

VIEWPOINT

Management of Amyloid Cardiomyopathy in Resource-Constrained Settings

Challenges and Opportunities



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Amyloid cardiomyopathy (AC) is characterized by extracellular deposition of amyloid fibrils and is an aggressive form of heart disease, often resistant to conventional heart failure (HF) therapies. Data regarding AC from resource-constrained settings such as India are sparse, although it is clear that most patients present late with symptomatic HF and without access to a full diagnostic workup. We provide a snapshot of the current clinical landscape of AC in India and highlight existing challenges and potential opportunities in this context. The discussion presented below is applicable to most resource-limited settings worldwide.

The incidence of myeloma in India ranges from 0.97 to 1.26 per 100,000 population, indicating approximately 15,000 new patients diagnosed every year. Of these patients, approximately 12%-15% are expected to have light-chain (AL) amyloidosis, with 50% having cardiac involvement (1). By this estimate, India should have approximately 900-1,200 newly diagnosed patients with AC per year. However, literature searches (PubMed with the terms “cardiac amyloid AND India” or “amyloid cardiomyopathy AND India”) highlighted only 6 patients in the largest published case series, with no data on amyloid protein characterization nor long-term treatment outcomes from India (2).

Our viewpoint is that this phenomenon is likely a result of shortcomings in disease diagnosis rather than low incidence. In the Trivandrum Heart Failure Registry data, ~26% patients had HF with preserved ejection fraction, of which some may be expected to secondary to AC. A recent series describing histopathologic findings in 927 patients who had undergone endomyocardial biopsy (EMB) in an Indian institution documented amyloidosis as the most frequent pathology, occurring in ~70 patients (3). In another analysis from the All India Institute of Medical Sciences, ~15% of patients with cardiomyopathy were found to have a restrictive pathology, awaiting a definitive diagnosis (4). All of these studies indicate a significant number of patients with possible undiagnosed AC, who can be best identified and treated by means of a multidisciplinary approach involving hematology/oncology, cardiology, and radiology.

Several factors may contribute to this gap in diagnosis and reporting of AC. AC diagnosis requires documentation of characteristic findings on echocardiography or cardiac magnetic resonance imaging (cMRI), with some patients requiring EMB. Subtyping with the use of mass spectroscopy is required to delineate the exact nature of amyloid protein to guide therapy and follow-up. However, these facilities and expertise for standardized reporting are available only in select referral centers, precluding access for a large majority of patients. The combined effect of these resource limitations on delayed diagnosis and treatment is reflected in data from India, where most patients present late, providing a very small window for clinical intervention. In the largest case series from India describing patients with symptomatic AC (n = 6), a significant majority of patients (83%) presented with symptomatic HF and 66% died within 1

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TABLE 1 Alternatives to Published Guidelines to Improve the Management of Amyloid Cardiomyopathy in Resource-Constrained Settings

Guideline Recommendation	Problems in Resource-Constrained Settings	Alternative Cost-Effective Solutions
Cardiac magnetic resonance imaging	Lack of wide availability or trained operators	Specific echocardiographic parameters, including E/e' ratio and global longitudinal strain assessment
Endomyocardial biopsy	Available in few select centers only	Biopsy from easily accessible tissue, eg, abdominal fat pad, rectal biopsy
Mass spectrometry for amyloid subtyping	Available in few select centers only or as part of research protocols	Evaluate for light-chain amyloidosis with the use of basic biomarkers to identify candidates for plasma cell-directed therapy. Connect with laboratories in India and abroad to facilitate subtyping for transthyretin amyloidosis.
Specific therapies targeting amyloid	Newer therapies often not available (patisiran, tafamidis, diflusal), possibly owing to low disease identification and classification	Optimize symptomatic control of heart failure. Identify patients for early autologous stem cell transplantation, which is more widely available in India.

year of diagnosis (2). A recent abstract from India presented at the European Hematology Association Congress in 2020 described 25 patients with AL amyloidosis, of which 92% presented with symptomatic HF and 44% died within a month after diagnosis (5).

However, implementing published guidelines *prima facie* in resource-constrained settings may not be the most effective strategy for AC and requires innovative approaches. First, with reduced access to cMRI, echocardiography assumes an important role owing to low cost and availability. Specific echocardiographic parameters, including E/e' ratio (a measure of diastolic evaluation) and left ventricular (LV) global longitudinal strain (GLS), are sensitive markers of cardiac amyloid before overt LV dysfunction becomes apparent and are more readily available in India. GLS demonstrates high sensitivity (area under the receiver operating characteristic curve: 0.95; 95% CI: 0.89-0.98) in identifying AC, even in patients with mild ventricular hypertrophy (6).

Second, utilization of resources to identify amyloid tissue by proteomics is unlikely to influence disease management for a majority of patients in India. With sparse facilities for amyloid protein characterization, identifying patients with AL amyloidosis should be the first pragmatic step in management. This assumes a greater importance in resource-constrained settings because patients with AL amyloidosis are candidates for plasma cell-directed therapy and autologous stem cell transplantation (ASCT). This can be achieved with standard evaluation for plasma cell dyscrasia, including bone marrow aspiration/biopsy and evaluation for monoclonal gammopathy of unknown significance. Inexpensive and universally available biomarkers—including abnormal levels of proteins such as N-terminal pro-B-type natriuretic peptide

and troponin T that suggest cardiac dysfunction and HF—could be obtained in patients at diagnosis for diagnostic and prognostic information in this setting (7). Patients with AL amyloidosis demonstrate a definite survival benefit with multiple myeloma-directed therapy followed by ASCT. This benefit is preserved even in selected patients with elevated cardiac biomarkers, who have traditionally been excluded from ASCT (8).

Amyloid cardiomyopathy without AL amyloidosis is most commonly due to abnormal deposits of the transthyretin amyloid (ATTR), which is primarily produced by the liver. ATTR amyloidosis may be hereditary/familial or acquired/wild type. Management of patients with AC due to ATTR amyloidosis is more challenging in resource-constrained settings because these patients may require orthotopic liver or cardiac transplantation, both inaccessible to a vast majority of the Indian population. However, analysis of TTR gene mutations for this cohort of patients can enable differentiation between familial and wild-type TTR amyloidosis, and allow for targeted therapies in the future (9). Facilities for genetic testing, including gene panels by next-generation sequencing (NGS), can be easily incorporated into the current infrastructure (10).

In patients with evidence of systemic amyloidosis and characteristic signs on cardiac imaging, EMB may not be essential and should not deter the diagnosis of AC. In India, EMB has a role in patients who have characteristic imaging findings but ambiguous results on fat pad or rectal biopsy. EMB also has a specific role in excluding endemic endomyocardial fibrosis, which can present with similar findings. Feasibility and safety of EMB in India was described in 572 patients more than 25 years ago and can be expected to be much safer at the present time (11). Widespread training for EMB, in combination with low-cost

cardiac catheterization (already available in India), will increase access to this sensitive diagnostic technique.

Finally, collaboration from centers across the country is essential to accurately collect data regarding the epidemiologic and clinical features in Indian patients. **Table 1** summarizes gaps between guidelines and real-world practice and presents viable adaptations in resource-constrained settings.

Thus, current data indicate significant underdiagnosis of AC in India and, by extension, other resource-constrained settings, which can be offset by appropriately modifying published guidelines for local use, augmenting low-cost diagnostic methods, and conducting collaborative data collection. Physician and echocardiographer training to assess these parameters can mitigate gaps in case detection and

offset the nonavailability of advanced imaging. We envision a hub-and-spoke model, where an apex institute trains regional centers in diagnosing AC based on echocardiographic findings. This will enable early diagnosis and facilitate improved outcomes for our patients.

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