441; **7.** Kastritis E, et al. *Blood*. 2024;144(Suppl 1):891 [Abstract and Oral Presentation]; **8.** Li X, et al. *J Cancer Res Clin Oncol*. 2024;150:193; **9.** Bomsztyk J, et al. *Blood*. 2024;143:1259-1268; **10.** Kastritis E, et al. *Blood*. 2023;142(Suppl 1):539 [Abstract and Oral Presentation]; **11.** Oubari S, et al. *Haematologica*. 2024;109:220-230; **12.** Chakraborty R, et al. *Am J Hematol.* 2024;99:477-479; **13.** Palladini G, et al. *Blood Cancer J.* 2023;13:19; **14.** Maurer MS, et al. *Circ Heart Fail.* 2022;15:e009038.

Diagnosis of AL Amyloidosis Is Commonly Delayed;[1,2] Patient Identification Is Critical to Minimize Organ Damage and Improve Outcomes[3]

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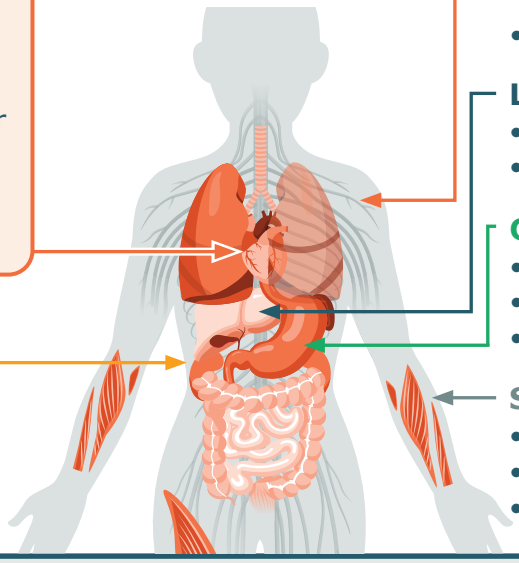
Multisystem Organ Involvement Results in Varied Clinical Presentation[4-6]

General symptoms:
Fatigue, weakness, weight changes

Heart (~70-80% of patients):
- Heart failure with preserved ejection fraction
- Diastolic dysfunction
- LV hypertrophy with interventricular septum thickening
- Dyspnea
- Arrythmia

Kidney (~60% of patients):
- Nephrotic syndrome
- Progressive renal failure
- Peripheral edema
- Proteinuria/frothy urine



Nerve (~15-20% of patients):
- Mixed sensory and motor peripheral neuropathy
- Autonomic dysfunction

Liver (~10-20% of patients):
- Hepatomegaly
- Elevated ALP

GI tract (~10% of patients):
- Diarrhea
- Constipation
- GI bleeding
- Nausea
- Malabsorption

Soft tissue (~15% of patients):
- Carpal tunnel syndrome
- Macroglossia
- Periorbital purpura

AL Amyloidosis Diagnostic Algorithm (Gertz MA *Am J Hematol.* 2024)[7]

"Red flags" for AL amyloidosis:
- Atypical MGUS or smoldering MM
- Heart failure with preserved ejection fraction
- Diastolic dysfunction
- Proteinuria
- Small fiber neuropathy
- Autonomic dysfunction
- Hepatomegaly
- Macroglossia
- Carpal tunnel syndrome

Test for monoclonal protein

Serum and urine immunofixation; Ig free light chains

If heart symptoms present, add cardiac PYP or DPD scan

+Ig

Biopsy for amyloid

Tissue biopsy with Congo red staining (bone marrow, fat aspirate)

Type amyloid

Mass spec of deposit to confirm amyloid subtype (e.g., AL, TTR)

AL amyloidosis will be either **localized** or **systemic**

Systemic AL amyloidosis
1. Use dFLC, NT-proBNP, and troponin to stage disease and determine extent of cardiac involvement
2. Initiate patient-specific treatment

−Ig

Light chain amyloid unlikely

If PYP scan is positive, screen for ATTR amyloidosis

Amyloid excluded in most cases

If high index of suspicion, biopsy involved organ and stain with Congo red
If positive, type amyloid

AL, light chain; ALP, alkaline phosphatase; dFLC, difference between involved and uninvolved free light chains; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; GI, gastrointestinal; Ig, immunoglobulin; LV, left ventricular; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; NT-proBNP, N-terminal pro B-type natriuretic peptide; PYP, pyrophosphate; TTR, transthyretin.

1. McCausland KL, et al. *Patient*. 2018;11:207-216; **2.** Hester LL, et al. *Eur J Haematol.* 2021;107;428-435; **3.** Sanchorawala V. *N Engl J Med.* 2024;390:2295-2307; **4.** Milani P, et al. *Mediterr J Hematol Infect Dis.* 2018;10:e2018022; **5.** Dima D, et al. *JCO Oncol Pract.* 2023;19:265-275; **6.** Hwa YL, et al. *J Adv Pract Oncol.* 2019;10:470-481; **7.** Gertz MA. *Am J Hematol.* 2024;99:309-324.

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