A Patients Guide to AL (Light Chain) Amyloidosis

What is amyloidosis?

Amyloidosis is a condition where proteins in your body don't fold properly, causing them to build up in tissues and organs. These misfolded proteins form clumps (called fibrils) outside cells, which can interfere with how your organs work. There are many types of amyloidosis, and they differ based on the type of protein involved, which organs are affected, how serious the condition is, and how it should be treated. That's why it's very important to figure out the exact type of amyloidosis a person has to ensure they get the right treatment. One of the most common and serious types of amyloidosis is called AL amyloidosis. It happens when abnormal proteins called light chains, made by certain cells in the bone marrow, build up in the body. Without treatment, this type of amyloidosis can lead to serious health problems.

There are different types of hereditary amyloidosis, including a type called ATTRv amyloidosis. This is a genetic condition that is passed down through families (autosomal dominant) and happens because of a small change (mutation) in a gene that affects a protein called transthyretin. This protein is made in the liver, and when it has this mutation, it can misfold and form harmful clumps (amyloid fibrils) in tissues. There are over 140 different mutations that can cause amyloidosis. Even without a genetic mutation, ATTRwt (wild-type) transthyretin protein can sometimes misfold and build up as amyloid fibrils. Wild-type amyloidosis is an age-related disease that is acquired. This pamphlet focuses on AL (light chain) amyloidosis. For more information about ATTR amyloidosis, please check a separate pamphlet available from the Amyloidosis Foundation.

What is AL (light chain) amyloidosis?

AL amyloidosis is a condition where abnormal proteins called light chains, made by certain cells in the bone marrow (called plasma cells), don't form correctly. These misfolded light chains

clump together and build up as amyloid fibrils in tissues and organs, interfering with their function. It is part of a group of conditions caused by abnormal plasma cells, which also includes multiple myeloma (a type of blood cancer), monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, and heavy chain disease.

In multiple myeloma, the bone marrow has a very high number of abnormal plasma cells (30% or more) that produce excessive proteins. However, only 10-15% of people with multiple myeloma develop AL amyloidosis. Most patients with AL amyloidosis have a more moderate increase in plasma cells, usually about 5-20% in the bone marrow.

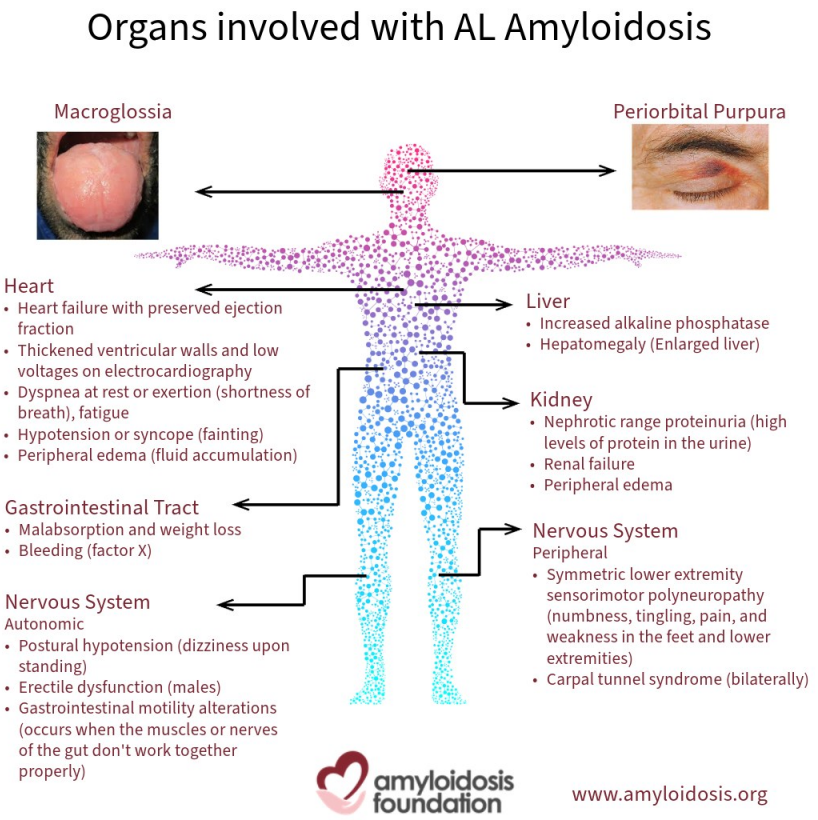
How common is AL amyloidosis?

AL amyloidosis is considered to be a rare disease, but it is about as common as other conditions like Hodgkin's disease or chronic myelocytic leukemia. In the United States, there are approximately 6,000–9,000 new cases diagnosed each year. Thanks to better technology and increased awareness among doctors, it's now easier to detect abnormal light chains in the blood and urine. This has helped diagnose AL amyloidosis earlier, when treatment may be more effective.

How do abnormal light chains cause disease?

Abnormal light chains (LCs) can harm tissues and organs in several ways. These proteins, made by clonal plasma cells, are unstable and go through changes in structure. As they change, they can form intermediate shapes (like monomers, dimers, and oligomers) that eventually clump together and build up in tissues as amyloid deposits. These amyloid deposits take up space in the tissues, making it harder for the affected organs to work properly. In addition to the physical buildup, the deposits in organs like the heart, liver, digestive system, kidneys, and peripheral nerves can trigger damage at the cellular level, causing stress and injury

to the cells. This includes processes like oxidative stress (an imbalance that damages cells) and cell death (apoptosis).



What organ systems are affected by AL amyloidosis?

AL amyloidosis is a systemic disease, meaning it can affect almost any organ in the body. Commonly affected systems include:

- ***Heart***: Amyloid deposits in the heart can lead to heart failure, which is associated with the poorest prognosis. Recent studies show that about 75% of patients with AL amyloidosis have heart involvement.

- ***Kidneys****:* Damage to the kidneys can cause protein to leak into the urine and may lead to kidney failure.
- ***Lungs****:* Amyloid buildup can affect lung function.
- ***Gastrointestinal system:*** This includes the liver and intestines, where amyloid can interfere with digestion and nutrient absorption.
- ***Nerves****:* Both peripheral nerves (causing symptoms like numbness or tingling in the hands and feet) and autonomic nerves (affecting things like blood pressure or digestion) can be impacted.
- ***Soft tissues****:* Amyloid can build up in areas like the skin or around the eyes, leading to swelling or other symptoms.

Heart involvement is the most critical, as it significantly affects survival and quality of life.

What are the common symptoms of AL amyloidosis?

People with AL amyloidosis often have symptoms that affect multiple organs. The most common problems involve the heart and kidneys, but other areas can also be affected.

Heart Symptoms

- ***Heart failure****:* Symptoms include shortness of breath (with activity or at rest), difficulty breathing while lying down (orthopnea), and swelling in the legs or abdomen (peripheral edema).
- ***Chest discomfort or pain:*** This may feel like typical angina or something less specific.
- ***Arrhythmias****:* Irregular heartbeats, such as atrial fibrillation, are common.
- ***Dizziness or fainting:*** These can result from abnormal heart rhythms or nerve damage (autonomic neuropathy).

Kidney Symptoms

- ***Protein in the urine (proteinuria*)**: This is often the first sign, sometimes accompanied by nephrotic syndrome (severe protein loss, swelling, and low blood protein levels).
- ***Swelling (edema):*** Due to kidney damage causing fluid retention.

Nerve Symptoms

- ***Peripheral neuropathy:*** Numbness, tingling, or weakness in the hands and feet.
- ***Autonomic neuropathy:*** Dizziness or fainting (especially when standing), digestive issues like slow stomach emptying, diarrhea, constipation, or erectile dysfunction.

Soft Tissue Symptoms

- ***Carpal tunnel syndrome:*** Numbness and tingling in the hands, often requiring surgery.
- ***Enlarged tongue (macroglossia):*** Only seen in AL amyloidosis, it may make swallowing, speaking, or breathing difficult.
- ***Hoarseness:*** Changes in the voice due to vocal cord involvement.
- ***Swelling:*** Lymph nodes, salivary glands, or submandibular glands.
- ***Skin changes:*** Easy bruising, purplish discoloration around the eyes (periorbital purpura), or brittle nails.

Digestive System Symptoms

- ***Liver issues:*** Pain or discomfort in the upper right abdomen, possibly due to liver enlargement.
- ***Bowel problems:*** Autonomic nerve damage can cause diarrhea, constipation, or changes in bowel habits.

General Symptoms

- ***Weight loss:*** Often unexplained.
- ***Fatigue:*** A general sense of tiredness or weakness.

Clues to Look for

- A history of carpal tunnel syndrome or recent surgery for it.
- Sudden improvement in high blood pressure (if previously treated).
- Voice changes or difficulty swallowing.
- Symptoms involving multiple organ systems (e.g., heart and kidneys) can signal systemic disease.
- If you experience signs of heart failure alongside symptoms like nerve damage, tongue enlargement, or unexplained weight loss, it's crucial to consider AL amyloidosis as a possibility. Early diagnosis is key to effective treatment.

What are the key physical exam findings in AL amyloidosis?

AL amyloidosis can present with various physical signs, often reflecting the organs affected by the disease. Here are the most notable findings:

Heart-Related Findings

Heart failure signs:

- Jugular venous distension (a swollen vein in the neck).
- Peripheral edema (swelling in the legs).
- Ascites (fluid buildup in the abdomen).
- Pulmonary crackles (sounds in the lungs from fluid buildup).
- Pleural effusion (fluid around the lungs).

Low blood pressure: Blood pressure is often low, and orthostatic hypotension (a drop in blood pressure when standing) is common.

Liver Findings

Hepatomegaly (enlarged liver):

- If due to amyloid deposits, the liver feels hard but is not tender.
- This contrasts with a firm, tender liver caused by chronic passive congestion.

Soft Tissue Findings

- ***Enlarged tongue (macroglossia):*** A unique sign of AL amyloidosis, leading to difficulty swallowing, speaking, or breathing.
- ***Submandibular swelling:*** Swelling under the jaw.
- ***Nail dystrophy:*** Brittle or slow-growing nails.

Laboratory and Diagnostic Findings

Cardiac markers:

- Elevated troponin due to heart muscle damage.
- Increased BNP or NT-proBNP, indicating heart stress, which is associated with a worse prognosis.

Liver tests:

- Elevated AST and ALT (liver enzymes).
- Elevated alkaline phosphatase, which can indicate liver or bone involvement.

Kidney tests:

- Increased creatinine and decreased glomerular filtration rate (GFR), signaling kidney damage.

Blood counts:

- Anemia, often due to kidney dysfunction or multiple myeloma.

Heart Imaging Findings

Echocardiogram:

- Thickened left ventricle.
- Diastolic dysfunction (impaired relaxation of the heart).
- Enlarged atria.
- Pericardial effusion (fluid around the heart).

Electrocardiogram (ECG):

- Low voltage (weaker electrical signals).

When to Suspect AL Amyloidosis

If a patient has signs of heart failure (e.g., shortness of breath, swelling) along with findings like a thickened heart on echocardiogram and low voltage on ECG, these should raise suspicion for cardiac amyloidosis. Further specialized testing is essential to confirm the diagnosis.

What tests are used to diagnose AL amyloidosis?

Diagnosing AL amyloidosis involves confirming amyloid deposits in tissues and identifying abnormal light chain (LC) production. Here are the steps and tests used:

Tissue Biopsy

- ***Congo red staining:*** A biopsy of tissue is checked under a microscope for amyloid deposits, which show a green birefringence under polarized light.

- ***Confirmation of LC type:*** Tests like immunohistochemistry or mass spectrometry confirm whether the amyloid contains kappa or lambda light chains.

Monoclonal Light Chain Detection

To confirm systemic AL amyloidosis, tests are done to detect abnormal light chain production:

- ***Bone marrow biopsy:*** Looks for clonal plasma cells producing abnormal light chains.
- ***Serum and urine immunofixation electrophoresis:*** Sensitive tests to detect monoclonal proteins in the blood or urine.
- ***Serum free light chain assay:*** Measures free kappa and lambda light chains.
- Kappa:lambda ratio:
    - A ratio <0.26 suggests clonal lambda light chains.
    - A ratio >1.65 suggests clonal kappa light chains.

  Kidney disease can raise both kappa and lambda levels, so the ratio is critical for diagnosis.

Tissue Sampling Options

Abdominal fat pad aspiration:

- A non-invasive procedure that is positive in over 70% of cases. This is often the first choice for biopsy.

Organ-specific biopsies:

- If fat pad aspiration is negative, tissue from a suspected affected organ (e.g., kidney, heart) may be biopsied.
- These biopsies are highly accurate (~100%) but carry a small risk.

Additional Information

Prognosis-related testing: The level of serum free light chains provides important information about disease severity and prognosis.

By combining tissue biopsy results with evidence of monoclonal light chain production, doctors can definitively diagnose AL amyloidosis and guide treatment.

Key Tests for Diagnosing AL Amyloidosis

Bone Marrow Biopsy

Used to detect increased plasma cells in the bone marrow. Immunoperoxidase staining determines whether plasma cells are producing kappa or lambda light chains (LCs).

Serum Free Light Chain (LC) Assay

A sensitive and straightforward initial test for suspected AL amyloidosis.

This test is recommended for patients with heart failure, thickened left ventricular walls, and low voltages on electrocardiogram (ECG).

Abdominal Fat Pad Biopsy

A minimally invasive first-line procedure to check for amyloid deposits.

Stains used: Congo red (for amyloid deposits), Alcian blue.

Advanced testing: Electron microscopy and immunohistochemistry can confirm the presence of light chain amyloid.

Endomyocardial Biopsy

Considered if other tissue samples fail to confirm amyloidosis.

Provides definitive evidence, especially in cases of suspected cardiac amyloidosis.

By combining these tests, physicians can confirm the presence of AL amyloidosis and its systemic effects, ensuring accurate diagnosis and guiding appropriate treatment.

How is AL Amyloidosis Treated?

Treatment for AL amyloidosis focuses on eliminating the abnormal plasma cells that produce harmful light chains and managing symptoms caused by organ damage. Here's an overview:

Definitive Treatment

The goal is to stop the production of amyloid-forming light chains by targeting the plasma cells:

- High-dose chemotherapy with autologous stem cell transplant (HDM/SCT):

- This involves using high-dose chemotherapy to destroy plasma cells, followed by a stem cell transplant to restore bone marrow function.
- Best suited for younger, healthier patients without advanced organ damage.

Other chemotherapy options: For patients unable to tolerate HDM/SCT, various drug regimens are available:

- Melphalan
- Dexamethasone or prednisone
- Thalidomide or cyclophosphamide
- Lenalidomide or bortezomib (Velcade)
- Newer agents being tested in clinical trials.
- Darzalex Faspro (daratumumab):

Approved in 2021 as the first FDA-approved immunotherapy for newly diagnosed AL amyloidosis.

Supportive Treatment

Supportive care is essential to manage symptoms caused by organ involvement:

Heart failure management:

- ***Diuretics:*** Help with fluid overload.
- ***Thoracentesis/paracentesis:*** For severe pleural effusions or abdominal fluid buildup.

Standard heart failure medications (e.g., beta blockers, ACE inhibitors, ARBs, aldosterone blockers) may be used cautiously due to low blood pressure and orthostatic hypotension.

- ***Anticoagulation:*** Strongly recommended for patients with atrial fibrillation to reduce the risk of blood clots.

Routine anticoagulation may be considered for patients at high risk of clot formation.

Advanced Cases

In patients with severe organ damage, additional options include:

Cardiac transplantation:

- Suitable for patients with advanced heart disease but good function in other organs.
- Typically followed by chemotherapy 6–12 months later to prevent recurrence.
- Specialized centers report encouraging outcomes, even with extended donor criteria.

Importance of Accurate Diagnosis

Since treatments for AL amyloidosis differ from those for other forms of amyloidosis, it's critical to confirm the protein type in the amyloid deposits.

Key Points

- ***First-line treatment:*** HDM/SCT for eligible patients.
- ***Alternative regimens:*** Chemotherapy or immunotherapy for those who cannot undergo aggressive treatment.
- ***Supportive care:*** Tailored to address symptoms of organ dysfunction, especially heart and kidney involvement.
- ***Ongoing research*****:** New therapies in clinical trials are providing hope for better outcomes.

Early diagnosis and specialized care are essential to improve survival and quality of life in patients with AL amyloidosis.

Prognosis for Patients with AL Amyloidosis

The outlook for AL amyloidosis patients has significantly improved in the last two decades due to advancements in treatment. Here's an overview:

Improved Survival

- ***Historical prognosis:*** 20 years ago, the average survival was 1–2 years, with worse outcomes for those with heart involvement.
- ***Current outcomes:*** Many patients now experience extended survival and improved quality of life, with some achieving long-term remission or even apparent cure.

Impact of Treatment

- ***High-dose chemotherapy with stem cell transplant (HDM/SCT):*** Effective in clearing circulating light chains, leading to long-term survival and remission in eligible patients.
- ***Other therapies:*** Less aggressive treatments also provide significant benefits and extended survival, even when HDM/SCT is not an option.

Newer treatments, such as immunotherapy, are further improving outcomes.

Chronic Disease Management

Advances in major and supportive therapies are shifting the perspective of AL amyloidosis: It is increasingly treated like a chronic condition, with ongoing management to control symptoms and maintain quality of life.

Key Factors in Prognosis

Early diagnosis and initiation of treatment are critical.

- ***Organ involvement:*** Cardiac involvement remains the most significant factor influencing prognosis.
- ***Treatment response*****:** The ability to reduce or eliminate the production of abnormal light chains is a key predictor of long-term survival.

With modern medical approaches, many patients now live longer, healthier lives despite this challenging condition.

NOTES:

To Locate an Amyloidosis Clinic, please visit the Resources page on our website:

www.amyloidosis.org

amyloidosis foundation

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