

STATE-OF-THE-ART REVIEW

AL Amyloidosis for the Cardiologist and Oncologist

Epidemiology, Diagnosis, and Management



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ABSTRACT

AL amyloidosis results from clonal production of immunoglobulin light chains, most commonly arising from a clonal plasma cell disorder. Once considered a nearly uniformly fatal disease, prognosis has improved markedly over the past 15 years, predominantly because of advances in light chain suppressive therapies. Cardiac deposition of amyloid fibrils is common, and the severity of cardiac involvement remains the primary driver of prognosis. Improvements in chemotherapy/immunotherapy have prompted a reassessment of the role of advanced cardiac therapies previously considered contraindicated in most patients, including the role of implantable cardioverter-defibrillators and cardiac transplantation. This state-of-the-art review highlights the current state of the field, including diagnosis, prognosis, and hematologic- and cardiac-specific therapies. (J Am Coll Cardiol CardioOnc 2019;1:117-30) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

AL amyloidosis is an increasingly diagnosed disorder (1) involving deposition of misfolded proteins (monoclonal immunoglobulin light chains) in 1 or more tissues in the body (2). The disease can be localized or systemic, a nuisance or life-threatening, and requires specialized expertise to best diagnose and treat. Along with transthyretin amyloidosis (ATTR), AL amyloidosis represents 1 of the 2 most common forms of amyloidosis with frequent cardiac involvement. This article will review the clinical aspects of AL amyloidosis, including diagnosis, prognosis, and state-of-the-art treatment.

PATHOPHYSIOLOGY

Although a detailed discussion of the pathophysiology of the disease is beyond the scope of this

review, the basic principles underlying the mechanisms of injury are critical for understanding the disease and treatment goals. *Amyloidosis* refers to a group of diseases in which there is extracellular deposition of amyloid fibrils composed of precursor proteins that self-assemble in a β -sheet conformation (3). The “L” in AL amyloidosis refers to the dominant protein that is depositing in AL amyloid fibrils, a clonal immunoglobulin light chain (most commonly secreted by a clonal plasma cell disorder). Because the clonal light chains circulate in the bloodstream, they can theoretically deposit as amyloid fibrils in almost any organ in the body; therefore, most patients have multiorgan deposition, although in each individual with the disease, the pattern of organ involvement varies (3). When amyloid fibrils infiltrate the heart, deposition is most commonly diffusely

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ABBREVIATIONS AND ACRONYMS

ASCT = autologous stem cell transplantation

BNP = B-type natriuretic peptide

CyBorD = cyclophosphamide, bortezomib, and dexamethasone

FLC = free light chain

ICD = implantable cardioverter-defibrillator

MGUS = monoclonal gammopathy of undetermined significance

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SAP = serum amyloid P

SPIE = serum protein electrophoresis with immunofixation

UPIE = urine protein electrophoresis with immunofixation

present throughout the myocardium, with amyloid deposits surrounding each cardiomyocyte (Figure 1).

When amyloid fibrils deposit, they can cause organ dysfunction by multiple mechanisms. Disruption of organ architecture routinely occurs; for example, with cardiac amyloidosis, increased wall thickness (due to amyloid fibril infiltration) directly leads to small end-diastolic volumes and can be a contributor to poor stroke volume/cardiac output. However, the primary mechanism of injury is likely to be from direct cellular toxicity from amyloid precursors (4-6); therefore, cardiac amyloidosis due to AL amyloidosis has been termed a “toxic-infiltrative cardiomyopathy” (7). Organ injury and prognosis are dependent not only on cumulative amyloid fibril deposition but also on the type of fibril being deposited; this has been clearly demonstrated with worse prognosis in cardiac amyloidosis due to AL fibrils than ATTR fibrils, despite greater cumulative fibril deposition in most patients with ATTR amyloidosis (8-12). Therefore, preventing amyloid precursor/fibril deposition (e.g., by

lowering circulating pathologic light chains in AL amyloidosis) may have a greater therapeutic impact than removing already-formed amyloid deposits. Perhaps not surprisingly, prognosis has been mainly dependent on earlier diagnosis and the successful reduction of circulating pathologic light chains after diagnosis, with limited success achieved so far with strategies of amyloid fibril removal.

DIAGNOSIS

LOCALIZED VERSUS SYSTEMIC DISEASE. The fundamental characteristic required for AL amyloid deposition is the production of monoclonal immunoglobulin light chains. Most commonly, this occurs with the proliferation of a plasma cell clone in the bone marrow, with resultant secretion of monoclonal light chains (with or without secretion of monoclonal immunoglobulins) into the bloodstream (2). However, clonal light chain production can occur from other sources as well, including the following:

- Production by clonal B-lymphocytes in lymphoma
- Production by clonal plasma cells in a location outside of the bone marrow (plasmacytoma)
- Production by clonal plasma cells or B-lymphocytes within tissue, often in the setting of inflammation

If amyloid deposits are only found at the site of production itself (e.g., within a lymphoma/plasmacytoma),

HIGHLIGHTS

- Systemic light chain amyloidosis usually arises from a clonal plasma cell disorder.
- Cardiac involvement in light chain amyloidosis is common and is the main driver of prognosis.
- Improvements in light chain suppressive therapy have led to markedly improved outcomes over the past decade.
- With improved outcomes, implantable cardioverter-defibrillator placement and cardiac transplantation are likely appropriate for select patients.

this represents localized AL amyloidosis. If amyloid deposits are found in other organs after being secreted into the bloodstream, this represents systemic AL amyloidosis (Table 1).

Localized AL amyloid deposits are typically found either incidentally on a biopsy being performed for another reason (e.g., gastritis with severe inflammation and associated AL amyloid deposits) or because of localized symptoms (e.g., rash from skin deposition or voice changes from laryngeal deposition). Localized deposits typically require either no treatment or local excision for symptom relief (e.g., excision of laryngeal deposits leading to voice changes). Most patients with localized AL amyloidosis do not have evidence of a circulating clonal light chain or immunoglobulin on serum or urine testing, although abnormalities can be detected in 7% to 20% of patients (13,14). Clonal plasma cell or B-cell populations on bone marrow biopsy are less commonly seen, occurring in only 0% to 2% of patients in 2 large series (13,14). This article focuses primarily on systemic AL amyloidosis, which is both more commonly diagnosed and a much more medically serious disorder.

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE VERSUS MYELOMA VERSUS AL AMYLOIDOSIS. As noted previously, systemic AL amyloidosis most commonly arises from clonal light chains produced by a clonal plasma cell proliferation in the bone marrow. Because 2 other more common conditions (monoclonal gammopathy of undetermined significance [MGUS] and myeloma) also arise from clonal plasma cell proliferation, this can lead to confusion as to how the diseases relate to one another (Table 2).

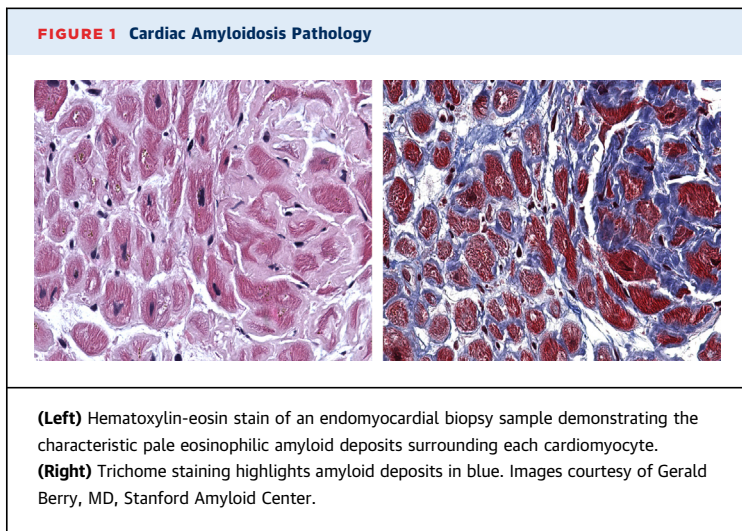
When a plasma cell clonally proliferates, it can cause illness in 2 distinct ways:

- The plasma cell clone itself can be proliferative, such that it occupies much of the marrow space (crowding out normal marrow), causing complications such as cytopenias, lytic bone lesions, or hypercalcemia.
- The plasma cell clone can produce monoclonal immunoglobulin and/or monoclonal light chains, which circulate in the bloodstream and cause damage.

Importantly, most plasma cell clones do not cause illness; frequently, the clone is not overly proliferative (taking over <10% of the marrow and not affecting the bone tissue), and the immunoglobulins and/or light chains are eliminated harmlessly in the urine. This scenario, called MGUS, is increasingly common as people age and itself does not require treatment (15,16). Although patients with MGUS should be monitored to make sure they do not develop myeloma or AL amyloidosis, most will never require treatment.

When the plasma cell clone is itself more malignant, proliferating to >10% of marrow cellularity, it is now called “myeloma.” Depending on whether or not the proliferation is causing certain laboratory abnormalities/organ dysfunction, it is considered “asymptomatic myeloma” (typically not requiring treatment) or “symptomatic myeloma” (typically requiring treatment). Traditionally, the criteria used to define symptomatic myeloma were the CRAB criteria (hyperCalcemia, Renal insufficiency, Anemia and lytic Bone lesions). However, more recently, additional myeloma-defining events have been identified including serum free light chain (FLC) ratio (involved:noninvolved light chain) ≥ 100 , clonal bone marrow plasma cells $\geq 60\%$, and lytic lesion detection by more sensitive imaging techniques (whole-body low-dose computed tomography, whole-body magnetic resonance imaging [MRI], or positron emission tomography/computed tomography) (17). For patients meeting these so-called “SLiM-CRAB criteria,” plasma cell-directed treatment is recommended (17).

Regardless of the local aggressiveness of the plasma cell clone, as long as it produces a monoclonal light chain, it is capable of causing AL amyloidosis. It is likely that the primary reason why one clone causes AL amyloidosis and another does not is the specific conformation of the light chain, which is different with every clone (and therefore in every patient with the disease). In particular, light chains that are more “kinetically unstable” (requiring less energy to transition from the native folded state to a transitional unfolded state) are more susceptible to endoproteolysis, resulting in the release and circulation of



amyloidogenic light chain fragments (18). If the light chain’s conformation is such that it is prone to misfold, AL amyloid deposits can occur, regardless of whether the light chain is produced in large quantities or if the plasma cell clone itself is particularly aggressive.

Because small clones are more common than large clones (e.g., MGUS is more common than myeloma) (15), it is common that patients with AL amyloidosis do not have concomitant myeloma, although nothing prevents the 2 from coexisting (because they both fundamentally arise from a clonal plasma cell population), and they do coexist in a sizable percentage of patients.

CLINICAL SUSPICION AND LABORATORY TESTING. AL amyloidosis is most commonly diagnosed when end-organ dysfunction prompts an evaluation. Ultimately, the diagnosis can only be made by biopsy, with the identification of extracellular amyloid

TABLE 1 Typical Characteristics of Localized Versus Systemic AL Amyloidosis*

	Localized	Systemic
SPIE or UPIE	Normal	Abnormal
Serum FLC ratio	Normal	Abnormal
Common locations for deposits	Skin, larynx, sites of chronic inflammation	Heart, kidneys, liver, GI tract, nerves
Bone marrow biopsy	Normal	Clonal plasma cell population
Presentation	Rash, voice change, incidental finding on biopsy	Vital organ dysfunction
Treatment	None, or localized treatment if symptoms	Systemic chemotherapy or immunotherapy

*Although these values represent the most common findings, patients with localized AL amyloidosis can have abnormal free light chain ratios or the presence of a monoclonal protein, and some patients with systemic AL amyloidosis can have normal SPIE, UPIE, or FLC.
 FLC = free light chain; GI = gastrointestinal; SPIE = serum protein electrophoresis with immunofixation; UPIE = urine protein electrophoresis with immunofixation.

TABLE 2 Spectrum of Clonal Plasma Cell Disorders

	MGUS	Asymptomatic Myeloma	Symptomatic Myeloma	AL Amyloidosis
How common is it?*	+++++++	+++++	+++	+
Typical clonal plasma cell percentage	<10%	10%-60%	>10%	Any
Typical concentration of paraprotein on SPIE/UIPE/serum FLC	Low	Moderate	High	Any
Treatment required?	No	No	Yes	Yes

*More + refers to being more common.
MGUS = monoclonal gammopathy of undetermined significance; other abbreviations as in Table 1.

deposits that are subtyped by either immunohistochemistry or mass spectrometry as arising from the deposition of monoclonal kappa or lambda light chains (19,20). Therefore, clinical presentation depends on which organs have significant organ deposition (Table 3).

Multiple clues can exist that should raise suspicion of a diagnosis of cardiac amyloidosis. Besides clues on imaging or electrocardiography (discussed later), clinical/laboratory clues include the following:

1. Persistently elevated cardiac-specific troponin or multiple presentations with elevated cardiac troponin without adequate explanation on coronary angiography
2. Heart failure combined with other characteristic organ findings (e.g., macroglossia, nephrotic syndrome, elevated alkaline phosphatase, or dysphagia)
3. Unexplained heart block, atrial arrhythmias, or ventricular arrhythmias in a patient with increased ventricular wall thickness

TABLE 3 Common Organ Involvement of Systemic AL Amyloidosis With Associated Symptoms/Laboratory Abnormalities

	Signs/Symptoms	Laboratory/Imaging Abnormalities
Heart	Diastolic > systolic dysfunction Arrhythmias (tachy/brady)	Increased wall thickness EKG abnormalities (low voltages, Q waves) Elevated troponin Elevated BNP/NT-proBNP
Kidneys	Edema	Albuminuria/hypoalbuminemia GFR reduction
Gastrointestinal tract	Dysphagia Macroglossia Diarrhea Constipation GI bleeding	
Liver	Hepatomegaly	Elevated alkaline phosphatase
Nervous system	Peripheral neuropathy Autonomic dysfunction Carpal tunnel syndrome (especially bilateral)*	
Lungs	Dyspnea	Pleural effusions, pulmonary nodules/infiltrates

*Carpal tunnel syndrome commonly occurs from soft tissue deposits within the carpal tunnel space, rather than from direct nerve infiltration.
AL = light chain; BNP = B-type natriuretic peptide; EKG = electrocardiographic; GFR = glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

If AL amyloidosis is suspected, laboratory testing should be initiated to evaluate for both monoclonal protein production and evidence of vital organ infiltration/dysfunction (Table 4). The combination of normal serum protein electrophoresis with immunofixation (SPIE), normal urine protein electrophoresis with immunofixation (UIPE), and a normal serum FLC ratio nearly rules out systemic AL amyloidosis (2,21). However, the presence of an abnormality in any of these tests is insufficient for a diagnosis of AL amyloidosis, because MGUS or myeloma without AL amyloidosis are possibilities. As such, biopsy evidence of amyloid deposits (with amyloid subtyping) is always needed (19).

During treatment with chemotherapy and/or immunotherapy, SPIE/UIPE/FLC can be followed to track treatment response; in general, FLC ratios are the main marker followed because they are more sensitive for low-level abnormalities, and they are measuring the protein that is depositing (light chains) rather than whole immunoglobulins.

BIOPSY SITES AND BONE SCINTIGRAPHY. The biopsy site can be chosen in 1 of 2 ways: minimizing false negatives or minimizing biopsy-associated risk. When aiming for the latter, biopsies can be attempted of the abdominal fat pad (most commonly), rectum, or skin. Reported sensitivities for abdominal fat pad biopsies in AL amyloidosis at high-volume centers are as high as 84%, with higher and lower rates observed, respectively, in patients with higher and lower total body amyloid burden (22,23). The sensitivity of fat pad biopsy is much lower in patients with ATTR amyloidosis, making fat pad biopsy a generally poor test for evaluation of that disease (22-24). Bone marrow biopsy, which is often being performed anyway to evaluate a patient with monoclonal immunoglobulin and/or light chain production, can also yield a diagnosis of amyloidosis if there are Congo red-positive deposits present. However, even when deposits are observed in the bone marrow, it is essential to confirm subtyping because other amyloid deposits (e.g., ATTR) can be observed in the bone marrow.

The alternative approach is to biopsy the clinically involved organ (e.g., endomyocardial biopsy if cardiac involvement is suspected, renal biopsy if renal involvement is suspected, and so on). This approach yields nearly 100% sensitivity and specificity and has the further advantage of yielding adequate deposits to accurately subtype the amyloid fibrils (19). Because of this higher yield and the importance of making a timely diagnosis and starting patients with AL amyloidosis on light chain suppressive therapy, proceeding to organ biopsy without first performing a fat

pad biopsy is a reasonable strategy. Given that there is still a significant false-negative rate with fat pad biopsy even in experienced hands, organ biopsy should almost always be pursued after a negative fat pad biopsy if clinical suspicion remains (**Central Illustration**).

When biopsying, it is crucial to not only determine the presence of amyloid deposits but also to subtype the amyloid deposits (e.g., AL, ATTR, etc.). This can be performed with either immunohistochemistry with custom-made antibodies or mass spectrometry; because immunohistochemistry interpretation is dependent on the preparation of the sample and the experience of the pathologist, we generally recommend mass spectrometry (performed at specialty centers) as the preferred approach unless immunohistochemistry is performed by a very experienced pathologist (20,25).

IMAGING. Most commonly, cardiac amyloidosis is suspected based on echocardiographic findings. The classic appearance of increased wall mass is observed in most cases, with particular clues including the following (26,27):

- Increased wall mass for both the left and right ventricles in a concentric/diffuse pattern
- Thickening of the interatrial septum and/or valves
- Presence of a pericardial effusion (most often small/not hemodynamically significant)

An abnormal echotexture (echobright or “sparkling” appearance) has been frequently associated with amyloidosis, although it is not sensitive for the disease and its absence should not dissuade one from pursuing the diagnosis (26,27). A characteristic pattern of abnormal longitudinal strain is commonly encountered in cardiac amyloidosis, in which there is relative sparing of strain abnormalities at the left ventricular apex compared with the base; this pattern has been referred to as a “cherry on top” pattern based on the bull’s-eye plot of global longitudinal strain (28-32). Some evidence also points to strain being useful as a marker of disease response to light chain therapy (31,32). Importantly, the abnormal strain pattern described does not differentiate AL amyloidosis from other forms of cardiac amyloidosis (31,32). Stroke volume index (stroke volume divided by body surface area) is similarly predictive of survival in AL amyloidosis compared with left ventricular strain and is a simple and straightforward value that can be obtained with echocardiography (33).

One of the most important clues to the diagnosis of amyloidosis can be the presence of a low “voltage:mass” ratio, comparing electrocardiographic

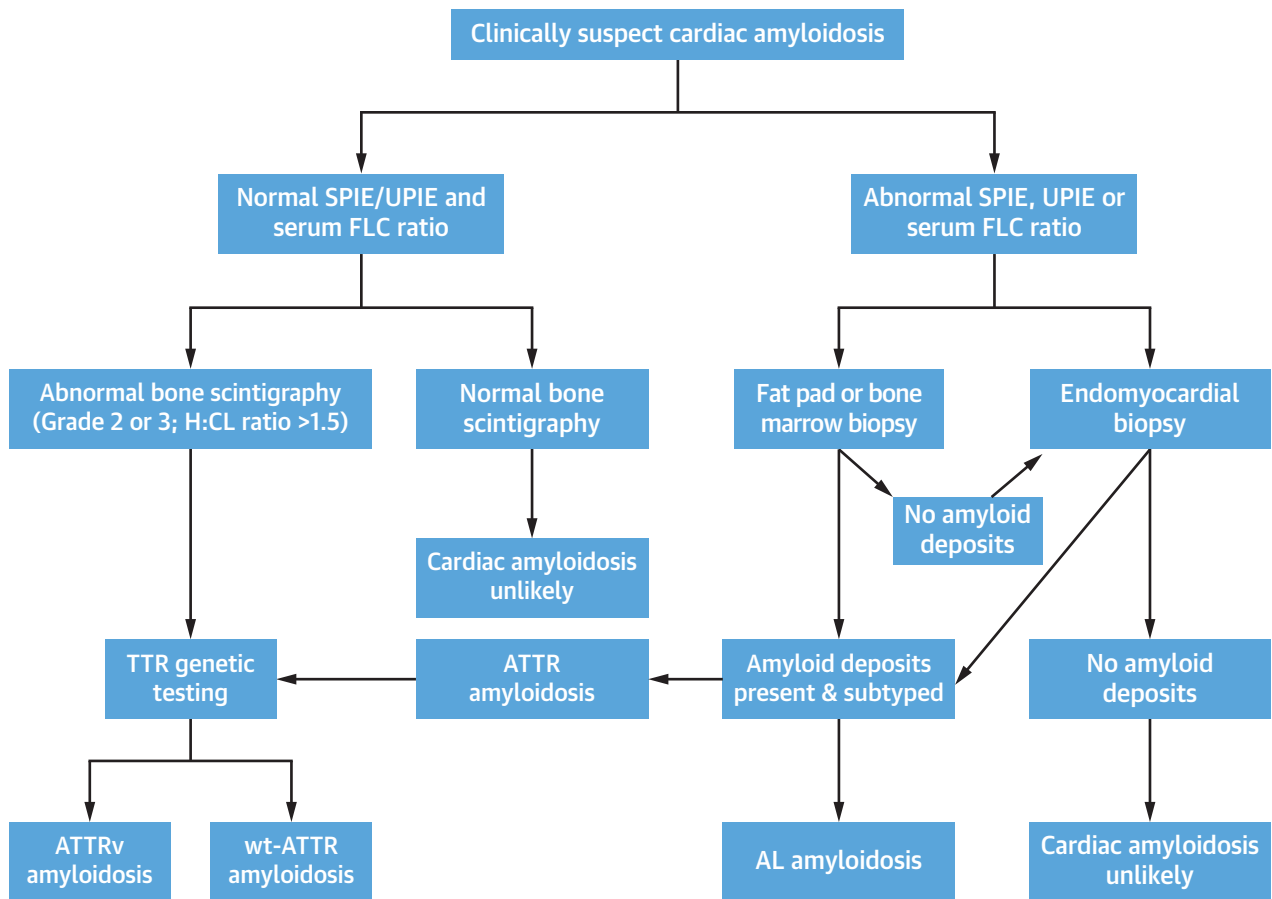
TABLE 4 Laboratory Testing in AL Amyloidosis

Test	Ordered to Test for	Normal Range*
SPIE†	Clonal immunoglobulin production	No M spike present
UPIE†	Clonal light chain production	No M spike present
Serum FLC assay	Detecting low-level clonal light chain production; clonality assumed if ratio is far from 1:1	Kappa:lambda ratio = 0.26-1.65‡
Cardiac troponin	Cardiomyocyte injury	Troponin I: <0.055 ng/ml Troponin T: <0.025 ng/ml
BNP or NT-proBNP	Abnormal cardiac function/heart failure (clinical or subclinical)	NT-proBNP: <300 pg/ml BNP: <100 pg/ml
Urine albumin:creatinine ratio§	Renal injury/proteinuria	<30 mg albumin/g creatinine
Alkaline phosphatase	Hepatic infiltration	35-105 U/l

*Normal ranges may vary slightly according to local laboratory standards. †SPIE and UPIE are more sensitive than protein electrophoresis without immunofixation and should be ordered as the preferred tests. ‡In patients with kidney disease, mild elevations in the kappa:lambda ratio are frequently encountered. In the setting of a normal SPIE/UIPE, a kappa:lambda ratio up to 2.5 can typically be considered normal. §Urine albumin:creatinine ratio is preferred over urine protein:creatinine ratio because the latter can detect light chain excretion, which is not itself a sign of renal injury; 24-h urine collection for albuminuria is a reasonable alternative test.
 Abbreviations as in Tables 1 and 3.

voltages with ventricular mass as assessed by imaging (34). Much like is the case for echotexture, relying on the presence of low voltages to make a diagnosis (or being dissuaded from making a diagnosis because of the absence of low voltages) is a mistake. Many patients with cardiac amyloidosis do not have low voltages; this is particularly true for ATTR amyloidosis but can be true for many patients with AL amyloidosis as well. Normalizing the actual voltage to the “expected” voltage based on left ventricular mass raises the sensitivity and specificity of using voltage as a diagnostic tool; specifically, the presence of “normal” electrical voltages in the setting of ventricular “hypertrophy” on echocardiography should raise a red flag for infiltrative disorders (34).

Cardiac MRI is frequently used in patients with suspected infiltrative cardiomyopathies or more generally in patients with unclassified nonischemic cardiomyopathies. The use of cardiac MRI can be helpful in suggesting a diagnosis of cardiac amyloidosis, including both nonspecific signs (e.g., increased concentric biventricular wall mass) and more specific signs (e.g., diffuse nonischemic pattern of delayed gadolinium uptake and difficulty nulling the myocardium) (27,35,36). However, because cardiac MRI is unable to definitively differentiate between AL and ATTR amyloidosis (or to differentiate them from less common forms of systemic amyloidosis) (37,38), it is almost always an intermediate step in the evaluation of patients. Therefore, although cardiac MRI can play an important role in raising suspicion, it is not the best diagnostic test to order if one is already

CENTRAL ILLUSTRATION Algorithm for Evaluation for Suspected Cardiac Amyloidosis

Witteles, R.M. et al. *J Am Coll Cardiol CardioOnc.* 2019;1(1):117-30.

If SPIE, UPIE, or FLC ratio are abnormal, it is reasonable to proceed with fat pad or bone marrow biopsy or to proceed directly to endomyocardial biopsy depending on institutional preference. However, if fat pad and/or bone marrow biopsy do not reveal amyloid deposits, endomyocardial biopsy should be pursued. H:CL = heart to contralateral lung ratio; other abbreviations in [Table 1](#).

concerned about evaluating for a diagnosis of cardiac amyloidosis specifically.

In recent years, bone scintigraphy (^{99m}Technetium pyrophosphate in the United States, ^{99m}Technetium 3,3-diphosphono-1,2-propanodicarboxylic acid in Europe) has been determined to be sensitive and specific for cardiac ATTR amyloid deposits, offering many patients a noninvasive option for establishing a diagnosis (39-41). Importantly, although specificity approaches 100% with this technique, this only holds true once a monoclonal protein has been ruled out. Bone scintigraphy is not specific enough for ATTR amyloidosis to exclude AL amyloidosis as a cause of tracer uptake if a monoclonal protein is present; in the largest study of bone scintigraphy, 27% of patients with AL amyloidosis proven by endomyocardial

biopsy had positive (grade 2 or 3) technetium pyrophosphate scans (41). As such, bone scintigraphy should not be performed without first confirming normal results for SPIE, UPIE, and serum FLC; if these tests are abnormal, biopsy must be pursued to confirm a diagnosis. A basic diagnostic flowchart is displayed in the [Central Illustration](#).

PROGNOSIS

The nearly universal factor in early trials of amyloidosis was a dismal overall survival. In the first major clinical trial to demonstrate an effective light chain suppressive therapy strategy, patients treated with melphalan and prednisone had more than twice the survival of patients in the nonchemotherapy arm,

but unfortunately this doubling was from only 8 to 18 months (42).

Despite AL amyloidosis being a disease that fundamentally arises as a result of a hematologic malignancy, the prognosis is primarily driven not by tumor characteristics but by extent of cardiac involvement. The first major attempt at a staging system was undertaken by Mayo Clinic and published in 2004 and was remarkable because the entire staging system was based solely on the presence/absence of elevations in cardiac biomarkers (troponin and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) (8). This system produced 3 stages with separate survival curves, but perhaps the most notable aspect was the overall poor prognosis throughout the cohort, with median survivals of 2.2, 0.9, and 0.3 years, respectively, for Stage 1, 2, and 3 patients. The same group subsequently updated the staging system 8 years later, adjusting their biomarker thresholds (including increasing the threshold for NT-proBNP elevation from 332 to 1,800 pg/ml) and adding a third variable, whether or not the difference in serum free light chain at diagnosis (pathologic light chain concentration – non-pathologic light chain concentration) was ≥ 18 mg/dl (10). These 3 dichotomous variables now defined 4 stages, but the most notable finding was the significantly improved survival across most stages (7.8, 3.4, 1.2, and 0.5 years for Stages 1, 2, 3, and 4, respectively) (10). Almost certainly, the primary reason for the improved survival between the cohorts was the improvement in chemotherapy over the same time period.

A European collaborative examined 230 patients treated with a combination of cyclophosphamide, bortezomib, and dexamethasone, still one of the most commonly used up-front chemotherapy regimens, and stratified results according to the 2004 Mayo Clinic staging system (12). For this study, particularly high-risk patients were separated in Stage 3 as having Stage 3a or Stage 3b disease, the latter defined as those with NT-proBNP $>8,500$ ng/l. The cumulative probability of survival at 3 years was 100% in Stage I, 52% in Stage II, 55% in Stage 3a, and 19% in Stage 3b. Importantly, this study included patients between 2006 and 2013, before the availability of some of the most recent light chain suppressive therapies (12).

A more recent staging system from Boston University was published in 2019 (11). The primary purpose of this system was to develop cutoffs for B-type natriuretic peptide (BNP) rather than NT-proBNP. In this system, the authors used a troponin I cutoff of 0.1 ng/ml and a BNP value of 81 pg/ml to divide patients into Stages 1, 2, and 3 and added a cohort of

higher-risk Stage 3 patients (Stage 3b) as those with BNP >700 pg/ml. Most notably, the median overall survival has clearly continued to improve, with median survivals not reached in Stage 1 at 10 years ($>80\%$ survival), 9.4 years for Stage 2, 4.3 years for Stage 3, and 1 year for Stage 3b. Difference in free light chains was no longer used as a prognostic factor in the Boston University system, possibly reflecting the improved ability to control abnormal light chain production in the present era.

Therefore, the main message from staging systems is as follows:

1. The severity of cardiac involvement remains the primary prognostic factor in AL amyloidosis.
2. Prognosis can be well stratified by 2 cardiac biomarkers: cardiac-specific troponin and NT-proBNP (or BNP).
3. Prognosis has markedly improved over the last 2 decades, with patients in all but the highest-risk groups having a median survival of >4 years, with some groups having a median survival of >10 years. Because all longitudinal survival studies include patients who began treatment before the advent of more modern light chain suppressive therapies, it is likely that the true life expectancy of a newly diagnosed patient is even higher than is reflected in even the most recent prognostic algorithms.

TREATMENT

LIGHT CHAIN SUPPRESSIVE THERAPY. Light chain amyloidosis is unique among malignancies in that the primary marker of disease (abnormal serum light chains) reflects the actual pathogenic driver of disease progression. Therefore, the primary goal of therapy in AL amyloidosis is to decrease the pathologic light chain levels as much as possible and to do so with the least treatment toxicity possible.

The first regimen demonstrated to improve outcomes in AL amyloidosis was a combination of an alkylator (melphalan) with a steroid (prednisone) (42,43). Although this regimen resulted in more than a doubling in the median survival in the largest trial, the overall outcomes were still dismal, with a median survival of only 18 months (42). Modestly improved outcomes were subsequently seen combining melphalan with high-dose dexamethasone rather than prednisone (44,45). Because of the poor outcomes with standard chemotherapy, high-dose melphalan followed by autologous stem cell transplantation (ASCT) was investigated as a treatment alternative. One study of 312 patients who received ASCT demonstrated a median survival of 4.6 years, with clear stratification of survival based on whether

	Examples	First Line?	Notable Toxicities
Steroids	Dexamethasone, prednisone	Yes	Hyperglycemia, neuropsychiatric effects, edema, immunosuppression
Alkylators	Melphalan, cyclophosphamide	Commonly	Myelosuppression, stomatitis
Proteasome inhibitors	Bortezomib, carfilzomib, ixazomib	Commonly	Neuropathy, thrombocytopenia, shingles reactivation, thrombosis/hypertension/cardiotoxicity (carfilzomib)
Immunomodulators	Lenalidomide, pomalidomide	Occasionally	Myelosuppression, rash, neuropathy, thrombosis, birth defects
Anti-CD38 Antibody	Daratumumab	No (ANDROMEDA trial investigating) (66)	Infusion reaction, hypogammaglobulinemia
Anti-SLAMF7 antibody	Elotuzumab	No	Infusion reaction, hypogammaglobulinemia

or not cardiac involvement was present (6.4 vs. 1.6 years); individuals who did not receive ASCT due to exclusion criteria (typically severe cardiac involvement) had a particularly poor median survival of 4 months (46). Two studies with long-term follow-up data of ASCT patients reported that up to 30% of patients are long-term survivors, with up to a 15- to 20-year follow-up (47,48).

Notably, the previously mentioned data (and other studies of ASCT) were nonrandomized, raising the potential that patients who received ASCT were overall healthier than those who did not. In addition, even at large referral centers that routinely perform ASCT in eligible patients, ASCT is not an option for most patients due to tight selection criteria; in 1 study, only 20% of patients evaluated within 1 year of diagnosis ended up receiving ASCT (49). One case-control study reported 1-, 2-, and 4-year survival rates of 89%, 81%, and 71%, respectively, for ASCT-treated patients versus 71%, 55%, and 41%, respectively, for patients who did not undergo ASCT (50). However, although “control” patients in the study were chosen to match specific clinical/laboratory variables, it is impossible to account for all clinical factors that can potentially affect the decision of both provider/patient to offer/undergo ASCT, raising the possibility that these results remain significantly confounded.

Only 1 randomized trial has addressed the question of standard chemotherapy versus ASCT, randomizing 100 patients in France to standard chemotherapy (melphalan and dexamethasone) or high-dose melphalan with ASCT. This study showed significantly better overall survival in the standard chemotherapy arm compared with the ASCT arm (51). Outcomes for low-risk patients (without significant cardiac disease) and high-risk patients (with significant cardiac disease) both trended toward benefit with standard chemotherapy. Although the trial has been critiqued because of relatively high ASCT-related mortality, a prespecified landmark analysis (only considering patients who received their

treatment and lived at least 6 months from randomization) also trended toward benefit of standard chemotherapy over ASCT (51).

Therefore, based on the available data to date, there is conflicting evidence regarding the role of ASCT for the treatment of amyloidosis. On one hand, there are multiple retrospective case-control studies and case series suggesting potential superiority for ASCT over standard chemotherapy. On the other hand, the only randomized trial showed superiority for standard chemotherapy over ASCT. Furthermore, because the trial was published in 2007, the “standard chemotherapy” arm did not include any newer chemotherapy/immunotherapy regimens, raising the potential that the “standard therapy” arm would perform even better versus ASCT if the trial was repeated in the present era. As such, based on current data, both approaches are reasonable, and we would recommend an approach of shared, informed decision making between the patient and the treatment team.

The modern era offers many newer options for light chain suppressive therapies (Table 5). Although these therapies were developed and approved for the treatment of myeloma, they are unsurprisingly useful for treating AL amyloidosis as well, given that both conditions arise from a clonal plasma cell disorder. Most commonly, patients with a new diagnosis of AL amyloidosis are begun on a regimen combining the alkylator cyclophosphamide, the proteasome inhibitor bortezomib, and the steroid dexamethasone (CyBorD). One European study of 230 patients treated with frontline CyBorD yielded overall hematologic response rates of 60%, including 43% achieving at least very good partial responses (12). Multiple smaller studies showed even higher hematologic response rates, up to 81% to 94% (52,53). Other proteasome inhibitors such as carfilzomib (54) and the oral agent ixazomib (55) have also shown promise, although both have their own treatment toxicities and are not typically chosen as first-line therapies.

Immunomodulators structurally related to thalidomide represent another commonly used group of agents used in AL amyloidosis. Lenalidomide has been used most commonly (56-61), but in recent years pomalidomide has also served as a useful agent (62), particularly in patients refractory to lenalidomide. Other agents, including venetoclax (63) and elotuzumab (64), have been tried in some patients as second- or third-line therapy, often in conjunction with other standard light chain suppressive therapies.

Perhaps the most promising agent from recent years is daratumumab, an antibody directed against CD38, a cell surface protein expressed on clonal plasma cells. In 1 study of 25 consecutive patients refractory to multiple other lines of treatment (median of 3 prior therapies), every patient had a decrease in pathologic light chains, with an overall hematologic response rate of 76% (65). Daratumumab as an up-front therapy (added to CyBorD) is currently under investigation in the phase 3 ANDROMEDA clinical trial (66).

The most notable toxicities of the commonly used chemotherapy/immunotherapy agents are summarized in **Table 5**. Of all of the agents, the greatest concern for cardiovascular toxicity is with the proteasome inhibitor carfilzomib, based mainly on clinical trials in myeloma patients (67-71). Although increased heart failure adverse events have been consistently reported with carfilzomib in myeloma trials (68-71), left ventricular systolic dysfunction is not commonly seen, with virtually no left ventricular ejection fraction declines observed in either of the 2 largest studies that used routine echocardiographic screening (68,71). The clearest cardiovascular safety signals, at least in myeloma trials, have been increased rates of thrombosis, hypertension, and heart failure with preserved ejection fraction (68-71). Therefore, differentiating whether the cause of worsening heart failure symptoms in AL amyloidosis patients treated with carfilzomib is from the disease or disease therapy can be challenging. Other proteasome inhibitors are not clearly associated with direct cardiovascular toxicity; a meta-analysis of 5,718 patients treated with bortezomib in myeloma trials showed no increased cardiovascular toxicity compared with controls (72).

Other important potential cardiovascular toxicities from AL amyloidosis therapies include steroid-related fluid retention, and increased rates of thrombosis in patients treated with thalidomide analogs such as lenalidomide and pomalidomide (particularly in patients with myeloma) (73-75). Two early studies of lenalidomide in AL amyloidosis raised the question of

a correlation between lenalidomide therapy and elevations in BNP/NT-proBNP levels, although it was difficult to differentiate if this was a direct treatment effect or represented disease progression during early therapy; notably, neither study demonstrated a clear increase in clinical heart failure with lenalidomide therapy (76,77).

Importantly, in virtually all studies, overall survival is tightly correlated with the degree of hematologic response, emphasizing the importance of moving to a different line of therapy expeditiously if a current treatment regimen is not adequately effective in reducing light chain production.

OTHER PHARMACOLOGICAL APPROACHES. All therapies described previously aim to eliminate the clonal cells that produce pathologic light chains. This is expected to reduce or eliminate ongoing amyloid deposition but will not directly lead to the removal of amyloid deposits; as such, significant interest has therefore existed for alternative pharmacological approaches.

One approach targeted serum amyloid P (SAP, a component of all amyloid fibril deposits) (78,79). In a phase 1 trial that administered both an agent to deplete circulating SAP and a monoclonal antibody targeting SAP, there was modest evidence of decreased amyloid deposits as assessed by SAP scintigraphy and MRI (80). Although 8 of the 16 patients included in this trial had AL amyloidosis, it is notable that patients with cardiac involvement were excluded for safety reasons (80). The same group later included 6 cardiac patients in a follow-up study (81), but clear efficacy data for this approach in cardiac amyloidosis have yet to be demonstrated. A phase 2 trial of an anti-SAP antibody specifically focusing on cardiac amyloidosis was recently terminated for a “change in benefit/risk profile” (82).

Another approach involved an antibody (NEOD001) aimed at the amyloid moiety itself, with the potential to both bind to soluble aggregates of amyloid protein and to aid in the clearance of amyloid deposits in tissues (83). However, despite promising results in a phase 1/2 study (84), a phase 3 study failed to meet its endpoints, prompting a review of a second phase 3 study, which was subsequently also halted for futility (85).

Other approaches have included the administration of agents that can potentially interfere with amyloid fibril formation, including doxycycline or the combination of doxycycline/ursodiol, for both AL and other systemic amyloidosis. Although some early studies have been encouraging (86), rigorous clinical trial data to date are lacking (87).

CARDIAC-SPECIFIC TREATMENTS

Although light chain reduction therapy is the backbone to AL amyloidosis treatment, treating organ dysfunction in parallel is of great importance, particularly cardiac dysfunction, given that cardiac involvement is the primary driver of mortality in AL amyloidosis. Therapies can be grouped into medical therapy, arrhythmia management, and cardiac transplantation.

MEDICAL THERAPY. Although no high-grade evidence exists to guide medical therapy in cardiac amyloidosis, generally accepted treatment principles are widely acknowledged (20). The mainstay of symptomatic therapy is volume management. Patients with systemic AL amyloidosis can be particularly prone to the challenging combination of hypotension with concomitant volume overload for the following reasons:

1. The presence of significant cardiac impairment due to:
 - a. Poor ventricular compliance/diastolic dysfunction
 - b. Reduced end-diastolic volume due to increased wall thickness
2. Coexisting renal (common) or hepatic (less common) amyloid deposition leading to reduced serum albumin concentrations, which can be severe
3. Concomitant autonomic dysfunction from amyloid deposition, leading to postural hypotension

Salt restriction and appropriate diuretic doses are essential for most patients, often best achieved by combining loop diuretics and aldosterone antagonists as allowed by serum potassium levels; in some cases, thiazide diuretics are necessary for sequential nephron channel blockade. If symptomatic hypotension limits the ability to achieve euvolemia, midodrine can be useful (particularly for patients with autonomic dysfunction); in select patients with severe nephrotic syndrome, intermittent albumin infusions may be necessary.

Standard systolic heart failure therapies are often poorly tolerated in patients with AL amyloidosis with cardiac involvement (20). Both β -blockers and vasodilators (e.g., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), in particular, can exacerbate the hypotension that is usually present for the reasons noted previously. Beta-blockers can also worsen bradycardia/heart block and blunt the compensatory tachycardic response to low stroke volume and/or vasodilatation from autonomic dysfunction. Digoxin has traditionally been considered contraindicated in cardiac amyloidosis because of the potential for tissue

toxicity (from direct binding of digoxin to amyloid fibrils), although recent studies suggest that digoxin can be cautiously used in appropriate patients, particularly when needed for rate control of atrial fibrillation (88).

ARRHYTHMIA MANAGEMENT. Atrial arrhythmias are common in patients with amyloidosis (89-91) and, because of the degree of baseline cardiac impairment, can be poorly tolerated. Anticoagulation is critical because patients with cardiac amyloidosis are at particularly high risk for thrombus formation. In 1 recent study of patients with cardiac amyloidosis undergoing planned transesophageal echocardiogram/cardioversion (50% of whom had AL amyloidosis), 28% had thrombus identified on echocardiogram compared with 2.5% of control patients without amyloidosis (92). For this reason, we and others recommend transesophageal echocardiography before elective cardioversion in all patients with amyloidosis, even if they have been on consistent therapeutic anticoagulation (92).

Bradycardias (particularly heart block) are also common in cardiac amyloidosis, although they are overall more common in ATTR than AL amyloidosis. Symptomatic bradycardia is an indication for pacemaker placement as in any form of heart disease; given the high rates of bradycardias in amyloidosis patients with syncope or presyncope, a low threshold should be considered for device placement in such patients (91).

Traditionally, implantable cardioverter-defibrillator (ICD) placement was considered contraindicated in patients with AL amyloidosis. The generally stated reasons included the poor overall prognosis in AL amyloidosis with cardiac involvement and a purported lack of success in resuscitating AL amyloidosis patients with ventricular arrhythmias with ICD shocks. In addition, many episodes of sudden death in AL amyloidosis can be caused by bradycardias or pulseless electrical activity rather than ventricular tachyarrhythmias (91). In 1 older study of patients who received ICDs before ASCT, 2 of 19 patients received successful/appropriate ICD shocks, with 1 patient still alive 30 months after receiving multiple therapies for ventricular tachycardia/fibrillation (93). Another study from a similar time frame (before the availability of newer AL suppressive therapies) found that 12 of 33 (36%) of AL amyloidosis patients received appropriate ICD shocks in the first year, but there was no overall survival advantage noted (94). It is notable that many patients in this cohort met "traditional" ICD indications (left ventricular ejection fraction <35%), implying later stages of disease, and the studies may have been

underpowered to detect an overall survival difference. Two other studies from a later time frame (after approval of more modern light chain suppressive therapies), each with 12 patients with AL amyloidosis, showed high rates of successful resuscitation with appropriate ICD shocks for ventricular arrhythmias (95,96).

Although high-quality evidence does not currently exist for guiding decisions of whether or not to place ICDs in AL amyloidosis patients, the preponderance of the data support the effectiveness of ICDs in successfully resuscitating AL amyloidosis patients with ventricular arrhythmias in most cases. Because current guidelines favor primary prevention ICD placement in high-risk heart failure patients with a life expectancy >1 year (97), we generally favor ICD placement in patients with AL amyloidosis who meet this life expectancy threshold and who either have a history highly suspicious for arrhythmia-associated syncope or who have evidence of ventricular arrhythmias on ambulatory telemetry (96).

CARDIAC TRANSPLANTATION. Early reports of cardiac transplantation for amyloidosis were overall discouraging. Of 24 transplants for amyloidosis in the United Kingdom from 1982 to 2002, 17 were for AL amyloidosis. The median survival in the whole cohort was only 29 months, and the 1-year survival for AL amyloidosis patients was an unacceptably low 59% (98). A subsequent report out of the United States covering a similar time period (1987 to 2002) of 69 patients with amyloidosis showed slightly better but still discouraging results; the 1-year survival rate was 75% with a 5-year survival of 54%, both statistically worse than for nonamyloidosis transplant patients (99). Notably, the United States does not differentiate between ATTR and AL amyloidosis in its national transplant registry. Men (overrepresented among ATTR amyloidosis patients) survived longer than women in this cohort, suggesting that results may have been worse if restricted to AL amyloidosis patients (99).

The Mayo Clinic subsequently published its experience transplanting 11 AL amyloidosis patients over 11 years, emphasizing strict screening to exclude clinically significant extracardiac amyloid deposition and following up each heart transplant with an ASCT (100). The median survival in this cohort was 76 months—still less than nonamyloidosis transplants but improved compared with prior cohorts. A subsequent report from the same institution examined 23 patients over 20 years, with a median post-transplant survival of only 3.5 years; however, for those patients who achieved a complete hematologic response, the median survival was 10.8 years (101). Our experience at the Stanford Amyloid Center transplanting patients in a

later time frame (after the availability of more effective light chain suppressive therapies) has been further encouraging. A report in 2015 of 19 amyloidosis patients (9 with AL amyloidosis) noted a similar overall survival to the overall transplant population; similar screening criteria to Mayo Clinic were used, but many patients were not treated with ASCT after heart transplantation (102). Our subsequent experience has continued to be positive, and our institution now does not routinely perform ASCT after heart transplantation, although we do emphasize pre-transplant and early post-transplant light chain suppressive therapy with chemotherapy and/or immunotherapy.

U.S. national data are also reflective of a large increase in heart transplantations for cardiac amyloidosis, with improved overall outcomes. Using 2008 as a landmark year based on the approval of newer light chain suppressive therapies, 1 study examined all heart transplants in the United States in era 1 (1987 to 2007) and era 2 (2008 to 2013). Transplantations for amyloidosis increased from 0.3% of all transplants in era 1 to 1.2% in era 2. Although transplant survival was worse in amyloidosis patients compared with all other restrictive cardiomyopathy patients in era 1, outcomes were similar to one another in era 2, likely reflecting better light chain suppressive therapy and a higher proportion of transplants for ATTR amyloidosis (103).

Importantly, AL amyloidosis patients needing a heart transplant have a much higher transplant waiting list mortality than other patients, with 35% dying while on the wait list in 1 study (104). As an acknowledgment of the high transplant waiting list mortality, the 2018 revision to the U.S. heart transplant policy listed amyloidosis as a higher status than most other diagnoses (status 4) (105).

SUMMARY

AL amyloidosis most commonly arises from a clonal plasma cell disorder, with deposition of pathologic light chains usually occurring in multiple vital organs. Cardiac involvement is common, and is the primary determinant of prognosis in the disease. Optimal care for patients involves close coordination between hematologists, cardiologists, and other subspecialists; patients should ideally be evaluated in a specialty center for the disease soon after a diagnosis is considered or has been made.

Although the disease remains life-threatening, advances in chemotherapy and immunotherapy have resulted in dramatically improved outcomes across all patient subgroups, although patients with severe cardiac involvement at diagnosis continue to have an overall poor prognosis. As such, early

diagnosis and prompt initiation of effective light chain suppressive therapy as soon as a diagnosis is made is critical. With improved prognosis, old paradigms of cardiac-specific therapy are being reconsidered, including the role of ICDs and cardiac transplantation for select patients.

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