DISEASE OVERVIEW

LIGHT CHAIN AMYLOIDOSIS (AL AMYLOIDOSIS)

Dan has AL amyloidosis.

Amyloidosis Research Consortium

ARCI.ORG

KNOWLEDGE IS POWER

ABOUT THE **AMYLOIDOSIS RESEARCH CONSORTIUM**

The Amyloidosis Research Consortium (ARC) is a nonprofit organization dedicated to driving advances in the awareness, science, and treatment of amyloid diseases. ARCs mission is to improve and extend the lives of those with amyloidosis. ARC is committed to collaborative efforts that accelerate the pace of discovery, expand patient access to the most effective care, and improve short- and long-term outcomes. Working with partners in industry, government, and academia, ARC seeks to spark innovation and to bring promising treatments from labs to clinics. Our outreach and educational efforts inform and empower patients, families, caregivers, physicians, and researchers.

To learn more about ARC or speak with a specialist on our team:

- Visit **www.arci.org**
- Call **1.617.467.5170**

Amyloidosis Research Consortium

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INTRODUCTION

A diagnosis of light chain amyloidosis (AL amyloidosis) can be confusing and stressful, bringing up many feelings and questions. It is important to learn as much as possible about the disease, its treatment, and how it might affect you.

A well-informed patient is better able to be an active partner with their health care team in making decisions about treatment, managing their care, and advocating for their needs.

This booklet is here to serve as a comprehensive resource and a guide for making informed treatment decisions.

AMYLOIDOSIS

WHAT IS AMYLOIDOSIS?

Amyloidosis is a group of diseases caused when misfolded proteins, called amyloid, build up and form fibrils that deposit in the body's organs and tissues, affecting their ability to function. Amyloid fibrils typically accumulate in the heart, kidney, and nerves; less often in the liver, spleen, gastrointestinal tract, and airway. These can impair multiple organs and nerves or be localized in one area of the body. Symptoms are often mistaken for more common conditions.

Over 30 different proteins cause various types of amyloidosis. Each is referred to by an "A" for amyloid followed by an abbreviation for the abnormal protein (for example, AL for amyloidosis caused by abnormal immunoglobulin light chains or ATTR for transthyretin amyloidosis). Treatment is determined by the type of amyloid and which organs and tissues are affected.

Amyloid is a starch-like substance caused by the misfolding of proteins. Amyloid binds together into rigid, linear fibers (fibrils) that accumulate in tissues and organs.

WHY ARE PROTEINS SO IMPORTANT?

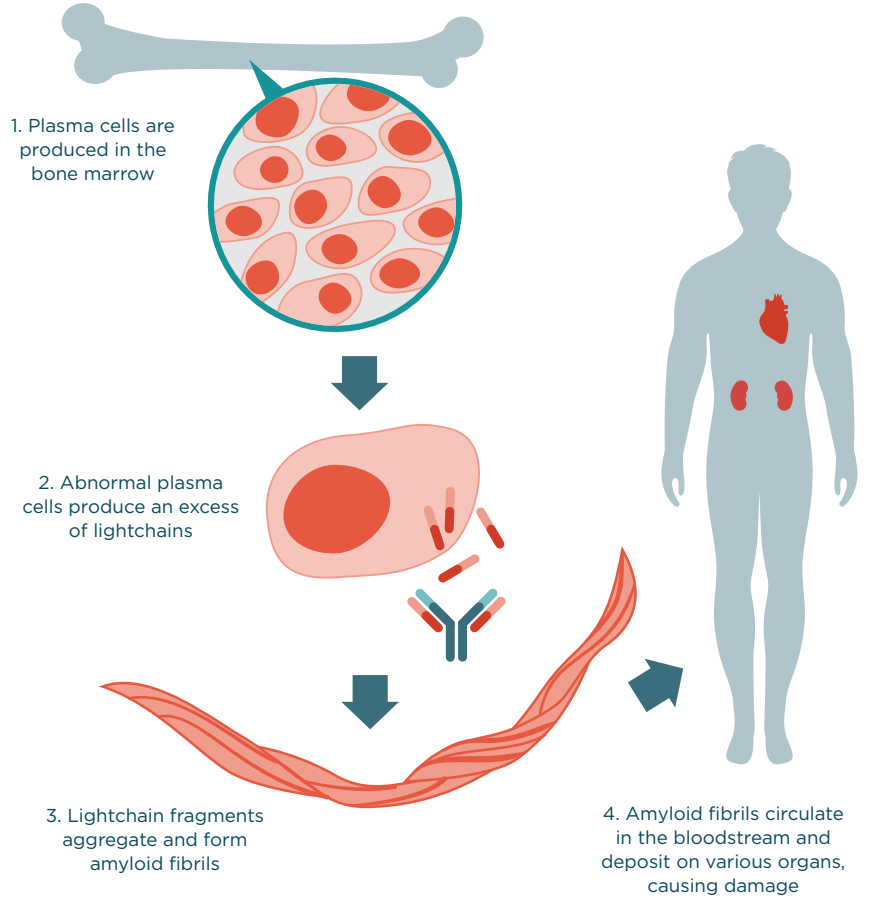
Many thousands of proteins do essential work inside our cells. Each has a specific job to keep us healthy.

DNA instructions control the shape and structure of proteins. Normal proteins fold into a specific shape, do their tasks, and are then recycled or removed from the body.

In amyloidosis, mutated proteins form incorrectly (misfold), which makes them unable to do their tasks and difficult for the body to

remove. These misfolded proteins then accumulate in the body and form fibrils, known as amyloid, in organs and tissues, such as the heart, kidney, or nerves. As they accumulate over time, they impact the function of organs causing symptoms to flare, telling us something is wrong. Many different proteins can misfold and lead to different types of amyloidosis, but they all share the same abnormal structure. Diagnostic tests can identify specific types of amyloid.

In AL amyloidosis, proteins produced by abnormal plasma cells misfold into amyloid fibrils that build up in the body, causing organ damage.



WHAT IS AL AMYLOIDOSIS?

Light chain amyloidosis (AL amyloidosis) is a rare, systemic disease caused by abnormal plasma cells located in the bone marrow. The function of our normal plasma cells is to form immunoglobulins (free light chains), also known as antibodies, that target and neutralize bacteria and viruses. In AL amyloidosis abnormal plasma cells create abnormal light chain proteins. Abnormal light chains misfold and form into amyloid fibrils (insoluble starch-like deposits). Normal light chains are excreted by the kidneys. Abnormal (mis-folded proteins) are not excreted causing them to build up in the blood. As they build up and accumulate these fibrils are deposited in organs, tissues, and nerve, causing damage.

Most AL amyloidosis patients are diagnosed after the age of 50, though some adult patients have been diagnosed as early as their 20s. AL amyloidosis affects both men and women, although there is a slight predominance in males. The pattern of amyloid build-up is different for each patient and often affects more than one organ. Early diagnosis and treatment are essential to prevent or slow disease progression.

Untreated, AL amyloidosis is progressive, and ultimately, fatal. Early diagnosis and treatment are essential for improved outcomes. Major therapeutic advances have been discovered over the last decade. These can put AL amyloidosis into prolonged remission and extend life.

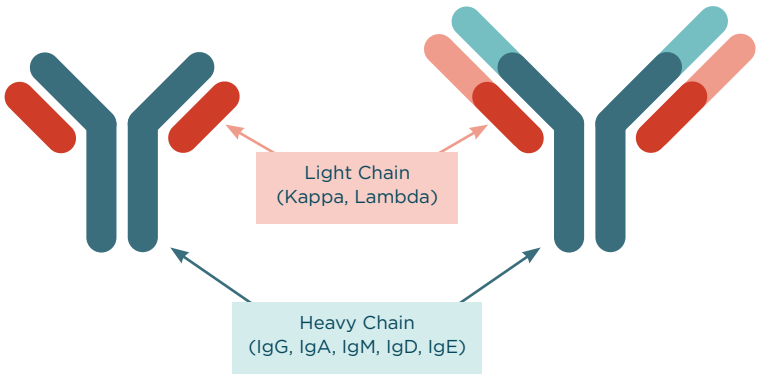
Major therapeutic advances have been discovered in the last decade. Current treatments can put AL amyloidosis into prolonged remission and extend life.

AN OVERVIEW OF PLASMA CELLS AND FREE LIGHT CHAINS

Blood cells are produced in bone marrow, a specialized tissue in the hollow center of bones. The main types of blood cells are red, white (including plasma cells), and platelets. Each plays a specialized role in your body's immune system.

Plasma cells produce immunoglobulins, a class of antibodies that fight infections. Antibodies are made up of two kinds of protein chains, heavy and light. In AL amyloidosis, there are too many plasma cells that produce an excess of either kappa (κ) or lambda (λ) light chain fragments. Your care team may also refer to these free light chains as "FLCs" or as "clones."

ANTIBODY STRUCTURE



As abnormal plasma cells multiply, they produce light chain fragments that aggregate and form amyloid fibrils and enter the blood stream. The goal of treatment is to reduce or eliminate the abnormal cells, decreasing or halting the accumulation of amyloid deposits and preserving organ function.

Plasma cells are a type of blood cell formed in the bone marrow. They are part of the body's immune system. These cells produce antibodies, or immunoglobulins. Each antibody has two main structural components—heavy and light chains. In AL amyloidosis, abnormal plasma cells produce excess lambda or kappa light chain fragments that aggregate into amyloid fibrils and accumulate in tissues and organs, causing damage.

The ratio between the kappa and lambda light chains indicates a potential overproduction of one light chain over the other. The ratio is used to track disease progression or remission.

FREQUENTLY ASKED QUESTIONS ABOUT AL AMYLOIDOSIS

WHAT CAUSES AL AMYLOIDOSIS?

AL amyloidosis is not inherited or contagious. Its cause is still unknown, but research suggests a link between environmental exposure and eventual onset. For example, some Veterans exposed to Agent Orange have been treated for AL amyloidosis. AL amyloidosis has also been diagnosed in many first responders to the 9/11 attacks. There is also suspicion that AL amyloidosis is linked to inflammatory conditions in the body, but more research is needed to confirm this.

HOW COMMON IS AL AMYLOIDOSIS?

Although once considered to be a very rare disease, with the education of health care professionals and better diagnostic tools, it is now considered more common than previously thought. Previously known as “primary amyloidosis” AL amyloidosis incidence is about 4500 patients diagnosed each year in the United States. Prevalence is higher in males than in females though why is still not understood.

Although once considered to be a very rare disease, with the education of health care professionals and better diagnostic tools, it is now considered more common than previously thought.

IS AL AMYLOIDOSIS RELATED TO MULTIPLE MYELOMA?

AL amyloidosis is not a cancer although it is sometimes diagnosed with multiple myeloma, which is a bone marrow cancer. Both diseases are plasma cell disorders. Plasma cells create antibodies that fight infections and kill germs. Metastasized plasma cells like multiple myeloma crowd healthy blood cells preventing the immune system from functioning properly.

AL Amyloidosis patients are sometimes also diagnosed with multiple myeloma. Though the diseases are different, both are treatable with combinations of multiple myeloma treatment protocols.

AL amyloidosis is caused by misfolded light chain proteins produced by plasma cells. Some 10% to 15% of patients with AL amyloidosis also have active multiple myeloma, known as myeloma-associated AL amyloidosis. Both AL amyloidosis and multiple myeloma are treatable diseases. Some myeloma drugs are used “off label” to treat AL amyloidosis. Autologous stem cell transplants may also be used in treating each of these diseases.

SYMPTOMS OF AL AMYLOIDOSIS

HOW DOES AL AMYLOIDOSIS AFFECT THE BODY?

AL amyloidosis is a progressive, systemic disease that can affect multiple organs, tissues, and nerves. The most common symptoms are weight loss, fatigue, swelling of the legs (edema), and breathlessness (dyspnea) with exertion.

The most frequently affected organs are the heart and kidneys. Others include the gastrointestinal (GI) tract, nervous system, and liver. Amyloid deposits in soft tissue, such as the skin or tongue, can also occur and are important signs of the disease. In some patients, only one organ is involved. In others, multiple organs are affected.

SIGNS AND SYMPTOMS OF AL AMYLOIDOSIS

AL amyloidosis can affect many parts of the body. Symptoms vary for each patient, with some people having more than others.

Hand and arm symptoms

- Carpal tunnel syndrome
- Numbness, burning, pain, and/or tingling (peripheral neuropathy)
- Weak fingernails, or other nailbed changes

Leg symptoms

- Swelling of the feet or legs
- Muscle weakness
- Weak/brittle toenails
- Peripheral neuropathy

Head and neck symptoms

- Lightheadedness or dizziness when standing up quickly (orthostatic hypotension)
- Purple color on the eyelids and/or around the eyes (periorbital purpura)
- Enlarged tongue/scalloped tongue
- Problems with breathing, talking, swallowing, or chewing
- Jaw pain

Heart and lung symptoms

- Shortness of breath (dyspnea)
- Palpitations (arrhythmia)
- Chest pain
- Fatigue
- Swelling in the legs (edema)
- Arrhythmia (abnormal heartbeat)
- Syncope (fainting)

Stomach or intestinal (GI Tract) symptoms

- Poor appetite
- Feeling full after eating small amounts of food (early satiety)
- Nausea and vomiting
- Unintentional and significant weight loss
- Bloating
- Diarrhea and/or constipation
- Gastrointestinal bleeding
- Heartburn

Kidney symptoms

- Foamy urine
- Less frequent urination
- Getting up in the night to urinate
- Swelling in the lower legs, stomach, arms (edema)
- Kidney (renal) failure requiring dialysis

Other signs or symptoms

- Obstructive sleep apnea
- Skin changes, such as thickening or easy bruising
- Hoarseness
- Enlarged shoulder pad (on the back)
- Purple color in skinfolds
- Bruising or bleeding easily
- Blood coagulation abnormalities

NONSPECIFIC SYMPTOMS

Nonspecific symptoms are those that can be caused by a wide range of illnesses. Fatigue is one example of such symptoms. Others include fever, general malaise, weight loss, difficulty concentrating, or stiffness. Because AL amyloidosis is a rare disease, physicians tend to attribute its symptoms to more common disorders. Misdiagnoses can lead to treatment for unrelated disorders and delayed access to therapeutic options.

WHAT SHOULD I TELL MY DOCTOR?

It is important to tell your doctor about all symptoms and if they have worsened over time. Certain symptoms, or clusters of them, can indicate AL amyloidosis.

SHOULD I SEE AN AL AMYLOIDOSIS SPECIALIST?

Ask your healthcare provider for a referral to a clinic or center that specializes in the diagnosis and management of AL amyloidosis. To develop the best treatment plan, your physician and other specialists should coordinate care with experts at these centers. ARC has tools to help you locate and access these resources.

MAP | My Amyloidosis Pathfinder

MAP is a free, easy-to-use tool that captures your treatment preferences, goals, and challenges so you can effectively communicate with your amyloidosis care teams.

As part of your MAP experience, you can also find and compare specialty treatment centers and receive personalized matches to clinical trials.

My Amyloidosis Appointment Companion

Treatment Center Selector

Clinical Trial Finder

www.myamyloidosispathfinder.org

HOW IS AL AMYLOIDOSIS DIAGNOSED?

OVERVIEW

Early and accurate diagnosis of AL amyloidosis is essential for effective and timely treatment, but the disease can be difficult to diagnose. Symptoms often mimic those of more common disorders, and no single imaging, blood, or urine test is sufficient to make an accurate diagnosis.

Some cardiologists trained in amyloidosis are successful in identifying amyloidosis in cardiac imagining. However, a definitive diagnosis requires the identification of amyloid fibrils in cells or tissue samples taken from suspected affected organs or proxy sites. These small biopsy samples are stained with a dye called Congo red and viewed under a microscope with polarized light. Amyloid has a characteristic apple-green color or birefringence that identifies it.

Many tests can be used to identify specific types of amyloid proteins. Some are performed once to confirm a diagnosis of AL amyloidosis; others are repeated many times to track disease progression and response to therapy.

WHAT TESTS WILL I NEED?

Your complete examination will include blood and urine tests, biopsies (small samples of cells or tissue), and imaging. Blood and/or urine tests can identify amyloid protein, but only bone marrow tests or other small biopsy samples of tissues or organs can confirm a diagnosis of AL amyloidosis.

TESTING PROTOCOLS

Initially, lab tests will look for abnormal plasma cells and an excess of either kappa or lambda free light chains in the blood and urine. These tests include serum free light chain levels, antibodies (immunoglobulins), and serum and immunofixation tests for

excess proteins. These tests may confirm the presence and level of the lambda or kappa light chain fragments in your blood or urine.

A positive test for light chain fragments in your blood or urine may lead to additional testing to determine which organs or tissues that may be affected. These tests may include blood tests for kidney, liver, and heart functions and a 24-hour urine test performed at home to evaluate the level of kidney involvement.

After the blood and urine tests, you may need imaging of certain organs to evaluate if amyloid is affecting them. These often include a chest X-ray to look for nodules in the lungs, an echocardiogram or cardiac MRI to evaluate the heart, and possibly a CT scan or ultrasound of the liver, kidneys, or lymph nodes. Patients with neurological symptoms may need additional testing of their muscles and nerves. These include electromyography and nerve conduction studies.

Your symptoms and your test results may indicate the need for a biopsy. Most patients require a biopsy of the bone marrow because it is the primary source of abnormal plasma cells. During the biopsy, a clinician will take a small sample of the bone and marrow, often from the hip area, to determine the concentration of plasma cells. These biopsies are also used to determine the results and the success of treatments. Your physician may also require an additional biopsy of and affected organ, heart, kidney, or liver, but not all patients require these.

SHOULD I SEEK A SECOND OPINION?

Although amyloidosis is a rare disease, clinical expertise has developed and expanded into amyloidosis treatment centers around the US and other parts of the world. Patients seeking a second opinion before starting treatment will find amyloidosis expertise in these treatment centers. Check with your insurance company about coverage of a second opinion.

ARC and other advocacy groups can help you locate centers that specialize in the diagnosis and treatment of AL amyloidosis.

Patients seeking a second opinion at another medical facility may need to repeat all or some of their previously performed tests. Ask your physician about your ability to transfer test results between sites.

MEDICAL ABBREVIATIONS YOU MIGHT ENCOUNTER

The language of diagnostics can be confusing or overwhelming. Don't let unfamiliar words or abbreviations get in the way of your understanding of AL amyloidosis and how it's diagnosed. Below is a brief checklist of abbreviations and terms you are likely to encounter. These and other terms are more fully defined in the Glossary on page 18.

SPEP – serum protein electrophoresis
IF – immunofixation electrophoresis
sFLC – serum free light chains
LFT – liver function tests
ECHO – echocardiogram or heart ultrasound
MRI – magnetic resonance imaging
IEM - Immunoelectron microscopy

GLOSSARY

AL amyloidosis. A progressive form of systemic amyloidosis caused by abnormal plasma cells that produce light chain proteins; these misfold into amyloid and circulate in the blood, building up deposits in multiple organs and tissues.

Alpha-helix shape. A coil of amino acid chain in a strong spiral shape.

Amyloid. An abnormal protein composed of peptides or peptide fragments with a β-pleated sheet shape at the molecular level.

Antibody. Protein produced by plasma cells that helps protect the body from infection and disease; also call immunoglobulin.

Autonomic nervous system. Regulates processes in the body's blood vessels, glands, and organs; works automatically, without a person's conscious effort, to control blood pressure, breathing, digestion, and other functions.

Beta pleated sheet. Polypeptide chains that have a wavelike appearance and run alongside each other.

Birefringence. The phenomenon shown by certain materials in which a ray of light is split into two rays (double refraction).

Blood urea nitrogen (BUN). A byproduct of protein metabolisms found in urine; high levels in the blood indicate decreased kidney function.

Bone marrow. Soft spongy tissue found in the center of many bones; the site of blood cell production.

Bone marrow biopsy. Removal by needle of a small sample of bone marrow for examination in a laboratory.

Cardiac magnetic resonance imaging (CMR). A diagnostic technique that uses harmless radio waves rather than x-rays to create images; currently the most accurate and reproducible technique for imaging the heart.

Cardiomyopathy. A type of progressive heart muscle disease in which the heart is abnormally enlarged, thickened, and/or stiffened.

Carpal tunnel syndrome. A common condition that causes pain, numbness, and tingling in the hand and arm; caused when one of the major nerves to the hand, the median nerve, is squeezed or compressed as it travels through the wrist.

Clinical trial. A study of the safety and effectiveness of a therapeutic agent in human subjects who have provided informed consent of potential risks and benefits.

Complete blood count (CBC). A blood test that measures the number of red blood cells, white blood cells, and platelets and the relative proportions of various white blood cells.

CT Scan. Computerized tomography is the use of computers and rotating X-ray machines to create cross-sectional images (slices) of the bones, blood vessels, and soft tissues inside your body; provides more-detailed information than standard X-rays.

Congo red. A histological staining technique that is the gold standard technique for the diagnosis of amyloidosis.

Creatinine. A product of energy metabolism normally filtered out of the blood and found in urine; elevated levels in the blood can indicate impaired kidney function.

Electrophoresis. A laboratory test used to measure the levels of protein in blood or urine; an electrical current is used to sort proteins by their charge.

Endomyocardial biopsy (EMB). A surgical procedure where a doctor takes a small sample of your heart muscle tissue for testing.

Fibrils. Long strands of normally soluble proteins that clump together to form insoluble fibers resistant to degradation.

Free light chain (FLC). Small molecules found in antibodies.

Immunofixation electrophoresis. A laboratory technique that allows the detection and typing of monoclonal antibodies or immunoglobulins in serum or urine; also called protein electrophoresis.

Immunoglobulin (Ig). A protein that helps protect the body from infection; also called an antibody.

Light chains. The shorter of two protein chains that make up an antibody, known as kappa or lambda.

Magnetic resonance imaging (MRI). A scanning technique that uses magnetic energy to create detailed images of bone and soft tissue.

Monoclonal blood cells. A group of cells produced from a single ancestral cell by repeated replication; also called clonal (clone) plasma cells.

Nerve conduction studies. Diagnostic tests used to evaluate the function, especially the ability to conduct electrical signals, of the motor and sensory nerves of the human body.

Nuclear imaging. A branch of medical imaging that uses small amounts of radioactive material to diagnose, determine the severity of, or treat a variety of diseases.

Peripheral neuropathy. Damage to or disease affecting nerves; may impair sensation, movement, gland or organ function, or other aspects of health.

Peripheral nervous system. The network of nerves that transmits information from your central nervous system (brain and spinal cord) to the rest of your body.

Plasma cell. An antibody-secreting immune cell that develops in bone marrow; in AL amyloidosis, these cells produce toxic light chain fragments that misfold into circulating amyloid.

Plasma cell dyscrasias. A diverse group of hematological (blood) diseases marked by an increased number of monoclonal bone marrow plasma cells that produce monoclonal immunoglobulins.

Platelets. Small cell fragments in the blood that enable it to clot.

Polyneuropathy. Damage that affects peripheral nerves (peripheral neuropathy) in roughly the same areas on both sides of the body; symptoms include weakness, numbness, and burning pain.

Proteins. Large, complex molecules coded by our genes that play a central role in biological processes. The work they do in cells is required to maintain the structure, function, and regulation of tissues and organs.

Red blood cell. Blood cell that carries oxygen throughout the body.

Scintigraphy. A nuclear diagnostic imaging technique in which a two-dimensional picture of internal body tissue is produced through the detection of radiation emitted by a radioactive substance administered into the body.

Troponin T and NT-proBNP (N-terminal-pro-brain natriuretic peptide). Biomarkers of heart function used to identify stress or strain in the heart.

Ultrasound. A medical test that uses high-frequency sound waves to capture live images from the inside of your body; also known as sonography.

White blood cell. A major cell type produced in bone marrow that attacks infection and cancer cells; they are part of the immune system.

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