AMYLOIDOSIS AWARENESS

For patients and their support network, including physicians, nurses and medical students

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Cover image: Amyloidosis often occurs in middle-age and older individuals, but also in patients in their 30s or 40s, and occasionally even younger.

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1. ONE MINUTE OVERVIEW

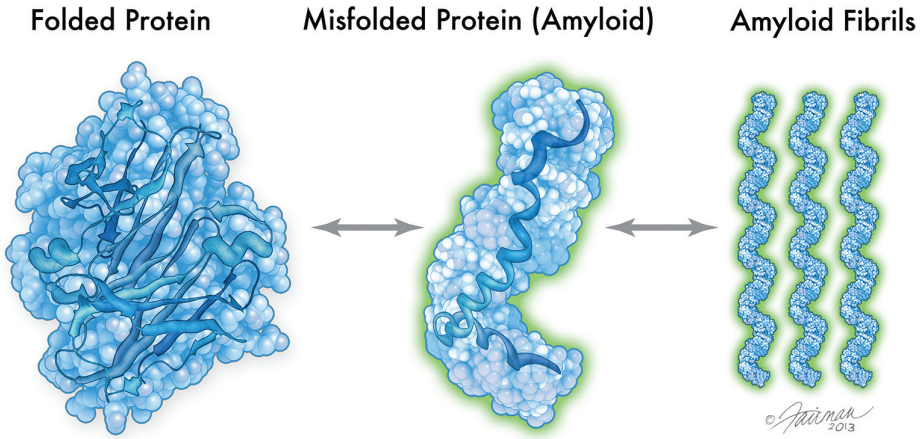
All of the normal proteins in our body are biodegradable and recyclable. Amyloidosis is a disease in which abnormal proteins (amyloid) are resistant to being broken down. As a consequence, the amyloid proteins deposit and accumulate in the body's tissues. If amyloid builds up in the kidney, heart, liver, gastrointestinal tract or nerves, it causes those organs to function poorly. Thus, the symptoms of amyloidosis are associated with the abnormal functioning of the organs involved. Typically, patients will have some of the following symptoms: unexplained weight loss, fatigue, shortness of breath, foamy urine, swelling in the ankles and legs, as well as numbness and tingling in the hands and feet. These are manifestations of damage to the underlying organs from the insoluble amyloid protein. Treatments are designed either to dissolve the amyloid deposits or to interrupt their production. Left untreated, the disease can be life-threatening. Therefore, early and accurate diagnosis is the key to promoting positive outcomes.

2. WHAT IS AMYLOIDOSIS?

Throughout our lifetime, our DNA is coding for the manufacture of small molecules called proteins. These proteins provide the structure and function for nearly all of life's biological processes. Enzymes that facilitate our cells' chemistry, hormones that affect our body's growth and regulation, and antibodies that form our immune response are all examples of proteins in action. Just about everything in our bodies – from the color of our eyes, to carrying oxygen in our blood, to whether we can digest milk – is determined by the proteins we make.

Once produced within the body, proteins will naturally fold into a particular shape. This natural form of a protein molecule is what allows for its specific function. Put simply, when proteins are folded properly, they work as they should, and we enjoy relatively good health. When proteins are misfolded, it affects our body's ability to function, and problems may arise over time.

Misfolded proteins can be produced because of genetic causes, or because of other factors related to chronic inflammation or increasing age. Regardless, our bodies are usually capable of identifying and removing these abnormal proteins. In some cases, though, we either produce too much of the abnormal proteins for our body to handle, or we are not able to break down and clean up the proteins at all. Such defects in protein production and processing are associated with many diseases.

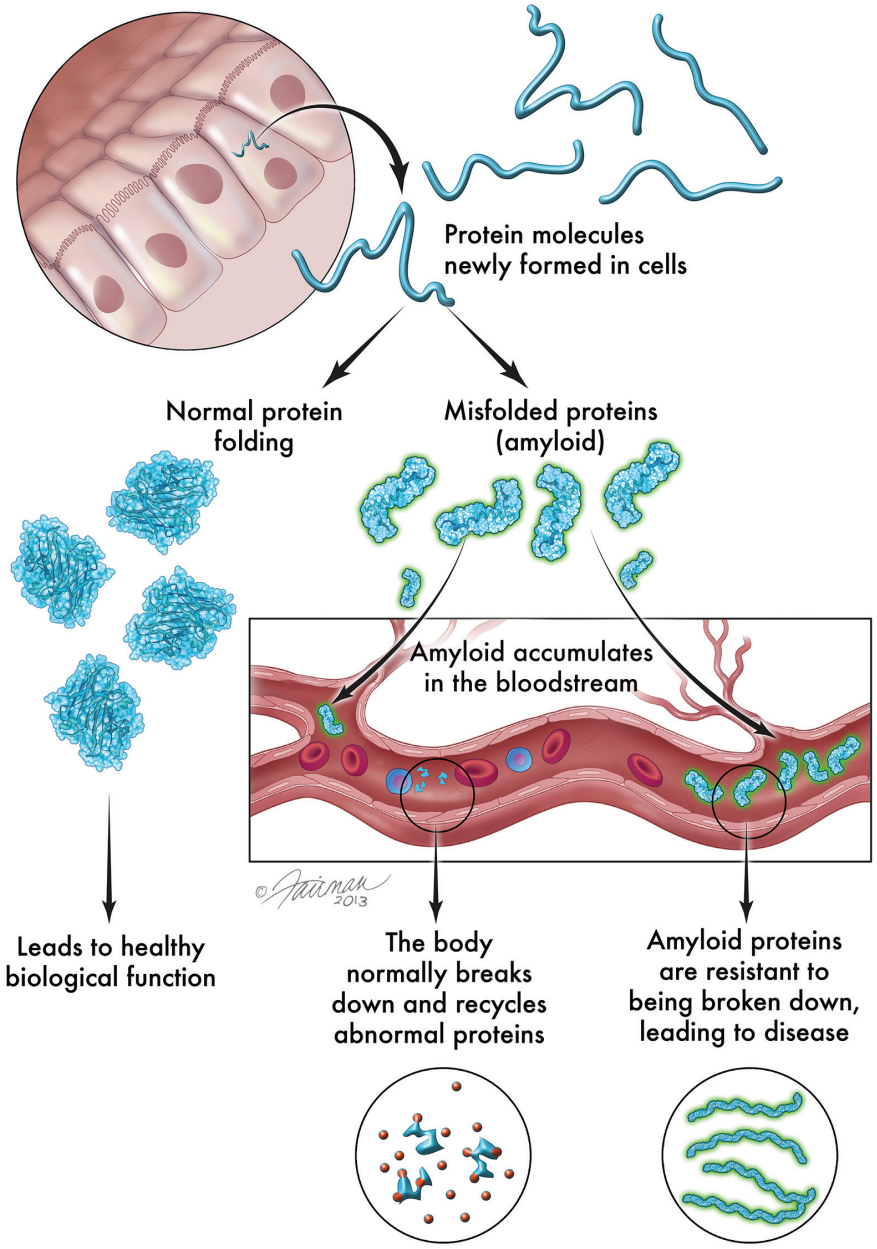


Amyloid is a starch-like substance caused by the misfolding of proteins. Amyloid binds together into rigid, linear fibers (fibrils) that deposit in the tissues and organs.

Broadly speaking, amyloidosis (pronounced 'am-uh-loy-*doh*-sis') is one class in a growing list of protein folding disorders. While there are many distinct types of amyloidosis, in all cases the misfolded proteins, called amyloid (meaning 'starch-like'), take on a particular shape that makes it difficult for the body to break down. Because of this misfolding, the amyloid proteins bind together to form rigid, linear fibers (or fibrils) that accumulate in our body's organs and tissues. Depending on where the amyloid builds up, such as in the kidney, heart and nerves, different symptoms and potentially life-threatening conditions become manifest.

While amyloidosis has been known since the 19th century, it is only within the last few decades that our understanding of it has matured. Presently, there are over 25 different proteins that have been identified as contributing to amyloidosis (the major forms of which are described in the next section). Additional types of precursor proteins that can lead to amyloid formation continue to be discovered through ongoing research.

Certainly, amyloidosis is a rare condition and often overlooked. Each year, an estimated 50,000 people worldwide will become afflicted with the disease, with more than 3,000 people being diagnosed in North America alone. This is about 1/5 of the incidence of multiple myeloma, and of similar incidence to that of Hodgkin's disease or chronic myelogenous leukemia. Because of its rarity, medical students



Misfolded proteins can be produced because of genetic causes, or because of other factors related to chronic inflammation or increasing age.

and physicians may not expect to see amyloidosis in their practice. Moreover, because the condition's nonspecific, ever-worsening symptoms (e.g., being tired or out of breath) may be mistaken for more common problems of lung and cardiovascular disease, it is very likely that the actual prevalence of amyloidosis is greater than now recognized.

It is imperative for clinicians and pathologists to consider amyloidosis as part of their differential diagnosis (discussed in section 4). Given the unique staining and spectroscopic properties of amyloid proteins, it is a simple matter to test for the disease. Early, accurate diagnosis is essential for patients to benefit from new treatments (discussed in section 5) that are available to improve and extend life.

3. TYPES OF AMYLOIDOSIS

There are many different proteins in our bodies that can become misfolded to produce amyloidosis. The predisposition to form abnormal proteins can be inherited from our parents, or even arise from DNA mutations acquired during our lifetime. In some instances, amyloidosis results from chronic inflammatory and infectious diseases, or long-term kidney dialysis. Most diagnosed cases, however, are caused by a bone marrow condition that has similarities with multiple myeloma.

As the amyloid proteins accumulate in our bloodstream, they ultimately deposit in organs and tissues. The resulting amyloid fibrils may impair multiple organ systems or localize in one area of the body. Amyloid will deposit most commonly in the kidney, heart and nerves, with the liver, spleen, gastrointestinal tract, and airways also occasionally affected. Amyloid is oftentimes found in the pancreas of people who develop diabetes as adults.

Although the precursor proteins that lead to amyloidosis come in various shapes and sizes, they all share the same misfolded structure as amyloid deposits. This unifying feature of amyloid, wherein a protein's normal alpha-helical shape misfolds into a beta-pleated sheet, allows for precise and timely diagnosis of the disease (discussed in the next section).

While the condition's symptoms and treatments depend on the organs affected, the several types of amyloidosis can be classified according to the precursor protein involved. As seen in Table 1 (next page), a convenient naming system is used, such that the prefix "A" refers to amyloid, followed by an abbreviation for the associated protein. For example, AL designates amyloid derived from light-chain antibodies; AA designates serum amyloid A protein; and ATTR designates amyloid from transthyretin.

As new amyloid proteins are characterized, and as our medical understanding deepens, it is possible to discuss the different types of amyloidosis from a wider perspective. Below is a brief description of AL amyloidosis; AA amyloidosis; familial amyloidosis; senile systemic amyloidosis; as well as ALECT2, dialysis-related, and localized amyloidosis.

AL Amyloidosis

AL (or primary) amyloidosis is the most commonly diagnosed form of the disease, accounting for 85% of all cases in developed countries. The disorder begins in the bone marrow, the soft tissue that fills the cavities of our bones, where red and white blood cells are formed. One kind of white blood cell, called plasma cells, produces antibodies that protect us from infections. These antibody proteins (immunoglobulins) are made up of light and heavy chain mol-

TYPE	SOURCE OF AMYLOID (Precursor Protein)	SYNDROME
AL, AH, ALH	**Plasma cells in the bone marrow** (Immunoglobulin light or heavy chains, or both)	Primary form of amyloidosis, similar to multiple myeloma, affecting the kidneys, heart, liver, gastrointestinal tract, and nerves.
AA	**Circulating inflammatory protein** (Serum amyloid A)	Secondary to chronic inflammatory and infectious diseases, affecting the kidneys and liver.
ALECT2	**White blood cells** (Leukocyte chemotactic factor 2)	Clinically resembles AL, affecting the kidneys and liver.
$A\beta_2M$	**Circulating serum protein** (β_2-microglobulin)	Dialysis-related, affecting the joints and tendons.
ATTR	**Mutant and wild-type protein produced in the liver** (Transthyretin)	Hereditary with over 100 mutations, affecting the nervous system, heart, and kidneys. The Val-122-Ile muta - tion is common in African Americans, causing cardiac disease. A non-hereditary, wild-type, senile form causes cardiac disease in the elderly.
AFib	**Mutant protein produced in the liver** (Fibrinogen A α-chain)	Hereditary, affecting the kidneys.
AApoAI	**Circulating serum protein** (Apolipoprotein AI)	Hereditary, affecting the liver, heart, kidneys, and nerves.
ALys	**Circulating serum protein** (Lysozyme)	Hereditary, affecting the gastrointesti - nal tract and kidneys.
AGel	**Circulating serum protein** (Gelsolin)	Hereditary, affecting the skin, nerves, and kidneys.
Localized	**Plasma cells in local tissues** (Immunoglobulin light chains)	Mostly occurs in the bladder, skin, and airways.

Table 1: Examples of amyloidosis. The naming system combines an "A" for amyloid with an abbreviation for the protein underlying the condition.

ecules. Normally, our plasma cells produce whole antibod-ies, and our body breaks down these proteins and recycles them after a short time. In AL, though, too many unas-sembled, misfolded light chains are being made. These "free light chains" (and, in rare cases, free heavy chains) cannot be broken down efficiently. They bind together to form amy-loid fibrils that build up in the extracellular space of organs and tissues. In this way, the body's normal functioning is impaired. Problems typically arise in the kidney, heart, liver, spleen, nerves, intestines, skin, tongue, and blood vessels.

AA Amyloidosis

AA (or secondary) amyloidosis results from increased levels of the circulating serum amyloid A protein. Serum amyloid A elevates in our blood as a natural response to infection and inflammation. In general, if a patient has an infection or inflammatory condition for six months or more, he or she is at risk for developing AA. The amyloidosis arises secondary to chronic inflammatory and infectious conditions, including: rheumatic disease, inflammatory bowel disease, tubercu-losis, osteomyelitis, lupus, and hereditary fever syndromes such as familial Mediterranean fever. Amyloid deposition usually begins in the kidneys, but the liver, spleen, lymph nodes, and intestines are also commonly affected.

Familial Amyloidosis

Familial (or hereditary) amyloidosis, as the name implies, is a heritable form of the disease. Whether a mutation has occurred in one's own DNA, or was inherited from one's parents, the most common form of familial amyloidosis is associated with a mutant transthyretin (TTR) protein produced in the liver. TTR is a protein that helps to transport thyroxine (a thyroid hormone) and retinol (vitamin A) around the body. There are over 100 known mutations of TTR that cause the protein to become unstable and misfold into amyloid. Various organs are affected, especially the nervous system and heart, with symptoms occurring in mid- to late life. If the nerves are primarily affected, the condition is known as familial amyloid polyneuropathy; if the heart is primarily affected, it is known as familial amyloid cardiomyopathy.

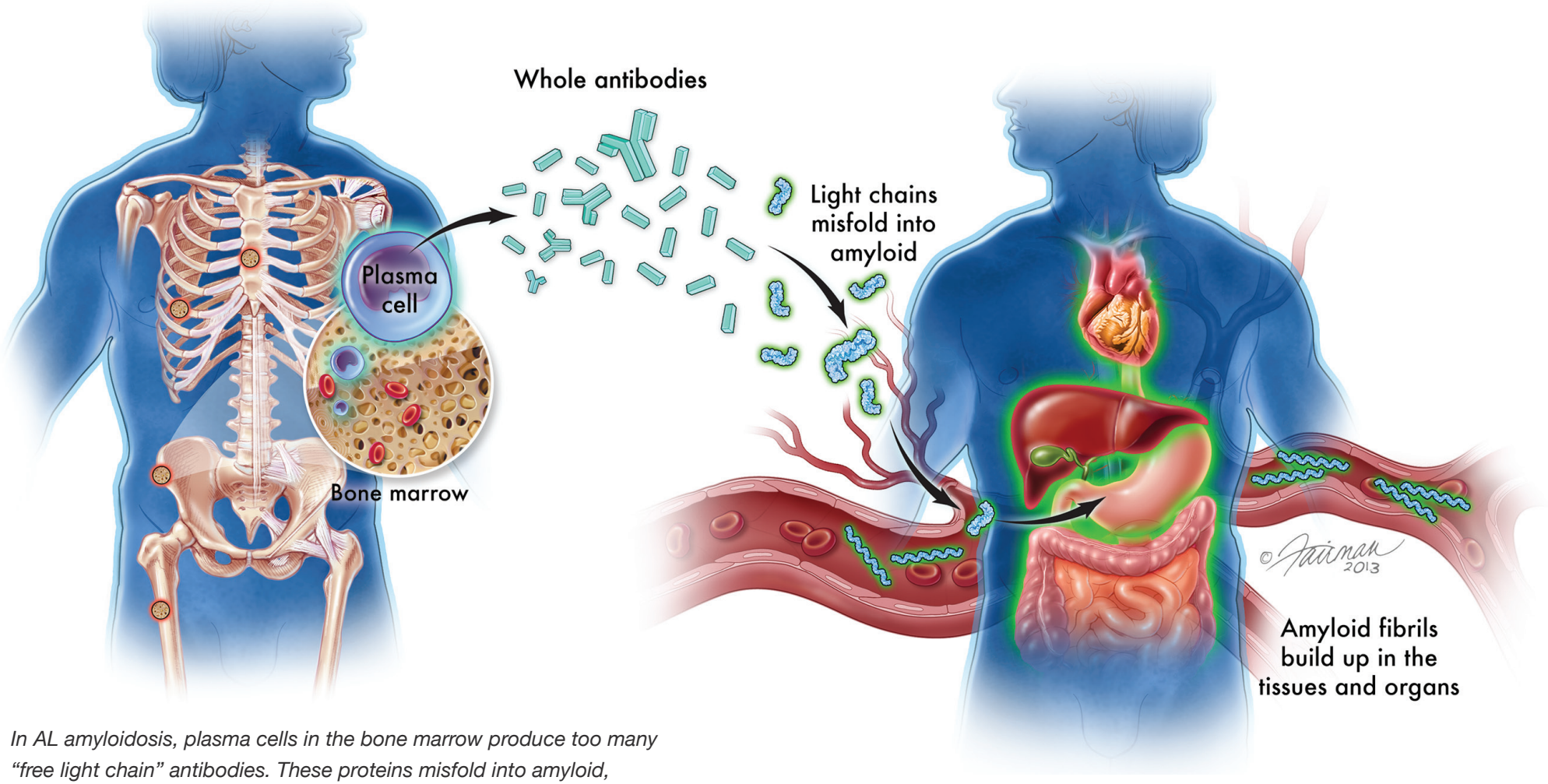
The most common known mutation of TTR is called Val-30-Met, causing nerve damage and electrical problems with the heart. Another common mutation in the United States is Thr-60-Ala which causes thickening of the heart muscle. While transthyretin-mediated amyloidosis (ATTR) occurs in families of nearly every ethnicity, there is one TTR variant, Val-122-Ile, that appears to be common in the African-American population. It is estimated that 4% of African Americans carry this mutant gene, comprising upwards of 25% of African American patients with amyloidosis. This mutation may be an often unrecognized cause of cardiac disease in African Americans.

In addition to ATTR, there are other gene mutations for different proteins that lead to amyloidosis. Though very rare, some of these include: AFib (from fibrinogen A α-chain); AApoAI (from apolipoprotein AI); ALys (from lysozyme); and AGel (from gelsolin).

Senile Systemic Amyloidosis

Senile systemic (or age-related) amyloidosis is a late onset disease that is acquired, not inherited. Amyloid deposits accumulate in the body from normal (wild-type) proteins. The best known example of senile systemic amyloidosis arises from the buildup of wild-type transthyretin (TTR) in the hearts of the elderly. Unlike familial amyloidosis, there are no mutations of the TTR gene, but the slowly progressive cardiac disease has similar symptoms. Whether mutant or wild-type, TTR-mediated amyloidosis is thought to be more common than AL amyloidosis, though it often goes undiagnosed. For example, wild-type TTR is found in up to 30% of patients showing clinical "heart failure with preserved ejection fraction."

Other examples of senile amyloidosis include: APro (from prolactin); ACal (from calcitonin); AIAPP (from amylin); and AANF (from atrial natriuretic factor). All are derived from the misfolding of wild-type proteins. Despite its name, this condition has no relationship to senility or dementia.



In AL amyloidosis, plasma cells in the bone marrow produce too many "free light chain" antibodies. These proteins misfold into amyloid, accumulate in the blood, and deposit in many organ systems.

ALECT2 Amyloidosis

One of the most recent additions to the class of amyloid proteins is ALECT2, derived from a protein made by white blood cells (leukocytes). As part of ongoing research, it has yet to be determined whether ALECT2 is the result of genetic mutations; however, the effect of the disease closely resembles that of AL, often affecting the kidneys. Because

amyloid deposits can result from normal (wild-type) proteins, as with senile systemic amyloidosis, this form of the disease may be mis- or underdiagnosed. One study, in fact, suggested that ALECT2 was the most common, undiagnosed type of amyloid, especially among patients of Mexican heritage. In an analysis of amyloid-containing kidney specimens over the last 8 years, ALECT2 was the third most common type (2.5%), as compared to AL (86%), AA (7%) and ATTR (1.4%).

$A\beta_2M$ Amyloidosis

$A\beta_2M$ (or dialysis-related) amyloidosis often occurs in patients suffering from kidney failure who have been on dialysis for many years. A circulating serum protein, beta-2 microglobulin (β_2M), accumulates in the blood because it is unable to cross through the dialysis filter. Because β_2M cannot be excreted from the body, the resulting amyloid builds up in tissues, particularly in the joints and tendons. This causes pain, stiffness and fluid in the joints, as well as carpal tunnel syndrome.

Localized Amyloidosis

Though the major forms of amyloidosis are described above, it is important to recognize that amyloid deposits may occasionally occur in isolated areas without evidence of a systemic disease. These localized, tumor-like deposits most often occur in the bladder and airways (e.g., trachea or lungs). Deposits have also been diagnosed in the eye, gastrointestinal tract, skin, and breast. Similar to AL amyloidosis, the localized amyloid deposits are made up of light chain proteins. However, in localized amyloidosis, the abnormal plasma cells producing the amyloid light chains are in the affected tissues, not in the bone marrow.

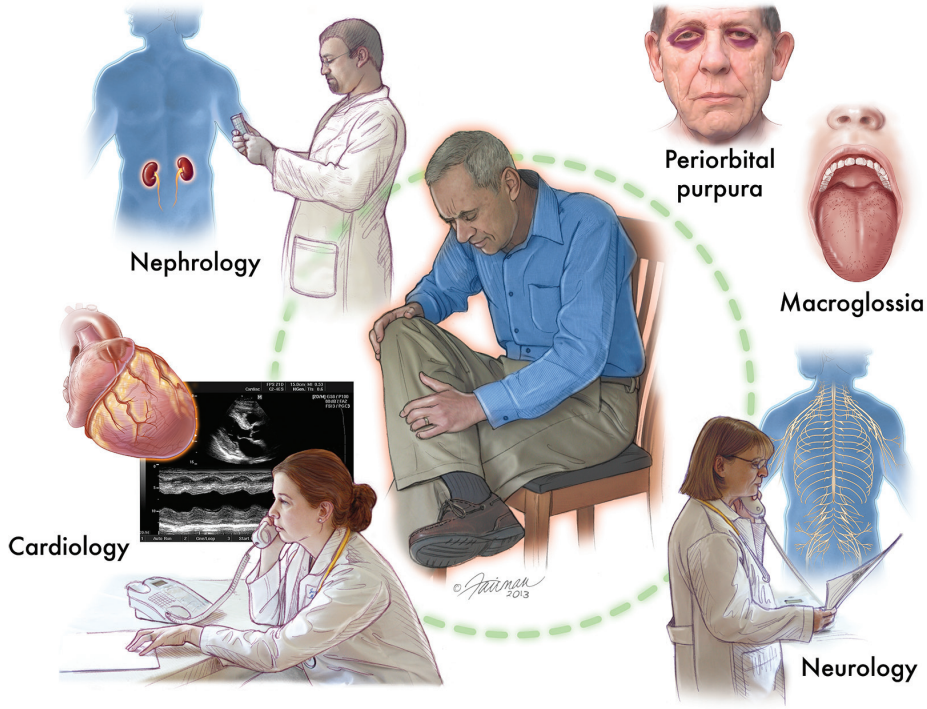
Other non-systemic types of amyloidosis are associated with hormone proteins, aging, or specific areas of the body. One special case of localized amyloidosis is cerebral amyloid angiopathy (CAA). While the cause is still unknown, in some individuals CAA may be hereditary. Amyloid protein deposits in the walls of the brain's arteries, increasing the risk of stroke and dementia. This neurological condition is mostly seen in older patients, and it is unrelated to Alzheimer's disease.

4. DIAGNOSIS

In some sense, amyloidosis is not easy to recognize. Its symptoms are vague and nonspecific, often mimicking those of other common conditions. For instance, shortness of breath can be an indicator of heart disease, which is usually caused by atherosclerosis and coronary artery disease. One would not initially think of amyloidosis. Also, protein in the urine is an early sign of kidney disease, as in patients with diabetes, but again, one does not normally think of amyloidosis.

Amyloidosis typically appears in middle-age and older individuals, but it can also occur during one's 30s or 40s, and occasionally even younger. Amyloid deposits can cause weight loss, fatigue, shortness of breath, dizziness upon standing, swelling in the ankles and legs, numbness and tingling in the hands and feet, foamy urine, alternating bouts of constipation and diarrhea, and feeling full quickly after eating. Also, if a patient bruises easily, especially around the eyes (periorbital purpura), or has an enlarged tongue (macroglossia), amyloidosis is very likely the underlying cause.

As a constellation of symptoms persists and worsens, many physicians do not consider (or remember) to look for such a rare, insidious disease. It is not uncommon for an individual to see several physicians before a biopsy (tissue sample) is taken, or to develop organ failure before a proper diagnosis



Symptoms are often vague, mimicking those of other common conditions. Therefore, a multidisciplinary approach among physician specialists is essential for diagnosis. In some cases, telltale signs of amyloidosis are an enlarged tongue (macroglossia) or bruising around the eyes (periorbital purpura).

is made. Indeed, if pathologists are waiting for clinical information to look for amyloidosis, they will miss the majority of cases.

While amyloidosis can affect just a single organ, it often causes systemic problems (i.e., affects more than one organ system). The organs most often involved are the kidneys (about 70% of patients), heart (50%), nervous system (30%),

and gastrointestinal tract. Therefore, in patients with combinations of kidney, heart, nerve, gastrointestinal or liver disease – with no obvious cause – it should prompt physicians to test for amyloidosis.

As part of the differential diagnosis (i.e., the process of distinguishing one disease from another), the four most common clinical settings in which amyloidosis should be considered are:

1. Loss of massive amounts of protein in the urine (proteinuria)
2. Stiff or thickened heart (restrictive cardiomyopathy) as seen on echocardiogram; low voltage seen on electrocardiogram; irregular heartbeat (arrhythmia) that is resistant to conventional treatment, often associated with normal or low blood pressure; or unexplained heart failure
3. Enlarged liver (hepatomegaly) without alcohol consumption or other explanation, often with abnormal liver blood tests
4. Numbness or pain in the fingers or toes (peripheral neuropathy), such as carpal tunnel syndrome, or alternating bouts of constipation and diarrhea (autonomic neuropathy), while also feeling light-headed (low blood pressure) when standing up.

Testing for Amyloidosis

Once amyloidosis is suspected, it can usually be identified, if present, with a very simple office procedure. Early detection and accurate evaluation are essential for patients to benefit from the many therapies now available (discussed in the next section).

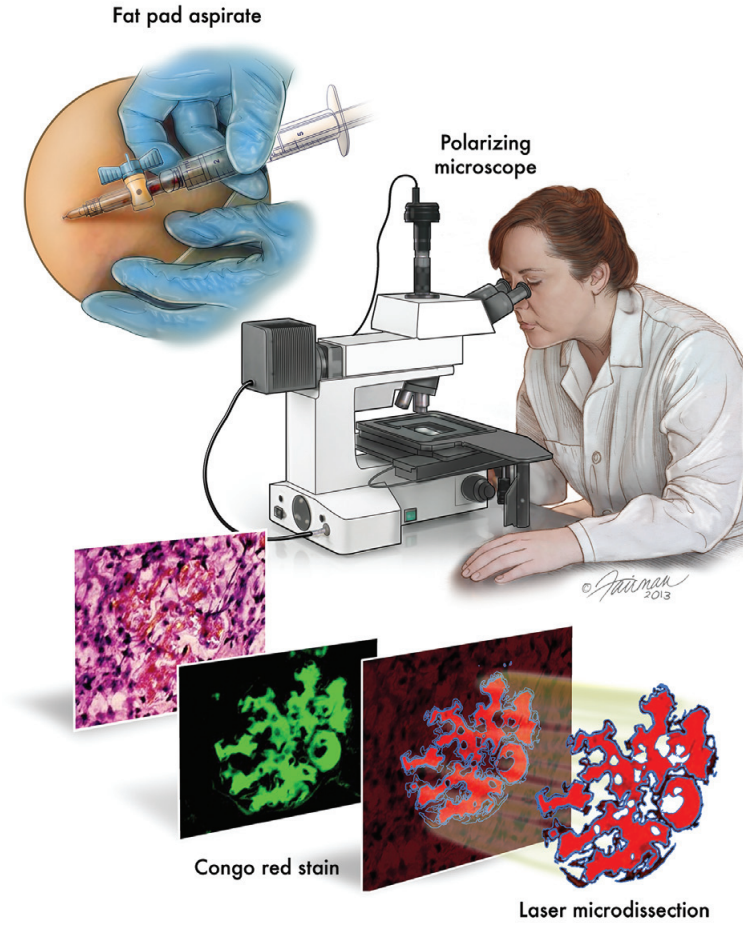
Blood and urine tests may reveal an abnormal protein in the body, but the gold standard for detecting amyloid deposits is to employ Congo red staining on a tissue sample. Biopsies can be taken from the gums, nerves, kidney, liver, or rectum. However, the easiest way to get a tissue sample is to aspirate fat from the abdomen. In this non-invasive procedure, the skin of the belly is numbed with a local anesthetic, and a needle is used to perform a mini-liposuction of fat cells from under the skin. Because of the common misfolded structure of all amyloid, it has a pink color when dyed with Congo red in the laboratory, and a characteristic apple-green birefringence when viewed with a polarizing microscope. This signature technique is able to diagnose amyloidosis in 70-80% of patients.

If the fat pad aspirate is negative for amyloidosis, but suspicion of the disease is high, a direct biopsy of the involved organ (e.g., the heart, kidney, or liver) should be done. If amyloid is present, the use of Congo red staining will yield a definitive diagnosis in nearly 100% of cases.

Immunohistochemistry must be performed and interpreted with caution. It is important to avoid over-staining the tissue sample with Congo red, as this may give false results. Visualizing the tissue with an electron microscope will show the classic structure of amyloid fibrils, thus confirming its presence.

Typing the Amyloidosis

Whether amyloid is found in the tissue biopsy or the results are inconclusive, it is recommended to contact specialized amyloidosis centers (see section 6) using more sophisticated methods. Proving that amyloid is present in an organ is only the beginning of the process. Now it must be determined what kind of amyloid is causing the disease in order to plan for an appropriate, individualized treatment.



The gold standard for detecting amyloidosis uses Congo red stain on a tissue sample, which appears apple-green when viewed with a polarizing microscope. Laser microdissection followed by mass spectrometry can determine the type of amyloid in virtually 100% of cases.

In all cases, identifying the amyloid type must be based on evaluation of the abnormal proteins deposited in the affected tissues. A simple blood test to measure the abnormal production of serum free light chains will show disproportionately elevated levels in roughly 98% of patients with AL (or primary) amyloidosis. Subsequently, a bone marrow biopsy, with appropriate immunohistochemical staining or flow cytometry analysis, will demonstrate a clonal population of plasma cells in most patients, which are producing the defective antibody light chains. If these tests are negative, a hereditary form of the disease should be investigated. Molecular and genetic testing can be performed on blood samples to see if the patient has any of the familial types of amyloid (e.g., TTR, fibrinogen, lysozyme, apolipoproteins AI and AII, and gelsolin). If one has such a mutation, then his or her children will have a 50% chance of inheriting it.

It should be emphasized that the presence of a genetic mutation does not always correlate with the type of amyloidosis. For example, a patient can have AL amyloidosis while also carrying a genetic variant that is not the cause of their disease. For this reason, the unequivocal identification of the amyloid protein must be made in concert with other diagnostic techniques. (Please note: In the United States,

the Genetic Information Nondiscrimination Act legislates that patients who have a hereditary disposition for diseases, such as amyloidosis, cannot be discriminated against with respect to employment or health insurance.)

For patients with chronic inflammatory or infectious conditions, or long-term kidney dialysis, blood tests will suggest the presence of AA or $A\beta_2M$ amyloidosis. If a patient is older than 50 years and presenting with congestive heart failure, or signs of dementia or stroke, a physician should consider clinically isolated types of the disease such as senile systemic amyloidosis (SSA) or cerebral amyloid angiopathy (CAA), as evidenced in echocardiograms and magnetic resonance imaging.

Meanwhile, recent advances in the field of proteomics promise to revolutionize the precise diagnosis of amyloidosis. Proteomics involves the study of the entire complement of proteins in an organism or environment. Unlike standard immunochemistry techniques, which can be limited in their availability, specificity, and sensitivity, proteomics can identify any protein – with or without genetic mutations – in one single test. This provides huge time- and cost savings in accurately identifying amyloid proteins from available tissue samples.

Thus, laser microdissection followed by mass spectrometry (LMD-MS) is the premier technique in typing amyloidosis. To perform the test, Congo-red positive samples are dis-

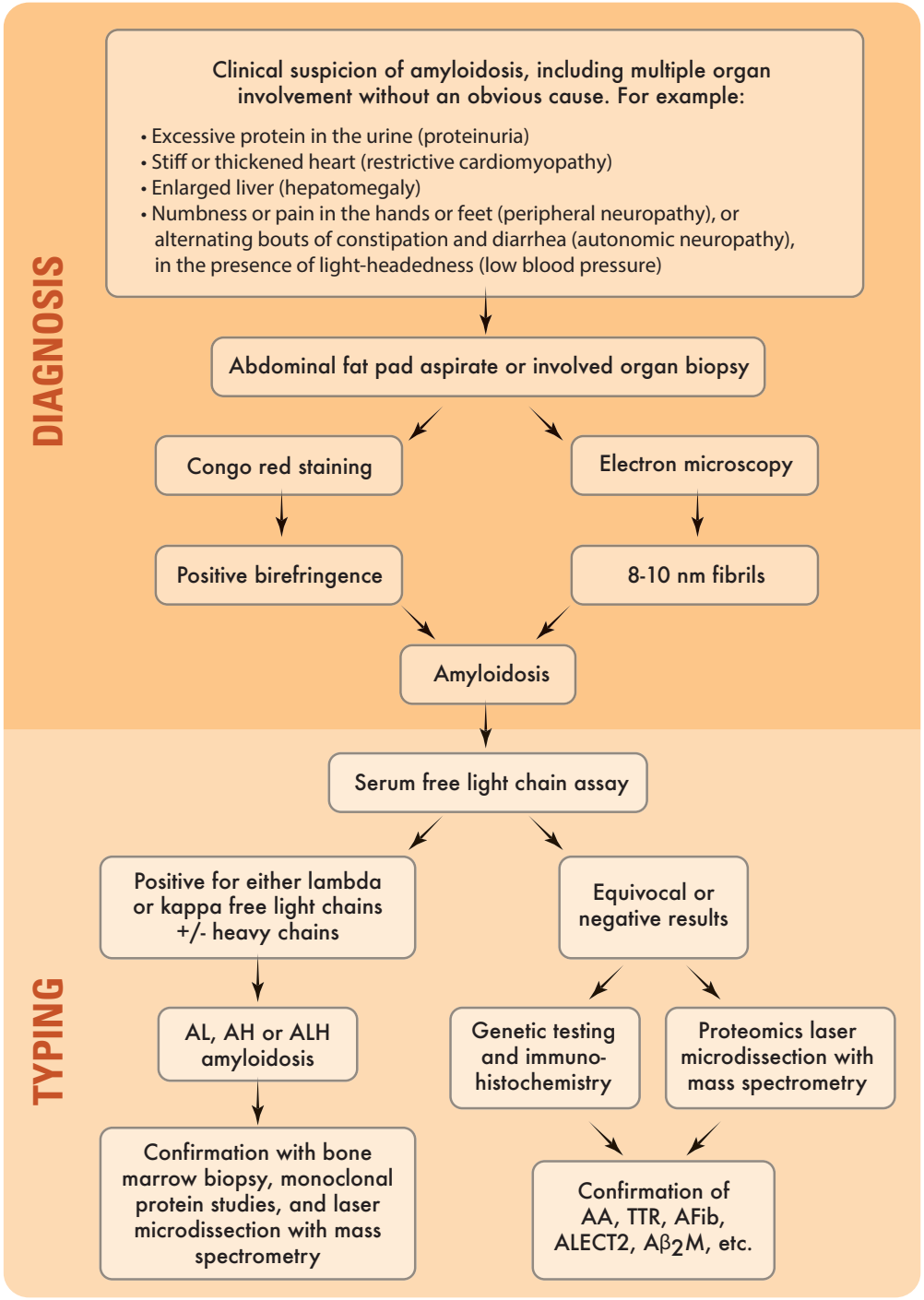


Table 2: Diagnosis flowchart. A general workflow for detecting amyloidosis and determining what type of amyloid is underlying the condition.

sected and broken down into smaller components of protein molecules (called peptides). The peptides are then analyzed using a process known as "liquid chromatography electrospray tandem mass spectrometry." LMD-MS can be performed on any tissue samples, including a fat pad aspirate if amyloid is present. Studies have shown that LMD-MS has the capability to identify all known amyloid proteins with virtually 100% accuracy, as well as the ability to characterize new ones. Regardless of a patient's symptoms, no previous clinical knowledge is necessary in typing the amyloidosis with LMD-MS.

While certain forms of amyloidosis often are underdiagnosed – such as the TTR variant, Val-122-Ile, that causes cardiac disease in African Americans, and the wild-type ALECT2 protein that causes kidney disease in patients of Mexican heritage – with LMD-MS this no longer has to be the case.

In summary, amyloidosis affects individuals of various ages and ethnicities, and the risk of developing the disease is greater in people who:

- Are 50 years and older
- Have a chronic infection or inflammatory disease
- Have a family history of amyloidosis
- Have multiple myeloma (about 10% of patients with multiple myeloma also develop amyloidosis)
- Have a kidney disease that requires dialysis for several years.

5. TREATMENTS

Some physicians used to assume that nothing could be done for a patient with amyloidosis. This is simply not true, especially as treatments have become more effective. Eventually, as therapies continue to develop and refine, amyloidosis will be little more than a treatable nuisance.

Working with a team of physicians – including hematologists, cardiologists, nephrologists and neurologists, among others – it is important to get a conclusive, accurate diagnosis of the disease as soon as possible. The treatments available depend on the type of amyloidosis and the organs affected, as well as on the patient's condition, age, and personal preference. If not treated in a timely manner, amyloid deposits will continue to damage tissues until organ failure, and possibly death.

Treatment of amyloidosis is a two-part process: (1) Manage symptoms to promote the patient's well-being, quality of life, and survival; and (2) Eliminate the supply of amyloid protein to improve organ function.

There are three general approaches to disrupt the formation and deposition of amyloid protein, which vary according to the type of amyloidosis. The most common treatment interferes with the production of the precursor protein leading to the disease. A second method uses drug therapy to stabi-

lize the normal structure of the precursor protein, thus preventing it from misfolding into amyloid. A third strategy is to target amyloid deposits directly, by destabilizing the amyloid fibrils so they can no longer remain misfolded.

All therapies have side effects, and one's doctors will be sure to recommend the best options. In many cases, if the source of abnormal protein is removed, existing amyloid deposits can be reabsorbed with time, and organ function can be restored.

AL Amyloidosis

For AL (or primary) amyloidosis, the most commonly diagnosed form of the disease, extensive organ involvement is usual. Without treatment, the average survival rate is about 12-18 months, and only about 6 months for patients with severely impaired heart function.

Chemotherapy, either orally or intravenously, forms the cornerstone of treatment for AL amyloidosis. The goal is to interrupt the growth of plasma cells producing the abnormal light-chain antibody proteins. For a number of years, therapies using melphalan (also known as Alkeran) or cyclophosphamide (Cytoxan) have been the treatment of choice. Newer drugs that are used in treating multiple myeloma, such as bortezomib (Velcade), lenalidomide (Revlimid) or carfilzomib (Kyprolis), also have proved effective. These therapies are often used in combination with dexamethasone, a steroid to help with the immune response. Undergoing chemotherapy may have side effects such as nausea, vomiting, hair loss, infection and extreme fatigue. If the side effects interfere with one's quality of life, different regimens may be available.

In carefully selected patients, chemotherapy is combined with stem cell transplantation. Stem cells are found in the bone marrow, and they develop into several kinds of blood cells, including our plasma cells. Once the plasma cells are destroyed using high doses of chemotherapy, the bone marrow is replenished with fresh stem cells from a patient's own body (autologous transplant). With eradication of the faulty plasma cells, amyloid production is slowed or stopped, and the bone marrow can become healthy again.

Chemotherapy followed by stem cell transplantation often achieves an excellent response, with significant improvement or stabilization of organ function. However, not all patients can tolerate this aggressive regimen, particularly those with advanced heart problems. Given the complexity of the disease, it is recommended that treatment be performed in a medical center which has experience with amyloidosis (see the next section). Alternatively, patients can have an initial evaluation at such a center, with continued communication during treatment in his or her local community.

Another medicine being developed aims to target directly the light-chain amyloid deposits which have accumulated in the body. Currently in clinical trials, this treatment uses

small molecules called monoclonal antibodies to find and attach specifically to the misfolded proteins of the amyloid fibrils. The monoclonal antibodies mimic the antibodies that our immune system naturally produces to protect us from disease. By targeting and destabilizing the amyloid deposits in this way, one's body can potentially identify and remove them more effectively. In the coming years, this promising drug may fulfill the final, missing piece of the treatment puzzle in helping to restore organ function and overall health.

AA Amyloidosis

AA (or secondary) amyloidosis is the second most common form of the disease worldwide. With its associated chronic inflammatory diseases (e.g., rheumatoid arthritis, Crohn's disease, and familial Mediterranean fever), amyloid deposition is very gradual. The survival rate is often more than 10 years, particularly with treatment for kidney disease. In contrast, untreated infections such as osteomyelitis or tuberculosis can cause a quicker accumulation of amyloid.

In all cases, the mainstay of therapy is to address the underlying infection or inflammatory condition. This can slow or stop the progressive buildup of amyloid by reducing the circulating precursor protein, serum amyloid A.

Moreover, an oral drug called eprodisate (Kiacta) has been found to inhibit the formation of amyloid fibrils. Kiacta prevents serum amyloid A from interacting with other molecules

that facilitate its misfolding into amyloid. Clinical trials have shown that, because the amyloid can no longer be formed and deposited, this treatment can effectively slow or stop the deterioration of kidney function. It is anticipated that Kiacta will be approved for widespread use in the next few years, following the confirmation of its efficacy through international studies.

For those patients with renal failure, dialysis and kidney transplantation are possible treatments. However, as with kidney transplants for AL amyloidosis, if the source of the abnormal protein is not addressed, amyloid may eventually appear in the donor kidney.

ATTR Amyloidosis

In TTR-mediated familial (or hereditary) amyloidosis, the heart and nervous system are most commonly affected. Without intervention, the survival rate ranges between 5-15 years from the onset of the disease.

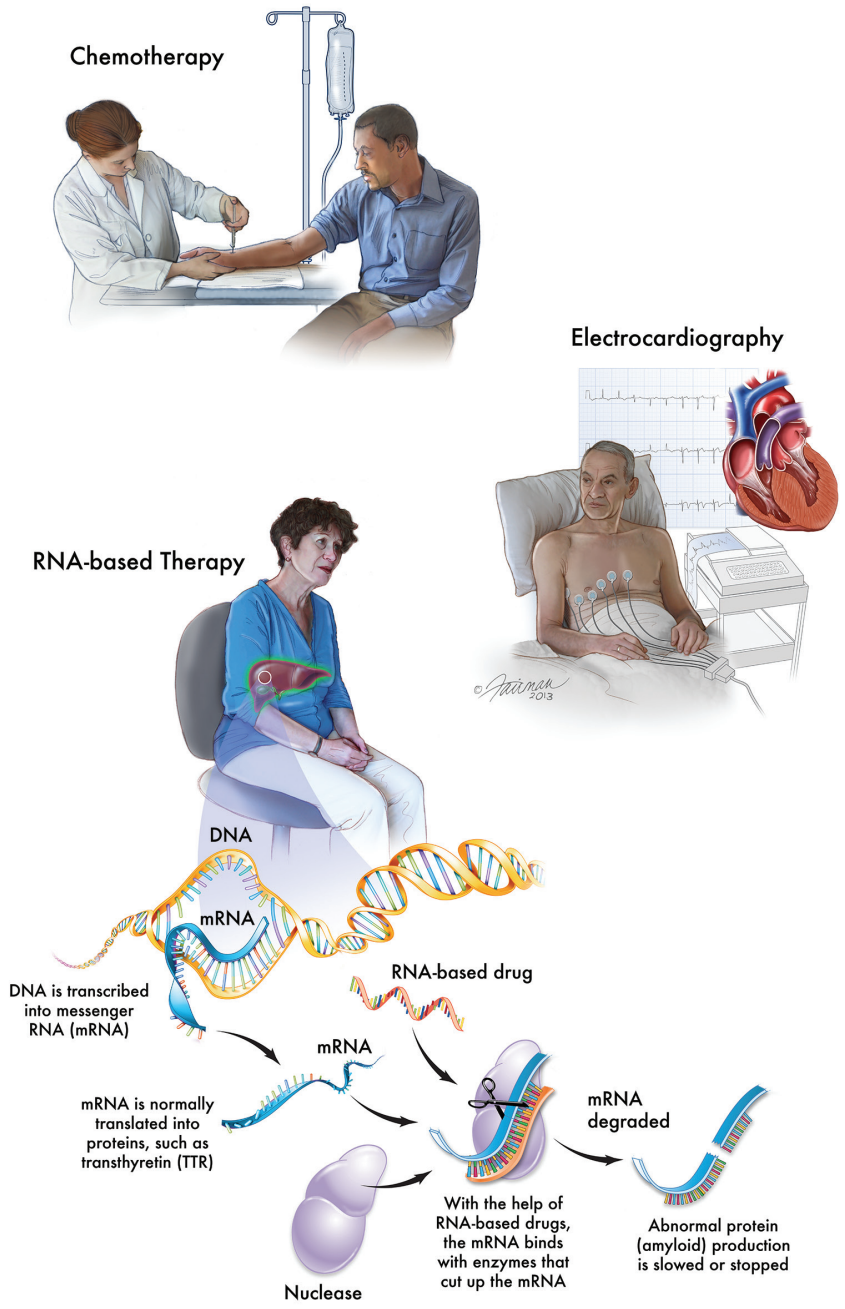
Since most of the abnormal proteins are produced in the liver, transplanting the liver can allow for the production of normal TTR. Waiting periods for organ donation are frequently long, but transplantation is a viable option for some patients whose disease is not too far advanced.

Meanwhile, new drugs are being developed to prevent familial amyloid deposits from forming in the first place. As

with liver transplantation, evidence shows that by reducing the abnormal protein available to become amyloid, organ function can improve. Two such drugs that may prevent the mutant TTR from misfolding into amyloid are diflunisal and tafamidis. These small molecules bind to the precursor proteins and stabilize their structure, so that they do not form amyloid fibrils and accumulate in the body.

A separate class of drugs using “gene silencing” techniques heralds a revolution in ATTR treatment. These therapies utilize the body’s natural process for regulating gene expression. Very briefly, here is how it works. In our cells, the genes coding for proteins are transcribed from DNA into messenger RNA (mRNA) molecules. These mRNA are then translated by our cells’ machinery to produce all of the proteins that make life possible. With gene-silencing therapy, small RNA-like molecules are carried in the blood to the liver. Once in the cells, the RNA-based drugs are able to bind specifically with the mRNA that would produce TTR proteins. When the drugs bind with the target mRNA, special cellular enzymes (nucleases) will break down and recycle the mRNA. Therefore, TTR amyloid production could be slowed or stopped at the source.

Because gene regulation naturally occurs in all human cells, RNA-based drugs may provide a safe and effective means to directly prevent the production of abnormal TTR. Administered either intravenously or subcutaneously, initial studies indicate that there may be a rapid reduction in a patient’s levels of ATTR protein.



It is recommended to visit a medical center with expertise in amyloidosis. Depending on the type of amyloidosis, treatments may include chemotherapy, cardiac care, organ transplantation or targeted drug therapy.

Senile Systemic Amyloidosis

In senile systemic (or age-related) amyloidosis, therapy is largely supportive for a patient's cardiac disease. In some cases, heart transplantation may be done.

For TTR-mediated forms of senile amyloidosis, the same drug treatments used in familial amyloidosis (e.g., diflunisal, tafamidis or RNA-based drugs) may inhibit the production of TTR amyloid. This could help to extend life by preventing further amyloid formation and deposition in the heart muscle.

$A\beta_2M$ Amyloidosis

In $A\beta_2M$ (or dialysis-related) amyloidosis, kidney transplantation is considered the best therapeutic option. Low copper dialysis membranes may prevent or delay onset of the disease.

Localized Amyloidosis

For amyloid deposits that occur in isolated areas, such as the bladder or airways, radiation therapy can slow down the disease's progression. Surgical removal of the amyloid deposit may be appropriate once a systemic condition is ruled out. As with all forms of amyloidosis, patients are encouraged to have periodic checkups to monitor their condition.

For cerebral amyloid angiopathy (CAA) which affects the brain, there is no known effective treatment. The goal is to relieve symptoms. This can include medications that help to improve memory, such as those used to treat Alzheimer's disease. Seizures, sometimes called "amyloid spells," may be treated with anticonvulsants such as phenytoin (Dilantin) or carbamazepine (Tegretol). In some cases, speech and physical therapies are needed.

Treating the Symptoms of Amyloidosis

It is very important to treat not just the underlying causes of amyloidosis, but the symptoms of the disease as well. This will ensure a patient's quality of life and longevity.

Normal, everyday activities can be carried out as usual. However, if fatigue or shortness of breath occurs, it is necessary to rest. One should not exert him- or herself beyond what is recommended by their doctor.

For supportive treatments of the kidneys and heart, patients may need to take a diuretic drug to pass urine, as prescribed by their doctors; limit the amount of salt in their diet; or wear elastic stockings and elevate their legs to lessen the swelling. For the gastrointestinal tract, certain medications can help with diarrhea and constipation. In general, it may be useful to make some dietary changes to help relieve symptoms or maintain body weight.

As treatment progresses, damage to the nerves (neuropathy) can improve. It may take up to 12-24 months for the nerves to recover, but numbness and weakness can subside. Medications to alleviate pain may be taken orally or applied to the

skin. For discomfort, tingling or burning, the use of a warm-water foot massager for 15 minutes before bed can help with sleeping. The warm water and vibrations stimulate non-pain transmitting nerves, and block the pain-transmitting nerves.

Participating in Clinical Research

Clinical trials are research studies that test new ways to diagnose and treat disease. Such research is essential to improve our understanding of amyloidosis and to develop more effective therapies. The treatments that are available today were all developed and refined through this ongoing clinical research. Now patients can achieve durable, long-term remission of their disease, along with major organ system improvement.

For qualifying patients, there is an opportunity to participate in clinical trials. Whenever new treatments are tested, they are expected to be as good as or better than the standard treatments. All proposed clinical trials must be approved and overseen by an Institutional Review Board (IRB). The IRB is comprised of physicians, scientists, clergy and lay people. They are there to ensure the safety of the studies and the accuracy of the results.

The new treatments are evaluated in groups of people who meet certain requirements for the study. Participation in clinical trials is completely voluntary, and participating patients sign an informed consent form. It is also okay to withdraw from the trial at any time. In many cases, the cost of treatment may be covered as part of the study.

Being involved in clinical research potentially allows patients to benefit from new, experimental treatments before they are widely available. In the long run, this leads to improved medicines and therapies for everyone. To learn what clinical trials are currently recruiting, one may consult with the amyloidosis centers or visit ‘www.ClinicalTrials.gov’. As well, patients can search ‘www.PubMed.gov’ to find scientific, peer-reviewed articles.

Early and accurate diagnosis, along with an individualized treatment plan, are key to achieving positive outcomes for patients and families. With an extended support community of healthcare providers and peers, you are not alone.

6. MAJOR AMYLOIDOSIS CENTERS

There are many qualified physicians to help with diagnosis and treatment of amyloidosis. As patients, you are not alone. In the United States, please contact the Amyloidosis Support Groups for 24-hour help and guidance. The toll-free number is (866) 404-7539, or email 'info@amyloidosissupport.com'.

The following is a list of major research and treatment centers in the United States and internationally. Because amyloidosis varies with each case, the invaluable expertise of these centers will help to promote positive outcomes for patients and families.

U.S. Amyloidosis Centers

- Mayo Clinic (Rochester, MN) – www.mayoclinic.org/amyloidosis
- Boston University Amyloidosis Center (Boston, MA) – www.bu.edu/amyloid
- Brigham and Women's Hospital Cardiac Amyloidosis Program (Boston, MA) – www.brighamandwomens.org/cvcenter/amyloidosis
- Columbia Multidisciplinary Amyloidosis Program (New York City, NY) – www.nyp.org/services/amyloidosis-program-overview.html
- Memorial Sloan-Kettering Cancer Center (New York City, NY) – www.mskcc.org
- Mount Sinai Hospital (New York City, NY) – www.mountsinai.org/patient-care/health-library/diseases-and-conditions/amyloidosis
- Cedars-Sinai Multiple Myeloma & Amyloidosis Program (Los Angeles, CA) – www.cedars-sinai.edu/Patients/Programs-and-Services/Multiple-Myeloma-and-Amyloidosis-Program
- Stanford Amyloid Center (Stanford, CA) – www.stanfordhospital.org/cardiovascularhealth/amyloid
- Indiana University School of Medicine Amyloid Research Group (Indianapolis, IN) – www.iupui.edu/~amyloid/team.htm

International Amyloidosis Centers

- Center for the Study of Familial Amyloidosis (Rio de Janeiro, Brazil) – www.ceparm.com
- Center for the Study & Cure of Systemic Amyloidosis (Pavia, Italy) – www.amiloidosi.it
- Groningen Unit for Amyloidosis Research & Development (The Netherlands) – www.amyloid.nl
- National Centre for Amyloidosis (London, U.K.) – www.ucl.ac.uk/medicine/amyloidosis
- Princess Alexandra Hospital (Brisbane, Australia) – www.health.qld.gov.au/pahospital
- Westmead Hospital (Sydney, Australia) – www.wslhd.health.nsw.gov.au/Westmead-Hospital
- Kumamoto University Hospital (Kumamoto, Japan) – www.kuh.kumamoto-u.ac.jp
- Princess Margaret Cancer Centre (Toronto, Canada) – www.theprincessmargaret.ca

7. ONLINE RESOURCES

For more information, including local support meetings and a detailed list of regional doctors, please visit:

Amyloidosis Support Groups

www.AmyloidosisSupport.com

Other helpful resources include:

- Amyloidosis Foundation
  www.amyloidosis.org
- Amyloid Support Group U.K.
  www.amyloidsupportgroup.co.uk
- Canadian Amyloidosis Support Network
  www.thecasn.org
- Leukemia & Lymphoma Society
  www.lls.org
- National Organization for Rare Disorders
  www.rarediseases.org
- RareConnect
  www.rareconnect.org

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www.alnylam.com

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