Published in final edited form as:

Heart Fail Clin. 2011 July ; 7(3): 385–393. doi:10.1016/j.hfc.2011.03.009.

Amyloidotic Cardiomyopathy: Multidisciplinary Approach to Diagnosis and Treatment

David C. Seldin, M.D., Ph.D., John L. Berk, M.D., Flora Sam, M.D., and Vaishali Sanchorawala, M.D.

Amyloidosis Treatment and Research Program, Department of Medicine, Boston University School of Medicine and Boston Medical Center, Boston MA 02118

Keywords

amyloidosis; cardiomyopathy; transthyretin; immunoglobulin light chain; matrix metalloproteinase; autologous stem cell transplantation; biomarkers

Amyloidotic cardiomyopathy (ACMP): not a rare disease?

Amyloidosis is the generic term for a family of fibrillar protein deposition diseases. In the mid-19th century, pathologist Rudolf Virchow found amorphous-appearing deposits in sections of kidney, spleen, heart, and other tissues in autopsies performed on patients succumbing to untreatable infections. He called them starch-like, or “amyloid”. We now know that amyloid deposits are composed of regular 10 nm polymeric protein fibrils; we surmise that Virchow was seeing amyloid composed of fibrils of serum amyloid A protein, an acute phase reactant, the cause of AA or secondary amyloidosis. AA amyloid is still found in patients with chronic mycobacterial or bacterial infections, in rare hereditary periodic fever syndromes such as familial Mediterranean fever, and in refractory autoimmune diseases. While AA amyloidosis most often involves the kidney, about 10% of patients develop cardiac involvement (Girnus *et al.*, in press).

Other forms of amyloidosis more frequently affect the heart, and are more likely to be diagnosed by cardiologists. Familial amyloidosis (AF) is caused by inheritance of mutations in DNA encoding abundant serum proteins that become prone to misfolding and aggregation. Inherited mutations of TTR are the most common cause of AF, producing syndromes of “FAC” (familial amyloidotic cardiomyopathy) and “FAP” (familial amyloidotic polyneuropathy) depending upon the tissue tropism of the particular mutant. TTR mutations are common in regions of Portugal, Japan, and Sweden, but can be found worldwide. More than 100 polymorphisms of TTR have been reported, of which more than

© 2011 Elsevier Inc. All rights reserved.

David C. Seldin, M.D., Ph.D. (corresponding author): dseldin@bu.edu Amyloidosis Treatment & Research Program K5, 72 E. Concord St. Boston MA 02118 617-638-4317 617-638-4493. John L. Berk, M.D. jberk@bu.edu Amyloidosis Treatment & Research Program K5, 72 E. Concord St. Boston MA 02118 617-638-4317 617-638-4493. Flora Sam, M.D. Flora.Sam@bmc.org Whitaker Cardiovascular Institute, Division of Cardiology 715 Albany Street, W507 Boston, MA 02118 Phone: 617 -638-8072 Fax: 617-638-4066. Vaishali Sanchorawala, M.D. Vaishali.Sanchorawala@bmc.org Hematology-Oncology Section, Department of Medicine FGH1, 72 E. Concord St. Boston MA 02118 Phone: 617-638-4317 Fax: 167-638-4493.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors have no conflicts of interest to disclose.

80 are amyloidogenic ⁶. Other serum proteins that can cause inherited amyloidoses include fibrinogen, lysozyme, gelsolin, and the apolipoproteins.

Immunoglobulin light chain (AL) amyloidosis, formerly termed primary amyloidosis, is caused by fibrils composed of immunoglobulin light chains (LC). This can occur in clonal B lymphoproliferative diseases, usually in low grade plasma cell dyscrasias, but also in multiple myeloma, B cell lymphoma, chronic lymphocytic leukemia, or Waldenstrom's macroglobulinemia. As many as 50% of patients with AL amyloidosis have cardiac involvement, which is often rapidly progressive and fatal if untreated.

The hereditary and acquired forms of amyloidosis are relatively rare. However, just as normal aging is accompanied by the development of A β plaques in the brain, it is also accompanied by the formation of amyloid deposits in other tissues, of which the heart is the organ in which this is most clinically apparent. This is the syndrome termed "senile systemic amyloidosis" (SSA), sometimes termed "senile cardiac amyloidosis". In SSA, the fibrils are formed of wild type TTR protein. Histopathologic evidence of SSA can be found in 10-25% of people over age 80, and almost all centenarians ¹⁶, but how frequently it causes ACMP is uncertain. Nonetheless, in an aging population, SSA and the associated ACMP are increasingly recognized by cardiologists investigating diastolic or systolic hypertrophic cardiomyopathy and heart failure in the elderly.

Thus, ACMP can occur as a consequence of a blood disorder, an inherited genetic disease, or as part of normal aging. As we begin to develop more and more effective therapies for these disorders, accurate and timely diagnosis has become increasingly important for our patients.

Diagnosis of ACMP: clinical suspicion + appropriate laboratory investigation

First and foremost, the key to the diagnosis of amyloidosis is to consider the diagnosis. (Table 1) Amyloidosis, not syphilis, is the great mimic of the 21st century, as it can masquerade as more common disorders capable of causing: nephrotic syndrome and renal insufficiency; cholestatic liver failure; malabsorption and gastrointestinal bleeding; or peripheral or autonomic neuropathy. For ACMP, the typical presentation is with symptoms of heart failure with preserved left ventricular (LV) function, manifest first as non-specific symptoms of fatigue, exertional dyspnea, and hypotension. These symptoms progress over time, eventually to systolic heart failure. As discussed below, heart failure (HF) due to amyloidosis is refractory to many of the usual interventions. The amyloidotic heart is also highly susceptible to heart block and arrhythmia, likely as a result of deposition of fibrils in the conducting system. Progressive HF and sudden death are the most common cause of death in patients with ACMP, due to ventricular arrhythmias or pulseless electrical activity (PEA). Atrial arrhythmias are also common.

Amyloidosis should be suspected in patients who present with unexplained nephrotic syndrome, cholestatic liver disease, autonomic neuropathy, peripheral neuropathy, or cardiomyopathy with concentric hypertrophy, or combinations of these syndromes. Pathognomonic symptoms and signs of amyloidosis include macroglossia and periorbital purpura, and these findings should be promptly pursued.

With respect to the heart, patients usually come to the attention of cardiologists for evaluation of exertional dyspnea, fatigue, or hypotension. Chest pain due to amyloid in epicardial coronary vessels is rare, although patients with amyloidosis in small arterioles and capillaries may develop atypical chest pain, jaw claudication with chewing, or buttock

claudication with ambulation. Hypotension can occur due to a combination of cardiac dysfunction and autonomic insufficiency.

Such symptoms would be evaluated by echocardiography to assess cardiac structure and function. Textbooks describe a classic “sparkly” pattern on echocardiography that was actually an artifact produced by low resolution imaging, and is not seen as commonly with modern equipment. The common echocardiographic features of ACMP are concentric hypertrophy of the ventricular walls, biatrial enlargement, and abnormal diastolic filling parameters and, commonly, mild to moderate valvular regurgitation. Heart failure symptoms can occur with minimal ventricular wall thickening. The standard electrocardiogram (ECG) can also provide a tip-off to the presence of an infiltrative cardiomyopathy, as the limb lead voltages are often reduced, rather than increased as in other hypertrophic cardiomyopathies. Cardiac magnetic resonance imaging (CMR) also can identify structural and functional abnormalities consistent with amyloidosis, and a phenomenon of delayed subendocardial enhancement with gadolinium has been seen³². The only specific scan for amyloid deposits is done using labeled serum amyloid P component¹⁷, an accessory protein that binds to amyloid fibrils and has been postulated to protect them from degradation. Unfortunately this scan is not useful for diagnosing cardiac amyloidosis because the tracer pools in the heart; furthermore, SAP-scanning is not available in the U.S.

The gold standard for diagnosing amyloidosis is a tissue biopsy demonstrating the presence of fibrils that bind the dye Congo red, producing “apple green” birefringence under polarized microscopy. (Table 2) Fibrils can also be identified by electron microscopy as rod-like bundles 10 nm in diameter. The most accessible site for demonstration of fibrils is in fat readily obtained by aspiration from the abdominal wall using an 18 g syringe needle after administering a local anesthetic. The fat is positive in 65-95% of cases, depending upon the type of systemic amyloidosis²³. If it is negative in a patient suspected of having amyloidosis, the next step is usually to proceed with biopsy of an affected organ, although biopsies of salivary glands and the rectum are other sources of tissue that are frequently positive. In patients with cardiac symptoms and signs indicative of amyloidosis without clinically detectable involvement of other organs, an endomyocardial biopsy should be carried out next. Biopsy material should be fixed in standard formalin and also in paraformaldehyde for immuno-electron microscopy, in case immunohistochemical studies fail to identify the subunit protein by light microscopy.

Once amyloid fibrils are identified, the next step is to establish the type of amyloid protein, a critical step in determining treatment. Multiple modalities are employed to do this. Patients with AL amyloidosis will almost always have evidence of a clonal plasma cell process by one or more of the following tests: bone marrow immunohistochemistry or flow cytometry for kappa and lambda LC; serum or urine immunofixation electrophoresis (the standard SPEP and UPEP are usually normal, as there is rarely enough monoclonal immunoglobulin to be detected with these techniques); or serum free light chain testing using the “Freelite Assay” a relatively new test marketed internationally by The Binding Site Co. Normally, almost all LC is associated with immunoglobulin heavy chains to form tetramers. In plasma cell diseases, the levels of free LC are elevated and can be detected by nephelometry using specific antibodies. Unlike whole immunoglobulins, LC are rapidly excreted by the kidney and have a half life of only 6 hrs, so measurement of serum free light chains provides a early measure of disease response in patients undergoing treatment, as well as aiding diagnosis.

Patients with ATTR or other hereditary forms of amyloidosis have DNA mutations that can be detected by gene sequencing. However, neither the presence of a mutation or of a plasma cell disorder conclusively identifies the amyloid type, and in many cases immunochemical or biochemical identification is essential. However, amyloid fibrils are notoriously “sticky”

and bind many antibodies non-specifically, so careful controls, immuno-electron microscopy with gold-labeled antibodies, and extraction or microdissection of the fibrils and identification by mass spectrometry are important confirmatory tests, available in specialized centers. Misdiagnosis and inappropriate application of chemotherapy should be avoided.

Mechanisms of cardiac dysfunction in ACMP

Cardiac dysfunction in amyloidosis has been attributed to the deposition of amyloid fibrils and physical disruption of the integrity of the myocardial syncytium. However, clinical observation has shown that the degree of cardiac dysfunction is not necessarily proportional to the thickness of the walls, thus, it has been hypothesized that amyloid may have other effects on the heart. For example, cardiomyopathy in AL amyloidosis has the worst prognosis and most rapid progression, although wall thickness may be much less than in patients with ATTR or SSA^{9,26}, where wall thickness can exceed 2 cm. A likely explanation is that prefibrillar LC oligomers have direct toxic effects on cardiomyocyte function, impairing excitation-contraction coupling via increased oxidant stress^{4,22} mediated by p38 MAPK signaling³⁴.

Extracellular amyloid fibrils also appear to disrupt cardiac matrix homeostasis and alter extracellular matrix (ECM) turnover³. Regulated ECM turnover is critical for the maintenance of myocyte-myocyte force coupling and proper myocardial function. Disruption of the ECM alters matrix metalloproteinases (MMP) and their tissue inhibitors (TIMP) in AL CMP. As a result, matrix degradation is impaired. Reactive oxygen species (ROS) alter myocardial MMP activity by translational and post-translational mechanisms, activating MMPs and decreasing fibrillar collagen synthesis in cardiomyocytes, contributing to the accelerated clinical manifestations of disease.

Cardiac biomarkers and risk stratification in AL amyloidosis

The extent of ACMP is the single most important determinant of outcome in AL amyloidosis²⁸. The cardiac biomarkers, B-type natriuretic peptide (BNP) and troponins, have been shown to be elevated with cardiac stress and cardiomyocyte damage caused by amyloidogenic LC. These biomarkers have been useful with both diagnosis and prognosis.

Criteria for the assessment of cardiac involvement at baseline and of cardiac response after treatment have been established by an international consensus panel¹³. Short of endomyocardial biopsy, electrocardiography and echocardiography were accepted as the gold standards for the diagnosis of heart involvement by amyloidosis. Recently, it has been shown that serum cardiac troponins-T and -I (CTnT and CTnI) and B-type natriuretic peptides (either BNP or N-terminal-proBNP, NT-proBNP) are highly sensitive markers of cardiac involvement, and normal values exclude clinically significant cardiac amyloidosis²⁹. Furthermore, an analysis of outcomes for 242 patients with AL amyloidosis demonstrated that patients could be divided into three prognostic groups based upon elevation of NT-proBNP and troponin (NT-proBNP > 332 ng/L; CTnT > 0.035 µg/L, CTnI > 0.1 µg/L)⁷. Patients with normal proBNP and troponin in this study had a median survival of about 2 years, and were designated Stage I. Patients with either biomarker elevated were categorized as Stage II, and had a median survival of slightly less than a year. Patients with both cardiac biomarkers elevated were Stage III, corresponding to a median survival of only 3-4 months (see Table 3).

In addition, among patients with cardiac involvement, cardiac troponins provide quantitative information about myocardial damage. Median survival of patients with elevated CTnT and CTnI was 6 and 8 months, respectively, and worse than that for those with undetectable

values (22 and 21 months, respectively). After multivariate analysis, CTnT provided a better predictor of survival than CTnI⁸. Nonetheless, the baseline CTnI has also been shown to be an excellent predictor of relative survival¹.

Based on these studies, biomarker criteria for cardiac involvement and improvement and progression after therapy are now being incorporated into the consensus for organ involvement and response¹². Furthermore, reductions in levels of cardiac biomarkers from baseline also correlate with improvement in survival after treatment in patients with cardiac involvement: a 30% or 300 ng/L decrease in the NT-proBNP level from baseline correlates with improved survival, while an increase of that magnitude correlates with progression and worse survival post-treatment.

AL amyloidosis treatment

Treatment in AL amyloidosis is aimed at eradicating the plasma cell clone that produces the deleterious fibril-forming LC. The first attempt to do this was by using oral dosing of the alkylating chemotherapy melphalan, accompanied by prednisone. In AL amyloidosis, two outcomes are assessed: hematologic responses (reduction in the plasma cell clone and light chain production) and clinical responses (improvement in organ function). Studies have demonstrated that these are linked, and treatments that significantly reduce production of the LC fibril precursor, *e.g.* by 90% or more, are those that can be associated with clinical improvement. Melphalan and prednisone are relatively ineffective, as partial (50%) responses occur in only 20-25% of patients and deeper responses and improvements in organ function were rare. Thus, there was little impetus to make the diagnosis and initiate therapy, and most patients died of their disease within the first 1-2 years of diagnosis.

About 15 years ago we and other centers took advantage of accumulating data from the myeloma field indicating that high dose intravenous melphalan (HDM) supported by transplantation of autologous bone marrow stem cells (SCT) could produce complete or near-complete hematologic responses, and transferred this approach, with some trepidation, to patients with AL amyloidosis. Over the next few years we learned that a high rate of complete hematologic responses can be achieved, and organ function can then improve. However, inexperienced centers have had treatment-related mortality (TRM) rates as high as 30-40%. In a multicenter randomized trial from France (published in the *New England Journal of Medicine* in 2007) that compared outcomes of HDM/SCT to oral melphalan chemotherapy, 25% of enrolled patients in the HDM/SCT group did not receive their transplant and another 25% died after due to TRM²⁰. At Boston Medical Center, our TRM in the early years was 14%³⁵, and more recently has been reduced to 5% (Seldin *et al.*, in press). Thus, with careful selection of patients and expert multidisciplinary care, morbidity and mortality during HDM/SCT can be minimized.

The first step in this treatment involves harvesting hematopoietic stem cells. Today, this is almost always accomplished by leukapheresis of peripheral blood following administration of high dose myeloid growth factors, usually G-CSF, that promote hematopoietic stem cell division and egress from the bone marrow. It is rare to subject patients to bone marrow harvest. For those patients that fail to mobilize enough cells with G-CSF, we now can administer plerixafor, an antagonist of the CXCR4 chemokine receptor, that promotes release of stem cells from the bone marrow stroma. Hematopoietic stem cells are then cryopreserved, while patients undergo treatment with high doses of anti-plasma cell chemotherapy that is myeloablative. Melphalan is the most useful alkylating chemotherapy agent for this. With the reinfusion of stem cells 1-2 days after chemotherapy, the hematopoietic system is soon reconstituted, with neutrophil engraftment typically occurring 10 days later, and platelets and erythrocytes a few days after. It is this period of

pancytopenia during which patients are at highest risk of infection, and also mucositis and enteritis due to the melphalan. During this time period, shifts in fluid and electrolytes, stress, fever, fatigue, cytokines, and infection provide a significant stress on the heart, and it is not infrequent for a patient to have their first atrial or ventricular arrhythmia during this time. Exacerbation of heart failure symptoms frequently occur. In fact, even the administration of high doses of G-CSF during the pre-chemotherapy period can precipitate such events. Guidelines for management of CHF and arrhythmias in amyloidosis patients are provided below.

However, if this treatment can be administered safely, the outcomes are excellent. Patients who have cessation of LC production after HDM/SCT are able to recover organ function. We have demonstrated significant improvement in nephrotic syndrome, and recently in wall thickness by echocardiography (Meier-Ewert *et al.*, in press). Hepatomegaly also regresses in many patients. More subjective symptoms of fatigue, lightheadedness, anorexia, and gut dysmotility also improve, as does quality of life. However, this is a slow process, and patients often require extensive supportive care for 6-12 months as their performance status and immunologic function slowly improves.

Patients with advanced ACMP are at high risk of complications, and such patients should be identified using clinical criteria or biomarkers and generally excluded from going through HDM/SCT. The standard alternative chemotherapy regimen is considered to be pulse oral melphalan combined with dexamethasone, which is fairly well-tolerated and can produce hematologic responses and organ improvement³⁰. Nonetheless, patients with ACMP are poorly tolerant of multi-day pulses of high dose corticosteroids, and we generally employ a less intensive regimen of dexamethasone once day a week, instead of four consecutive days once or twice a month. It is also common for patients with significant ACMP or edema due to nephrotic syndrome to require dose reduction from the typical starting dose of 40 mg each day to 20 mg or even 10 mg.

The multiple myeloma field has undergone a transformation in the last 5 or so years with the advent of novel anti-plasma cell agents. These fall into two major classes of proven efficacy: the immunomodulator drugs (so-called IMiDs), of which thalidomide was the first-in-class; and the proteasome inhibitors, of which bortezomib (Velcade) was the first and only one so far reaching FDA approval. The IMiDs are believed to act on the bone marrow microenvironment, affecting stromal-plasma cell interactions, cytokines, and angiogenesis. The proteasome inhibitors appear to be more directly plasmacytotoxic, perhaps because plasma cells are antibody factories particularly susceptible to disruption of intracellular proteolytic pathways. Thalidomide, newer analogs lenalidomide and pomalidomide, and bortezomib, have all been studied in AL amyloidosis patients and shown to provide effective anti-plasma cell activity. They clearly will have a role in treatment of AL amyloidosis, alone or in combination. It is too soon to argue that they can replace HDM/SCT in good risk patients, but further clinical trials will undoubtedly demonstrate that they have a role in patients ineligible for that therapy, or those who fail or relapse, or perhaps in induction or as maintenance therapy.

However, these agents are not benign, particularly in AL amyloidosis patients. Thalidomide was marketed in Europe as a sedative, until a high rate of birth defects was appreciated; thus, these the IMiDs are highly regulated and pregnancy must be avoided during their use. In addition, they are prothrombotic, and patients must take aspirin or full warfarin anticoagulation when they are on them. They also have cardiac effects: thalidomide has been reported to cause bradycardia, and lenalidomide has been noted recently to raise the BNP. It also can also produce worsening azotemia in patients with amyloid renal disease (Specter *et*

al., in press). These agents are used at lower doses in AL than in multiple myeloma, and patients must be monitored closely for these and other side effects.

Bortezomib has a different spectrum of toxicities, with neuropathy being a common dose-related side effect. Its cardiac side effects are less well-understood, although exacerbation of CHF and arrhythmia have been seen, and cardiotoxicity has been replicated in animal models ²⁷. These agents should still be considered to be investigational in AL amyloidosis patients.

Hereditary transthyretin amyloidosis, ATTR

Variant transthyretin amyloid (ATTR) arises from point mutations in exons 1-4 of the TTR exons on chromosome 18, resulting in over 100 identified single amino acid substitutions. Disease prevalence is estimated at 1:100,000 population in the USA, giving ATTR orphan disease status (< 200,000 affected in the USA). One ATTR mutation, V122I, is found in 3.9% of the African American population, however the rate of clinical expression is undefined, and African-Americans are still more likely to present with symptomatic AL CMP than FAC ⁵. In contrast, ATTR carrier frequency in northern Portugal is 100 times the US prevalence and, in certain northern Swedish communities, affects 3-5% of the population.

The clinical spectrum of ATTR disease is variable, and dependent upon the nature of the mutation. Most TTR mutations induce peripheral and/or autonomic neuropathy (FAP), followed by amyloid cardiomyopathy (FAC) and, less frequently, renal disease. V30M typically induces neuropathy and rarely affects the heart, whereas T60A and V122I almost exclusively produce cardiomyopathy and infrequently affect peripheral nerves. FAC is predominant for approximately 40 ATTR variants. In the USA, the most frequently identified variants associated with FAC are V122I, T60A, S77Y, V20I, V30A, T49P, A81V, I84N, and A97S. The course of transthyretin FAC differs from AL-related heart dysfunction. In contrast to the rapidly deteriorating course of AL CMP, FAC develops slowly and patients are often asymptomatic until the amyloid involvement of the myocardium is advanced in late stages of disease. Interestingly, while oligomeric light chains themselves appear to be deleterious on myocardial contractility, variant TTR does not appear to affect heart function (personal communications, Connors, LW 2010). However, ATTR CMP more often presents with conduction delays or complete heart block than does AL CMP.

Transthyretin is almost exclusively produced by the liver, with minor quantities made by the choroid plexus and retinal epithelium. In an effort to eliminate variant transthyretin production and prevent continued amyloid fibril formation, liver transplantation was first performed in Sweden in 1990. To date, more than 1700 liver transplants have been undertaken in ATTR patients (see the Familial Amyloidotic Polyneuropathy World Transplant Registry at <http://www.fapwtr.org/>). Although well tolerated, liver transplants have not proved the panacea they were predicted to be. Unfortunately, once fibril formation has begun, it appears that in some cases wild type TTR made by the transplanted liver can be incorporated into the amyloid deposits and the disease can progress ^{10,24}. These findings led to recommendations to limit liver transplantation in ATTR to patients with early neurologic and minimal to no signs of cardiac amyloid deposition. For those with ATTR cardiomyopathy, two therapeutic options remain: heart and liver transplantation or experimental medical therapies.

Over the past decade, experiments examining the thermodynamic landscape of ATTR fibril formation determined that disaggregation of native TTR tetramer represented the critical and rate limiting step. Small molecules occupying the thyroid binding sites raised the activation barrier for TTR tetramer dissociation, effectively tightening the associations of these 4

proteins. Using X-ray crystallography to characterize the thyroid binding site and high throughput modeling, Dr. Jeffery Kelly (The Scripps Research Institute) identified a non-steroidal anti-inflammatory drug (NSAID), diflunisal, as a pre-existing candidate small molecule inhibitor of ATTR fibril formation. At the same time, FoldRx Pharmaceutical (Cambridge, MA) synthesized a proprietary small molecule inhibitor, Tafamadis, designed to maximize ATTR tetramer binding and eliminate potential NSAID toxicities. Both agents inhibit ATTR fibril formation *in vitro*. These independent investigational programs led to separate international, multi-center randomized, placebo-controlled studies; results are pending. Small molecule inhibitors, RNA interference, or protein stabilizers appear to be the future of ATTR management – particularly in patients with amyloid cardiomyopathy at disease presentation in whom liver transplantation may not halt progression.

Management of heart failure and arrhythmias in patients with ACMP

Regardless of the specific treatment directed against the plasma cell dyscrasia, supportive care to decrease symptoms and support organ function plays an important role in the management of disease and requires coordinated care by specialists in multiple disciplines.

The mainstay of the treatment of heart failure in ACMP is sodium restriction and the use of diuretics; higher doses may be required if the serum albumin level is low as a result of concomitant nephrotic syndrome. Furthermore, achieving a balance between heart failure and intravascular volume depletion is particularly challenging, especially in patients with autonomic nervous system involvement or nephrotic syndrome. Diuretic resistance is common in patients with severe nephrotic syndrome, and metolazone or spironolactone may be required in conjunction with loop diuretics. In a patient with anasarca, intravenous diuresis is often needed because absorption of diuretics may be impaired. Diuretic resistant large pleural effusions may indicate the presence of pleural amyloid². Such effusions can be managed with repeated thoracenteses or placement of indwelling pleural catheters for continuous drainage; pleurodesis is often ineffective and is frequently complicated by pneumothorax due to friable pleural tissue.

In contrast to other types of heart failure, in ACMP there is no evidence that drugs such as β -blockers or angiotensin-converting enzyme (ACE) inhibitors are beneficial, and in fact their use can be quite dangerous. Any of these should be used cautiously in ACMP, starting with a low dose administered in a monitored setting, as even small doses may result in profound hypotension. β -blockers and calcium channel blockers may produce hypotension because of their negative inotropic effect^{14,15,31}. Patients with ACMP may be hypersensitive to ACE inhibitors because in the setting of amyloid-induced autonomic dysfunction there may be increased reliance upon the renin-angiotensin system for maintenance of adequate blood pressure. There are no published data on the use of intravenous inotropic or vasodilator drugs in patients with severe heart failure resulting from amyloidosis. Renal-dose dopamine (1 to 3 $\mu\text{g}/\text{kg}/\text{min}$) can be helpful for the treatment of anasarca, provided that renal function is unimpaired. Patients may be particularly prone to dysrhythmias at higher doses of dopamine, or with dobutamine therapy.

Digoxin is also not generally useful in amyloidosis, and patients may be at increased risk of digoxin toxicity, despite therapeutic serum digoxin levels. Digoxin has been shown to bind avidly to amyloid fibrils³³, leading to high local levels of the drug in the myocardium.

Thus, options for medical management of patients with severe ACMP are limited. In highly selected cases, orthotopic heart transplantation may be considered. Early experience with cardiac transplantation in AL amyloidosis suggested that mortality did not differ from that in other disorders¹⁹, but with longer follow-up, greater mortality than expected was observed, usually because of disease progression in the heart or other organs¹⁸. As a result of these

observations, many solid organ transplantation centers consider AL amyloidosis a contraindication to heart transplantation. However, with the advent of high-dose chemotherapy and stem cell transplantation, it is possible to transplant the heart and to perform chemotherapy 6 to 12 months later to eliminate the underlying plasma cell dyscrasia, preventing amyloid deposition in the transplanted heart and other organs. A number of patients have been treated successfully with this combined approach and have an actuarial survival that is similar to that of patients undergoing heart transplantation for other indications (Chung *et al.*, in press and ²¹).

The management of arrhythmias in patients with ACMP lacks strong evidence-based support. Atrial fibrillation can often be suppressed with amiodarone. Patients who fail amiodarone or do not tolerate it may be candidates for ablation procedures. Patients with atrial fibrillation should be anticoagulated if possible, although patients who have amyloidosis are often prone to bleeding due to capillary fragility or deficiency of circulating clotting factors. Furthermore, in severe ACMP, the atria as well as the ventricles are infiltrated, and atrial contractile dysfunction may be present even during sinus rhythm, predisposing to atrial thrombus formation ²⁵. It is therefore prudent to anticoagulate patients with amyloidosis if there is defective left atrial mechanical activity on echocardiography, even in the absence of fibrillation ¹¹.

Management of ventricular arrhythmias is challenging, and evidence-based guidelines are lacking. Patients with recurrent syncope or symptomatic ventricular arrhythmias may also be treated with amiodarone, which can suppress ectopy but has not been proven to reduce mortality from sudden death due to ventricular fibrillation or pulseless electrical activity. Implantable defibrillators have been employed, again without real proof of efficacy. The infiltrated myocardium may be difficult to cardiovert. Nonetheless, anecdotal evidence supports their use in selected cases.

Summary

Amyloidotic cardiomyopathy occurs in the setting of genetic diseases, blood dyscrasias, chronic infections and inflammation, and with advanced age. Cardiologists are on the front lines of diagnosis of amyloidotic cardiomyopathy when evaluating patients with unexplained dyspnea, congestive heart failure, or arrhythmias. Non-invasive detection of diastolic cardiac dysfunction and unexplained LV hypertrophy should be followed by biopsy to demonstrate the presence of amyloid deposits, and by appropriate genetic, biochemical, and immunological testing to accurately define the type of amyloid. A growing menu of treatment options exist for these diseases, and timely diagnosis and institution of therapy is essential for preservation of cardiac function.

Acknowledgments

Funding support: NIH R01 NS051306.(J.L.B.); HL079099, HL095891, and HL102631(F.S.)

REFERENCES

1. Apridonidze T, Comenzo R, Hoffman J, et al. Troponin as a prognostic marker in cardiac amyloidosis. *Amyloid*. 2010; 17:167a.
2. Berk JL, Keane J, Seldin DC, et al. Persistent pleural effusions in primary systemic amyloidosis: etiology and prognosis. *Chest*. 2003; 124:969. [PubMed: 12970025]
3. Biolo A, Ramamurthy S, Connors LH, et al. Matrix metalloproteinases and their tissue inhibitors in cardiac amyloidosis: relationship to structural, functional myocardial changes and to light chain amyloid deposition. *Circ Heart Fail*. 2008; 1:249. [PubMed: 19808299]

4. Brenner DA, Jain M, Pimentel DR, et al. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. *Circ Res.* 2004; 94:1008. [PubMed: 15044325]
5. Connors LH, Prokaeva T, Lim A, et al. Cardiac amyloidosis in African Americans: comparison of clinical and laboratory features of transthyretin V122I amyloidosis and immunoglobulin light chain amyloidosis. *Am Heart J.* 2009; 158:607. [PubMed: 19781421]
6. Connors LH, Richardson AM, Theberge R, et al. Tabulation of transthyretin (TTR) variants as of 1/1/2000. *Amyloid.* 2000; 7:54. [PubMed: 10842707]
7. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol.* 2004; 22:3751. [PubMed: 15365071]
8. Dispenzieri A, Kyle RA, Gertz MA, et al. Survival in patients with primary systemic amyloidosis and raised serum cardiac troponins. *Lancet.* 2003; 361:1787. [PubMed: 12781539]
9. Dubrey SW, Cha K, Skinner M, et al. Familial and primary (AL) cardiac amyloidosis: echocardiographically similar diseases with distinctly different clinical outcomes [see comments]. *Heart.* 1997; 78:74. [PubMed: 9290406]
10. Dubrey SW, Davidoff R, Skinner M, et al. Progression of ventricular wall thickening after liver transplantation for familial amyloidosis. *Transplantation.* 1997; 64:74. [PubMed: 9233704]
11. Feng D, Syed IS, Martinez M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation.* 2009; 119:2490. [PubMed: 19414641]
12. Gertz M, Merlini G. Definition of organ involvement and response to treatment in AL amyloidosis: an updated consensus opinion. *Amyloid.* 2010; 17:48a.
13. Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. *Am J Hematol.* 2005; 79:319. [PubMed: 16044444]
14. Gertz MA, Falk RH, Skinner M, et al. Worsening of congestive heart failure in amyloid heart disease treated by calcium channel-blocking agents. *Am J Cardiol.* 1985; 55:1645. [PubMed: 4003314]
15. Gertz MA, Skinner M, Connors LH, et al. Selective binding of nifedipine to amyloid fibrils. *Am J Cardiol.* 1985; 55:1646. [PubMed: 4003315]
16. Gustavsson A, Jahr H, Tobiasen R, et al. Amyloid fibril composition and transthyretin gene structure in senile systemic amyloidosis. *Lab Invest.* 1995; 73:703. [PubMed: 7474944]
17. Hawkins PN, Aprile C, Capri G, et al. Scintigraphic imaging and turnover studies with iodine-131 labelled serum amyloid P component in systemic amyloidosis. *Eur J Nucl Med.* 1998; 25:701. [PubMed: 9662591]
18. Hosenpud JD, DeMarco T, Frazier OH, et al. Progression of systemic disease and reduced long-term survival in patients with cardiac amyloidosis undergoing heart transplantation. Follow-up results of a multicenter survey. *Circulation.* 1991; 84:III338. [PubMed: 1934428]
19. Hosenpud JD, Uretsky BF, Griffith BP, et al. Successful intermediate-term outcome for patients with cardiac amyloidosis undergoing heart transplantation: results of a multicenter survey. *J Heart Transplant.* 1990; 9:346. [PubMed: 2398427]
20. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med.* 2007; 357:1083. [PubMed: 17855669]
21. Lacy MQ, Dispenzieri A, Hayman SR, et al. Autologous stem cell transplant after heart transplant for light chain (AL) amyloid cardiomyopathy. *J Heart Lung Transplant.* 2008; 27:823. [PubMed: 18656793]
22. Liao R, Jain M, Teller P, et al. Infusion of light chains from patients with cardiac amyloidosis causes diastolic dysfunction in isolated mouse hearts. *Circulation.* 2001; 104:1594. [PubMed: 11581134]
23. Libbey CA, Skinner M, Cohen AS. Use of abdominal fat tissue aspirate in the diagnosis of systemic amyloidosis. *Arch Intern Med.* 1983; 143:1549. [PubMed: 6191729]
24. Liepnieks JJ, Benson MD. Progression of cardiac amyloid deposition in hereditary transthyretin amyloidosis patients after liver transplantation. *Amyloid.* 2007; 14:277. [PubMed: 17968687]

25. Modesto KM, Dispenzieri A, Cauduro SA, et al. Left atrial myopathy in cardiac amyloidosis: implications of novel echocardiographic techniques. *Eur Heart J*. 2005; 26:173. [PubMed: 15618074]
26. Ng B, Connors LH, Davidoff R, et al. Senile systemic amyloidosis presenting with heart failure: a comparison with light chain-associated amyloidosis. *Arch Intern Med*. 2005; 165:1425. [PubMed: 15983293]
27. Nowis D, Maczewski M, Mackiewicz U, et al. Cardiotoxicity of the anticancer therapeutic agent bortezomib. *Am J Pathol*. 2010; 176:2658. [PubMed: 20519734]
28. Obici L, Perfetti V, Palladini G, et al. Clinical aspects of systemic amyloid diseases. *Biochim Biophys Acta*. 2005; 1753:11. [PubMed: 16198646]
29. Palladini G, Campana C, Klersy C, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. *Circulation*. 2003; 107:2440. [PubMed: 12719281]
30. Palladini G, Perfetti V, Obici L, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. *Blood*. 2004; 103:2936. [PubMed: 15070667]
31. Pollak A, Falk RH. Left ventricular systolic dysfunction precipitated by verapamil in cardiac amyloidosis. *Chest*. 1993; 104:618. [PubMed: 8339658]
32. Ruberg FL, Appelbaum E, Davidoff R, et al. Diagnostic and prognostic utility of cardiovascular magnetic resonance imaging in light-chain cardiac amyloidosis. *Am J Cardiol*. 2009; 103:544. [PubMed: 19195518]
33. Rubinow A, Skinner M, Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. *Circulation*. 1981; 63:1285. [PubMed: 7014028]
34. Shi J, Guan J, Jiang B, et al. Amyloidogenic light chains induce cardiomyocyte contractile dysfunction and apoptosis via a non-canonical p38alpha MAPK pathway. *Proc Natl Acad Sci U S A*. 2010; 107:4188. [PubMed: 20150510]
35. Skinner M, Sancharawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. *Ann Intern Med*. 2004; 140:85. [PubMed: 14734330]

TABLE 1

Symptoms And Signs Of Cardiac Amyloidosis

Common Symptoms	Uncommon Symptoms	Physical Findings	ECG Findings	Echo Findings
Fatigue	Jaw or buttock claudication	Rales	Low voltage ECG	Concentric hypertrophy
Exertional dyspnea	Atypical chest pain	Pitting edema	Atrial fibrillation	Thickened IVS
Edema		Elevated JVP	Ventricular arrhythmias	Diastolic dysfunction
		Hepatojugular reflux		Systolic dysfunction (late)
		S3		

TABLE 2

Workup Of Cardiac Amyloidosis

Assay	AL	ATTR	AA	SSA	Source
Congo red fibrils	+	+	+	+	Pathology lab
Serum, urine immunofixation electrophoresis for monoclonal Ig	+	-	-	-	Clinical lab
Serum free light chains	+	-	-	-	Binding Site; Quest
Abnormal TTR isoelectric focusing	-	+	-	-	Specialty lab
Abnormal TTR gene sequence	-	+	-	-	Specialty lab; Athena
Kappa or lambda IHC	+	-	-	-	Pathology lab
TTR IHC	-	+	-	+	Pathology lab
AA IHC	-	-	+	-	Pathology lab
Mass spec protein identification	+	+	+	+	Specialty lab

TABLE 3Cardiac Biomarker Staging System⁷

Staging	NT-proBNP, 332 ng/L; CTnT, 0.035 µg/L	Median Survival
I	Neither elevated	26 m
II	One elevated	11 m
III	Both elevated	4 m