Light-chain cardiac amyloidosis: strategies to promote early diagnosis and cardiac response

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ABSTRACT
Amyloid light chain (AL) amyloidosis is a systemic disease characterised by the aggregation of misfolded immunoglobulin light chain (LC), predominantly in the heart and kidneys, causing organ failure. If untreated, the median survival of patients with cardiac AL amyloidosis is 6 months from the onset of heart failure. Protracted time to establish a diagnosis, often lasting >1 year, is a frequent factor in poor treatment outcomes. Cardiologists, to whom patients are often referred, frequently miss the opportunity to diagnose cardiac AL amyloidosis. Nearly all typical cardiac support measures, with the exception of diuretics, are ineffective and may even worsen clinical symptoms, emphasising the need for accurate diagnosis. Patients with severe cardiac involvement face poor outcomes; heart transplantation is rarely an option because of multiorgan involvement, rapid clinical decline and challenges in predicting which patients will respond to treatment of the underlying plasma cell disorder. Early diagnosis and prompt treatment with 'source therapies' that limit the production of amyloidogenic LC are associated with better survival and improvement in organ function after a median of 2.4 months following haematological complete response. However, organ recovery is often incomplete because these source therapies do not directly target deposited amyloid. Emerging amyloid-directed therapies may attenuate, and potentially reverse, organ dysfunction by clearing existing amyloid and inhibiting fibril formation of circulating aggregates. Improved recognition of AL amyloidosis by cardiologists allows for earlier treatment and improved outcomes.

INTRODUCTION
In amyloid light chain (AL) amyloidosis, misfolded immunoglobulin light chain (LC) produced by clonal plasma cells deposits in organs, causing their dysfunction (figure 1). The disease predominantly (~70% of patients) affects the heart, kidneys or both. 1 2 Advanced (Mayo stages IIIa, IIIb) cardiac AL amyloidosis is particularly lethal; median survival is <1 year versus ~8 years in patients without cardiac involvement. 2

In AL amyloidosis, LC fibrils infiltrate the myocardium, interfere with cell–cell coupling, disrupt cellular integrity 3 4 and may contribute to cell injury and death. LC monomers also can elicit oxidative damage by interacting with proteins involved in cell viability and metabolism, 5 suggesting that LC may be internalised. LC may promote cardiac stress hormone brain natriuretic peptide (BNP) expression through p38 mitogen-activated protein kinase (MAPK). 6 Sudden death in patients with AL amyloidosis is usually attributed to pulseless electrical activity, followed by ventricular arrhythmias, but may result from thromboembolic complications or bradyarrhythmias and conduction system disease secondary to amyloid infiltration or autonomic dysfunction. 7

Systemic amyloidoses, including AL amyloidosis, are frequently undiagnosed. 8 Despite advances in therapeutic regimens to stanch AL amyloidosis LC production—so-called source therapies—and to increase overall survival, the frequency of sudden death within ≤90 days of diagnosis remains at 23%–30% 9 and likely reflects advanced organ dysfunction. Thus, a critical need exists for earlier diagnosis of AL amyloidosis by cardiologists, to whom most patients without diagnoses are initially referred but who, based on a recent patient survey, diagnose amyloidosis in only ~18% of patients. 10 The other primary cause of cardiac amyloidosis is deposition of mutant or wild-type transthyretin amyloid (ATTRm or ATTRwt amyloidosis, respectively), which is outside the focus of this review but is similarly important (table 1).

CARDIOLOGIST IDENTIFICATION OF PATIENTS WITH CARDIAC AL AMYLOIDOSIS
AL amyloidosis may develop in patients with multiple myeloma (10%–15%) or may progress from monoclonal gammopathy of undetermined significance (MGUS) (9%). 9 These disorders are thus important diagnostic considerations; however, AL amyloidosis can be diagnosed in the absence of either disorder. The overall incidence of AL amyloidosis is estimated to be only 8.0–14.4 million persons per year in the USA 10 and suggests that a physician may diagnose only a few cases annually. Nonetheless, based on its prevalence, most cardiologists have encountered patients with cardiac AL amyloidosis. The nature of the patients' cardiac dysfunction may go undiagnosed, however, because symptoms of cardiac AL amyloidosis may mimic those of other restrictive cardiomyopathies, despite their being predominantly caused by AL amyloidosis (see online supplementary table 1).

AL amyloidosis is rarely diagnosed before symptoms appear; the vague, variable signs and symptoms of AL amyloidosis reflect advanced organ manifestation or involvement. Clues to diagnosis include heart failure associated with neuropathy, nephrotic syndrome, hepatomegaly, peribital bleeding and macroGLOSSIA. Cardiac ATTR amyloidosis is also frequently associated with neuropathy, primarily in patients with ATTRm amyloidosis, again highlighting the need for physician awareness in differential diagnosis. For patients with many forms of systemic amyloidosis, diagnosis ≥1 year after initial presentation to a physician is, unfortunately, common. It is estimated that one-third of patients may visit five or more physicians before...
diagnosis. Early detection allows for treatments that can halt cardiac damage, potentially reducing the risk for sudden death and allowing for spontaneous or therapeutically induced amyloid clearance and improved cardiac function.

The diagnosis of suspected AL amyloidosis, irrespective of organ involvement, involves identification of clonal disease and amyloid typing (figure 2). Serum-free light chain (FLC) should be measured, and serum and urine immunoelectrophoresis should be performed in all patients. If indicated based on initial screening tests, bone marrow biopsy is performed to determine whether plasma cell dyscrasia is present and to determine the percentage and type of λ- or κ-producing plasma cells. Routine use of the immunoglobulin FLC assay in patients with unexplained heart failure may be a relatively efficient, economical and non-invasive means to screen patients with AL amyloidosis. Nonetheless, healthcare providers must recognise that ATTR commonly affects the heart and will not be detected by the serum FLC assay. ATTRwt is an increasingly recognised form of amyloid, particularly in men older than 60 years.

Diagnosis must be confirmed by the detection of amyloid in organ or other tissue biopsy, using Congo red or other histological staining, and accurate typing. The choice of biopsy site depends on clinical findings and local expertise. Cardiac biopsy conclusively identifies cardiac AL amyloidosis; however, initial assessment of amyloid from periumbilical fat aspirates or from bone marrow or labial salivary gland biopsy specimens is a less invasive approach in patients with suspected AL amyloidosis with relatively high sensitivity (~80%) treated in experienced centres. Accurate amyloid typing is critical because treatment of cardiac amyloidosis depends entirely on amyloid type. Inaccurate typing exposes patients to inappropriate and ineffective treatment regimens with significant treatment-related morbidity and mortality. The current gold standard of amyloid typing is to determine the precursor protein using laser microdissection mass spectrometry. Although, this is available in only a few centres, specimens—including those fixed in paraffin—can be sent for analysis. Immunohistochemistry techniques have been misleading, even in experienced centres, and are discouraged. Mass spectrometry amyloid typing is not limited by selection of specific antibodies, thus allowing proper identification of the rarer forms of amyloid (eg, AA, apolipoprotein A1, gelsolin) that may affect the heart.

Organ manifestation or involvement can be assessed using a combination of biomarker assays, imaging assessments and functional tests (table 2). Cardiac involvement is defined by consensus guidelines as mean left ventricular (LV) wall

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**Table 1** Comparison of causes, clinical presentation and clinical outcome of the main types of cardiac amyloidosis

| Amyloidosis type | Clinical presentation | Clinical outcome |
|------------------|----------------------|------------------|
| AL | Heart failure, often with multiorgan involvement especially hepatomegaly, peripheral and autonomic neuropathy, nephrotic syndrome, macroglossia and periorbital purpura | With treatment and haematological response, patients’ outcomes vary with organ involvement; patients with advanced cardiac involvement may experience sudden cardiac death despite haematological response Without treatment, patients with cardiac involvement live <1 year |
| ATTRm | Heart failure with peripheral or autonomic neuropathy; only 50% positive family history | Cardiomyopathy is slowly progressive, and patients may not present with symptoms until ventricular wall thickening causes functional deficits in cardiac function Without treatment, patients with ATTR cardiac amyloidosis can survive from years to decades |
| ATTRwt | Heart failure with carpal tunnel syndrome, biceps tendon rupture and spinal stenosis Atrial fibrillation is a common feature, often several years before heart failure | |

AL, amyloid light chain; ATTRm, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; LV, left ventricular.
thickness ≥12 mm in the absence of other causes, N-terminal fragment of the pro-brain natriuretic peptide (NT-proBNP) >332 pg/mL in the absence of renal failure or atrial fibrillation or both. Cardiac biomarkers are the most robust predictors of prognosis in AL amyloidosis and underlie the Mayo 2004 and 2012 staging systems. Of note, the general features of cardiac involvement detailed in the aforementioned criteria and the functional assessments enumerated below, and in figure 3 and online supplementary table 1, do not specifically define cardiac AL amyloidosis in many patients because the presentation of disease is heterogeneous, but they do define the most common cardiac AL amyloidosis features. Furthermore, the simultaneous interpretation of a patient’s ECG, echocardiographic and imaging data can be instrumental in evaluating the relationship between functional and structural cardiac changes.

Patients with MGUS are at increased risk for AL amyloidosis. The differentiation of AL amyloidosis is based on the detection of organ damage and associated LC amyloid. Tissue diagnosis is

![Image](https://heart.bmj.com/first-published-as-10.1136/heartjnl-2016-310704-on-29-April-2017.jpg)
important given that MGUS is common in patients with ATTRwt, but it is unrelated to amyloid deposition in these patients.

**ELECTROCARDIOGRAPHY**

Infiltration of cardiac tissue with LC deposits is associated with electrical disturbances. Several studies have observed lowered QRS voltage (≤5 mV), particularly evident in limb leads, with cardiac AL amyloidosis. This finding distinguishes infiltrative from hypertrophic cardiac conditions and may be apparent at early stages of cardiac involvement and correlated with worse outcome. Low-voltage QRS complex occurs in approximately 45% of patients with AL amyloidosis and is more common than in patients with ATTR amyloidosis, perhaps related to the direct myocardial toxic effects of circulating LC independent of the degree of infiltration. Pseudo-infarct patterns are present in approximately 45% of patients with AL amyloidosis and should prompt consideration of amyloid in patients with ECG infarct patterns in the absence of regional wall motion abnormalities. Fragmented QRS is a common finding in AL amyloidosis and is associated with worse prognosis. The absence of low-voltage QRS complex does not exclude the diagnosis of AL amyloidosis; in fact, in one series, 16% of patients with cardiac biopsy-proven AL amyloidosis met ECG criteria for LV hypertrophy. Simultaneous interpretation of ECG and echocardiographic findings, as discussed below, is an important strategy.

**ECHOCARDIOGRAPHY**

Increased cardiac wall thickness without a known cause (eg, uncontrolled hypertension) may be the first red flag for cardiac amyloidosis. Characteristic echocardiographic findings in amyloidosis include increased left and right ventricular wall thickness with greater echogenicity (granular sparkling), though the latter is less specific in the era of harmonic imaging, and normal or mildly reduced LV cavity size with enlarged atria. Patients typically have preserved or moderately decreased LV ejection fraction (LVEF) but poor longitudinal function, which in some patients may predominate over fibrillatory dysfunction, which in some patients may predominate over fibrilatory dysfunction. These abnormalities of longitudinal ventricular function demonstrated by strain imaging are independent predictors of survival. Furthermore, abnormal right ventricular strain may be an early diagnostic clue. The severity of echocardiographic abnormalities and the rapidity at which they develop may correlate with worse prognosis. Atrial thrombi are common in AL amyloidosis, detected by echocardiography in 35% of patients in one series, and may occur even in the absence of sinus rhythm. Although most patients with significant cardiac AL amyloidosis have increased LV wall thickness, heart failure can occur in those with normal wall thickness. This may be explained by cardiotoxicity of the circulating LCs causing myocardial dysfunction, which in some patients may predominate over fibrillatory deposition. In addition, patients with wall thickness in the lower normal range at baseline may have significant amyloid deposits, yet the measured wall thickness may fall within the ‘normal’ range for age, sex and body surface area. An important distinction is that patients with ATTR, as opposed to AL, amyloidosis...
can experience a longer period of chronic disease before diagnosis, which may account for the increased wall thickness.

Although cardiac AL amyloidosis is generally considered a condition in which LVEF is preserved, a subset of patients may present with reduced LVEF and minimal or no ventricular wall thickening, again perhaps because of direct LC toxicity or predominant vascular involvement. Last, some patients with AL amyloidosis present with primarily endocardial involvement, leading to atypical imaging findings with thickened valves and endocardial surfaces but normal or only mildly increased wall thickness.

**CARDIAC MR (CMR) AND NUCLEAR IMAGING**

CMR and nuclear imaging should be considered for patients with unexplained heart failure and arrhythmias, especially when there is a suspicion of amyloid. Difficulty nulling the myocardium, abnormality of late gadolinium enhancement and abnormal T1 signal are all characteristic findings of cardiac amyloidosis. CMR is particularly helpful when the echocardiogram is inconclusive, and it is often the first clue to cardiac amyloidosis when the diagnosis has not otherwise been considered. However, CMR does not distinguish amyloid type, is limited because of restrictions in patients with renal impairment and pacemakers/defibrillators and does not definitively establish the diagnosis. Furthermore, patchy deposits may not cause abnormalities of late gadolinium enhancement and may lead to false-negative results. Two newer imaging agents, N-[methyl-11C]2-(49-methylamino-phenyl)-6-hydroxybenzothiazole ("1C-PiB; "1C-Pittsburgh B compound") and florbetapir, specifically bind cardiac amyloid and may be useful when combined with structural and functional imaging assessments. Although these agents are not specific to LC amyloid, florbetapir may offer significantly higher binding to LC than transthyretin. Although these agents are not specific to LC amyloid, florbetapir may specifically bind cardiac amyloid and may be useful when combined with structural and functional imaging assessments. However, although decreasing glomerular filtration rate and cardiac function in patients with both renal and cardiac amyloidosis. However, although decreasing glomerular filtration rate required a higher threshold for detecting heart involvement and predicting survival, NT-proBNP levels have been found to predict survival in patients with glomerular filtration rates ≥15 mL/min/1.73 m2.

**TREATMENT OF PATIENTS WITH AL AMYLOIDOSIS**

There are no approved therapies for AL amyloidosis; instead, modified treatment regimens for multiple myeloma are generally used. The ultimate goal of therapy is improved organ function; optimal therapies will target both the clonal plasma cell disorder (to stop production of the precursor protein) and existing amyloid deposits in organs and tissue (table 3).

### Plasma cell-directed therapies

Treatment regimens are based primarily on those for multiple myeloma and will reduce amyloidogenic LC precursor protein production from plasma cells; these regimens are the topic of evolving treatment algorithms. Patients are frequently treated with high-dose chemotherapy in combination with autologous therapies and/or heart transplantation Ameliorate symptoms of heart failure while patient is treated with other therapies or awaiting heart transplantation

| Table 3 | Treatments for patients with cardiac amyloid light chain (AL) amyloidosis and clinical outcome |
| --- | --- |
| **Treatment** | **Mechanism of action** | **Clinical outcome** |
| Plasma cell-directed therapies | Eliminate the production of amyloidogenic LC | Patients with advanced cardiac amyloidosis often die despite HR, whereas patients with less severe cardiac involvement may experience rapid improvement in cardiac biomarkers and cardiac function when FLC can be reduced by 50%–90% |
| Cardiac support therapies and/or heart transplantation | Ameliorate symptoms of heart failure while patient is treated with other therapies or awaiting heart transplantation | Patients with isolated cardiac deposition of amyloid may respond best to transplantation, but these treatments are supportive and not disease modifying |
| Amyloid-directed therapies | Inhibit amyloid fibril formation or neutralise and clearing circulating and deposited LC aggregates | Published clinical trial data have demonstrated cardiac and other organ responses with anti-LC and anti-SAP immunotherapy |

PLC, free light chain; HR, haematological response; LC, light chain; SAP, serum amyloid P component.

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stem cell transplantation (ASCT), alkylating agents, steroids, proteasome inhibitors and/or immunomodulatory drugs. The Mayo Stratification of Myeloma and Risk-Adapted Therapy consensus statement recommends initial stratification of patients with newly diagnosed AL amyloidosis to determine their eligibility for ASCT and indicates agents that may offer improved outcomes for first-line and second-line therapy (figure 4). Only a small number of patients with severe cardiac involvement are eligible for ASCT. Nonetheless, patient heterogeneity and the lack of clinical trial data, both heavily influenced by the relative rarity of the condition, confound these guidelines. Overall, plasma cell-directed (source) therapies can reduce the concentration of the proteotoxic LC by ≥50% (partial response or better) in ~60% of patients, which sometimes results in organ response; however, such improvement is often partial or incomplete. Moreover, sudden death can occur even in patients who experience haematological response (HR). In the first-line setting, cardiac response defined by consensus criteria (>30% and >300 pg/mL decrease in NT-proBNP) is observed in ~25% of patients who experience partial HR or better. In addition, patients who do not achieve organ response to first-line therapy have a lower probability of achieving organ response to second and subsequent lines of therapy. Although cardiac imaging studies are critical in the diagnosis of AL and often provide the first clue to diagnosis, use of these techniques to assess organ response is challenging. Wall thickness measurements are subject to variation based on multiple technical issues, and assessment of diastolic function can be affected by loading conditions and heart rate. Serial assessment of strain has been shown to correlate with clinical response but is subject to variability and differences between imaging platforms. Cardiac MRI findings are subject to similar limitations, though serial T1 mapping holds promise in assessing response to therapy.

Cardiac support therapies
Heart failure caused by cardiac AL amyloidosis poses a unique therapeutic challenge because of the complex nature of cardiac dysfunction in patients with renal and autonomic comorbidities and because typically used supportive measures are contraindicated. Conventional medications, such as beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, may contribute to early mortality and worsening of symptoms, further underscoring the importance of prompt diagnosis in directing treatment. Diuretics (loop diuretics and aldosterone receptor antagonists), in addition to monitoring electrolytes and creatine, are predominant supportive treatments. Use of an LV assist device presents challenges in patients who...
have small LV cavities with thickened walls and coexisting right ventricular dysfunction.43 Implantable cardioverter defibrillators (ICDs) have not been associated with survival benefit in patients with cardiac AL amyloidosis in retrospective series.46 Use of ICDs in selected patients with cardiac AL amyloidosis, especially those meeting the usual criteria for device implantation, remains controversial. Biventricular circulatory support is necessary for most patients, but a total artificial heart is available only as a bridge to transplantation. Concerns regarding infection, bleeding and thrombosis pose additional challenges for the use of circulatory support devices in patients with cardiac AL amyloidosis. As devices evolve, opportunities for circulatory support will likely improve.

Heart transplantation

In addition to the typical constraints associated with organ transplantation, the inadequacy of pretransplantation cardiac support measures and the risk for re-deposition of amyloid in the transplanted heart diminish the success of heart transplantation.47 Nonetheless, some patients with isolated cardiac involvement may be eligible for heart transplantation and may experience enhanced survival. Emerging therapeutic developments may lead to improved organ function, thereby reducing the need for heart transplantation.11

EMERGING TREATMENTS: AMYLOID-DIRECTED THERAPIES

Immunotherapeutics

Antibody-mediated phagocytosis combined with the clearance of amyloid is a promising approach to reverse organ dysfunction. Three antibodies are in clinical development.

An interim phase 1/2 report of 27 patients with AL amyloidosis treated with NEOD001 (ClinicalTrials.gov, NCT01707264), an antibody that targets misfolded LC, was recently published,48 and confirmatory results in an expansion phase of this study have been presented.49 Favourable renal and cardiac responses were observed in evaluable patients. NEOD001 was well tolerated; no patients experienced infusion-related hypersensitivities. Reductions in NT-proBNP underscore the potential for increasing survival with NEOD001. Moreover, organ responses were evident in patients >2 years after their last plasma cell-directed therapy, supporting that NEOD001 directly improves organ function. Two ongoing randomised, placebo-controlled, global trials (ClinicalTrials.gov, NCT02632786 and NCT02312206) specifically address the safety and efficacy of NEOD001 in patients with cardiac AL amyloidosis.

Richards et al,50 in their interim phase 1 trial report (ClinicalTrials.gov, NCT01777243), observed reduced serum amyloid P (SAP) component, an amyloid-binding protein that stabilises fibrils and promotes fibril formation after a single anti-SAP antibody infusion, in eight patients with AL amyloidosis also treated with the small molecule circulating SAP-binder CP4HPC ((2R)–1-[6-[(2R)–2-carboxypropylidin-1-yl]-6-oxohexanoyl] pyrrolidine-2-carboxylic acid). This trial detailed two patients with AA (inflammatory) amyloidosis, one patient with AApoAI amyloidosis and four patients with AFib amyloidosis. Treatment was associated with increased liver resiliency in patients with liver stiffness, a sign of amyloid infiltration. Although the clinical significance of these changes is unknown, this trial validates the immunotherapeutic approach; cardiac responses were not addressed. The safety of anti-SAP treatment, however, requires further study; several patients treated with anti-SAP experienced infusion-related inflammatory responses.

Preliminary results of a phase 1a trial (ClinicalTrials.gov, NCT02245867) of eight patients who previously received systemic treatment and were each administered a single infusion of 11–1.5F4, which, like NEOD001, targets misfolded LC, have also been presented. In this small ongoing study, organ responses were observed within 8 weeks after treatment.51

Antifibril formation therapy

Preclinical studies have shown that doxycycline inhibits fibrillogenesis.52 Preliminary results of a case-matched study of 30 patients with stage III cardiac AL amyloidosis (Alchemy; UK National Amyloidosis Centre)53 demonstrated extended survival in response to twice-daily doxycycline (100 mg) and meticulous standard of care. If confirmed, these results may bolster the efficacy of doxycycline in patients who achieve HR.

CONCLUSION

Delays in diagnosis and treatment likely contribute to the poor life expectancy of patients with cardiac AL amyloidosis despite improved treatments; increased clinical suspicion among cardiologists is needed. Improved survival in patients with less advanced disease highlights that cardiac AL amyloidosis is not a hopeless condition and may be effectively treated. Accurate diagnosis and appropriate treatment will ensure patients are not needlessly subjected to standard medications for heart failure that may be ineffective or even harmful. Emerging interventions may specifically target amyloid, potentially improving cardiac function.

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