Restrictive Cardiomyopathy
Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy

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Abstract: Restrictive cardiomyopathy (RCM) is characterized by nondilated left or right ventricle with diastolic dysfunction. The restrictive cardiomyopathies are a heterogeneous group of myocardial diseases that vary according to pathogenesis, clinical presentation, diagnostic evaluation and criteria, treatment, and prognosis. In this review, an overview of RCMs will be presented followed by a detailed discussion on 3 major causes of RCM, for which tailored interventions are available: cardiac amyloidosis, cardiac sarcoidosis, and cardiac hemochromatosis. Each of these 3 RCMs is challenging to diagnose, and recognition of each disease entity is frequently delayed. Clinical clues to promote recognition of cardiac amyloidosis, cardiac sarcoidosis, and cardiac hemochromatosis and imaging techniques used to facilitate diagnosis are discussed. Disease-specific therapies are reviewed. Early recognition remains a key barrier to improving survival in all RCMs. (Circ Res. 2017;121:819-837. DOI: 10.1161/CIRCRESAHA.117.310982.)

Key Words: amyloidosis ■ cardiomyopathies ■ diagnosis ■ hemochromatosis ■ sarcoidosis

Restrictive cardiomyopathy (RCM) is a myocardial disorder that usually results from increased myocardial stiffness that leads to impaired ventricular filling. Biventricular chamber size and systolic function are usually normal or near-normal until later stages of the disease. Affecting either or both ventricles, RCM may cause signs or symptoms of left or right heart failure. Arrhythmias and conduction disturbances are frequently encountered.

RCM may result from inherited or acquired predispositions and disease or a combination thereof, which broadly can be classified as infiltrative, storage disease, noninfiltrative, and endomyocardial (Table 1). Because of the heterogeneous nature of the origins and manifestations of the RCMs and the concomitant challenges in diagnosing these diseases, it is difficult to accurately estimate the incidence and prevalence of any of the RCMs. Based on the current evidence, RCM is the least common of the cardiomyopathies. There are regional differences among the prevalence of RCM according to the cause. For example, endomyocardial fibrosis is primarily seen in the tropics and sub-Saharan Africa, whereas cardiac amyloidosis (CA) is more commonly diagnosed in other regions. Most causes of RCM are acquired. However, mapping several gene mutations as a cause of RCM have been recognized. These include mutations in the sarcomere subunits, such as troponin T (TNNT2 gene), troponin I (TNNI3), α-actin (ACTC), and β-myosin heavy chain...
MYH7). Most of these mutations are inherited in an autosomal dominant fashion.2

The diagnosis of RCM should be suspected in a patient with normal or near-normal systolic function and evidence of diastolic dysfunction with a restrictive filling pattern on echocardiography. Echocardiography-based 2-dimensional and Doppler are essential for determining diastolic dysfunction and for distinguishing patients with RCM from patients with restrictive physiology because of constrictive pericarditis. Echocardiography may also provide information to suggest a specific diagnosis such as the presence of regional wall motion abnormalities in a noncoronary distribution and aneurysms, which would raise the suspicion for cardiac sarcoidosis (CS). Cardiac magnetic resonance (CMR) imaging can aid in the diagnostic process, but the use should be determined on an individual basis. Endomyocardial biopsy (EMB) may be helpful for establishing a diagnosis in some cases. Ultimately, diagnosis of any of the RCMs relies on a constellation of clinical, laboratory, and imaging findings.

Treatment of RCM includes treating the underlying cause (if identified) and heart failure management. Diuretics are the mainstay of treatment to reduce volume overload. However,
volume status in patients with RCM may be challenging to manage, as patients with RCM rely on high filling pressures to maintain cardiac output and excessive diuresis may result in tissue hypoperfusion. The use of β-blockers or calcium channel blockers to increase filling time or to manage arrhythmias should be carefully introduced, as some patients may be intolerant. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may also be considered, but the proof of benefit is lacking and these agents may not be well tolerated. Anticoagulation is required in patients with atrial fibrillation, mural thrombus, or evidence for systemic embolization and may be helpful in most patients because of propensity for thrombus formation in the left atrial appendage. Advanced heart failure therapies, including cardiac transplantation, may be beneficial for selected patients. Left ventricular assist device (LVAD) therapy may be particularly applicable in patients with RCM as a bridge to transplant or as definitive therapy.3

In this review, we focus on CA, CS, and cardiac hemochromatosis (CH), 3 of the most common RCMs that illustrate the broad clinical spectrum of RCM. These 3 myocardial disorders are likely to be encountered in clinical practice, and tailored therapy is available for each of them. Clinical manifestations and diagnostic clues, modes of diagnosis, and evolving treatment strategies for each of these 3 disorders are reviewed in detail.

**Cardiac Amyloidosis**

Amyloidosis is a syndrome characterized by the extracellular deposition of a misfolded protein as amyloid, leading to organ functional loss. Amyloid deposition in the heart leads to cardiomyocyte separation, cellular toxicity, apoptosis, and tissue stiffness. Amyloid deposits are insoluble and accumulate continuously, leading to heart failure from mechanical, biochemical, and electric dysfunction. There are >30 recognized amyloidogenic proteins, which differ in pathogenesis, organ tropism, disease course, and treatment. This review will focus on the 3 most common types of CA: light chain immunoglobulin (AL), wild-type transthyretin (ATTRwt), and mutant transthyretin (ATTRm) amyloidoses.

**AL Amyloidosis**

AL amyloidosis is a rare clonal plasma cell disorder, characterized by the production of monoclonal kappa or lambda light chains (LCs), immunoglobulin fragments that can misfold. LC burden is usually low. With the introduction of the serum free LC assay, detection of a monoclonal protein is feasible in >98% of patients and is an important clue to diagnosis.4 Most patients have ≤10% plasma cells in their bone marrow. AL amyloidosis differs from myeloma with a different pattern of genetic events in the clonal plasma cells.4 Infrrequently, AL amyloidosis can arise from other immunoglobulin LC-secreting hematologic cancers, such as Waldenström macroglobulinemia.

**Wild-Type Transthyretin Amyloidosis**

TTR (transthyretin) is produced primarily in the liver. Other sources for TTR are the choroid plexus in the brain and the pigmented retinal epithelium. This protein serves as a transporter for thyroxin and for retinol-binding protein. TTR functions as a tetramer, but has an innate ability to dissociate into monomers, which have the amyloidogenic properties. ATTRwt CA, formerly referred to as senile CA, occurs primarily in elderly men. However, with increased awareness and more sensitive detection techniques, it is being recognized more frequently in women and occasionally can be diagnosed as early as age 40 years.3

**Mutant TTR Amyloidosis**

Several point mutations in the TTR gene, causing single amino acid substitutions, increase the likelihood of the TTR tetramer to dissociate into monomers and form amyloid fibrils. ATTRm is an autosomal dominant disorder. Symptom onset is in adulthood and tends to be consistent within a pedigree. There are >130 mutations described to date, with V30M (replacement of valine by methionine at position 30) the most common worldwide, prevalent in Japan, Sweden, and Portugal. In the United States, the most common mutations are the V122I and the T60A, the former has a carrier rate of ~4% among blacks. The V122I mutation carries a higher prevalence of symptomatic heart failure (hazard ratio, 1.47; confidence interval, 1.03–2.1) although the absolute rate is low (7%).4 This suggest an incomplete penetrance, modified by unknown factors.

**Other Types of CA**

Amyloid A (AA) amyloidosis is a rare complication of long-standing infectious or inflammatory condition, leading to excess production of serum AA, which has the ability to form amyloid fibrils. Although in the past chronic infections were the most common cause of AA amyloidosis, the most common causes currently are rheumatologic diseases, although in one third of patients, a cause remains unknown. AA amyloidosis rarely involves the heart.

Isolated atrial amyloidosis is a localized amyloidosis, confined to the walls of the atria, where the precursor protein is atrial natriuretic peptide. The presentation is atrial fibrillation. Premortem recognition is uncommon.

ApoA-I amyloidosis, caused by a mutation in the APOA1 gene, should also be considered in the differential diagnosis of CA although infrequently seen.

**Prevalence**

The incidence of AL amyloidosis is estimated between 3 and 9 cases per million/y. Between 60% and 80% of patients with AL amyloidosis have cardiac involvement. The prevalence of ATTRm CA is not known, reflecting both the global variation in mutation prevalence and disease awareness. In a series of 100 patients with EMB-proven disease, 74% had AL-type, 22% had ATTRwt-type, and 4% had ATTRm-type.7

**Clinical Characteristics**

As discussed above, CA presents with signs and symptoms of heart failure and poor exercise tolerance because of diminished cardiac output. Low blood pressures are often seen, complicating heart failure management. Pulmonary edema is uncommon. Syncope occurs occasionally, often exertional, reflecting the limited ability of the heart to increase diastolic filling and is an ominous sign. Syncope may also be aggravated by antihypertensive medications. Concomitant autonomic
neuropathy can precipitate orthostatic hypotension as can volume contraction from nephrotic syndrome.

Arrhythmias and conduction disturbances are frequent. The incidence of atrial fibrillation is type dependent, higher in ATTRwt (45%) than in AL (12%) or in ATTRm (15%). Although not found to be associated with increased mortality, the occurrence of atrial fibrillation is linked to symptomatic heart failure. Sudden cardiac death (SCD) is seen mainly with the AL type and probably represents electromechanical dissociation rather than ventricular tachycardia/fibrillation (VT/VF). Less frequent cardiac manifestations include dynamic LV outflow obstruction, often confused with hypertrophic cardiomyopathy; cardiac ischemia caused by amyloid deposition in intramural coronary arteries; and intracardiac thrombosis caused by atrial wall standstill, with a risk for systemic embolization.

**Red Flags to Guide Disease Recognition**

As the presentation is nonspecific, CA recognition is challenging. Patients frequently undergo extensive cardiac evaluation, including coronary angiography, without a diagnosis. There are, however, clues that can aid in early recognition. Thickened heart walls in the absence of known hypertension or valvular disease and low-to-normal voltage in the QRS complex despite thickened heart walls suggest CA. However, heart involvement can be seen without thickened walls in AL amyloidosis, and a low-voltage ECG is not uniformly present. In ATTRwt, extracardiac involvement is infrequent. However, >50% of patients have a history of carpal tunnel syndrome caused by amyloid deposition in the carpal tunnel synovium, with symptoms typically preceding cardiac symptoms by almost a decade. In ATTRm and in AL amyloidosis, extracardiac organ involvement is more frequent, the most common being nephropathy (nephrotic syndrome and/or renal failure); autonomic or peripheral neuropathy and gastrointestinal symptoms. Hepatopathy (hepatomegaly or increased level of serum alkaline phosphatase) is seen in >15% to 20% of patients with AL amyloidosis, but not in patients with ATTRm. The presence of a large tongue can be seen without thickened walls in AL amyloidosis, and a low-voltage ECG is not uniformly present. In ATTRwt, extracardiac involvement is infrequent. However, >50% of patients have a history of carpal tunnel syndrome caused by amyloid deposition in the carpal tunnel synovium, with symptoms typically preceding cardiac symptoms by almost a decade. In ATTRm and in AL amyloidosis, extracardiac organ involvement is more frequent, the most common being nephropathy (nephrotic syndrome and/or renal failure); autonomic or peripheral neuropathy and gastrointestinal symptoms. Hepatopathy (hepatomegaly or increased level of serum alkaline phosphatase) is seen in >15% to 20% of patients with AL amyloidosis, but not in patients with ATTRm. The presence of a large tongue can be seen without thickened walls in AL amyloidosis, and a low-voltage ECG is not uniformly present. In ATTRwt, extracardiac involvement is infrequent. However, >50% of patients have a history of carpal tunnel syndrome caused by amyloid deposition in the carpal tunnel synovium, with symptoms typically preceding cardiac symptoms by almost a decade. In ATTRm and in AL amyloidosis, extracardiac organ involvement is more frequent, the most common being nephropathy (nephrotic syndrome and/or renal failure); autonomic or peripheral neuropathy and gastrointestinal symptoms. Hepatopathy (hepatomegaly or increased level of serum alkaline phosphatase) is seen in >15% to 20% of patients with AL amyloidosis, but not in patients with ATTRm. The presence of a large tongue is invariably seen in AL amyloidosis (15%–25% of patients), whereas vitreous involvement is exclusively seen in ATTRm. Family history, focused on cardiomyopathy and neuropathy, should be sought in all patients.

In addition to organ-specific symptoms, patients with amyloidosis, regardless of type, have constitutional symptoms, such as fatigue and weight loss and quality of life is significantly impaired. These symptoms, albeit nonspecific, reflect the systemic nature of the disease.

**Noninvasive Imaging**

**Echocardiography**

Echocardiography is the standard diagnostic imaging modality for CA. It carries both diagnostic and prognostic utility. Two-dimensional transthoracic echocardiography reveals a concentric thickening of the LV free wall and septum (Figure 1). However, unlike hypertrophic cardiomyopathy or hypertensive cardiac disease, right ventricular (RV) free wall and atrial septum thickening is frequently present in CA along with enlarged atria. Wall thickening is greater in patients with ATTRwt than in patients with ATTRm and AL amyloidosis, but cannot be used to differentiate between types. Patients with ATTRwt live longer and are less symptomatic, suggesting that organ dysfunction in amyloidosis is not caused simply by mechanical disruption of the organ. Other echocardiographic findings to support CA include thickened valves and the presence of pericardial effusion, albeit both are nonspecific. The sparkling appearance of the myocardium is nonspecific, and its absence should not be used to rule out CA. Doppler imaging reveals a restrictive pattern in a transmitral tracing, with an abnormally high E/A ratio, indicating accentuated early filling with diminished late filling.

Echocardiographic strain imaging has the advantage of detecting early cardiac involvement, even before thickened walls or symptoms are apparent. Strain refers to the deformation of the myocardium on contraction and is given as a percentage length change. In its early stages, strain imaging was assessed by tissue Doppler imaging, but non-Doppler speckle-tracking strain imaging has become a standard practice, with the advantage of nonangle-dependent measurements. In CA, global longitudinal strain (GLS) is typically more impaired in the basal and midwall segments than in the apex (basal-apical gradient; bull’s eye plot), irrespective of the type. Strain imaging is prognostic.

**Cardiac Magnetic Resonance Imaging**

In clinical practice, CMR is an ancillary imaging modality that can support the diagnosis of CA, especially where echocardiographic findings are equivocal and clinical suspicion for cardiac involvement remains high. CMR provides morphological and flow-based data. However, its enhanced ability to recognize CA lies in the characteristic late gadolinium enhancement (LGE) pattern (Figure 2). Gadolinium rapidly migrates into the extracellular space. As amyloidosis is characterized by expansion of this compartment, LGE is highly suggestive of amyloidosis, distinct from other causes of cardiac wall thickening. The pattern of LGE can be global or focal, subendocardial or transmural. LGE is associated with an inferior survival, regardless of the amyloid type, and survival is further impaired in those with a transmural versus a subendocardial pattern.

**Nuclear Imaging**

Many nuclear tracers have been studied in CA, mainly with bone-seekers, technetium-labeled bisphosphonates (99mTc-DPD, 99mTc-HMDP, and 99mTc-PYP). These tracers have greater avidity to myocardium in ATTR than in AL amyloidosis (Figure 3). Recently, a collaborative study showed >99% sensitivity in cardiac involvement detection among patients with ATTR with a specificity of 86%. Ninety-four percent of biopsy-proven cardiac ATTR had moderate-to-high uptake (uptake equal or greater than bone), whereas only 21% of patients with cardiac AL had this level of uptake, with similar results for all the above-mentioned tracers. With the exclusion of patients with a monoclonal gammopathy, a moderate-to-high uptake has high specificity and a positive predictive value of 100% for cardiac ATTR.

**Biomarkers**

Cardiac troponin and B-type natriuretic peptide (BNP) (or its N-terminal fragment [NT-proBNP] (N-terminal pro-B-type
natriuretic peptide) are useful markers for diagnostic and prognostic purposes. Elevation in BNP/NT-proBNP reflects myocardial stretch exerted by the amyloid deposits, whereas elevation in cardiac troponin is thought to represent myocyte damage. Both cardiac biomarkers are renally excreted and therefore are elevated in the presence of renal impairment. BNP may be preferred in patients with end-stage renal failure. As AL amyloidosis has a high frequency of simultaneous renal involvement biomarker interpretation can be challenging. Although troponin T is considered specific for cardiac tissue, it can be elevated from amyloid deposits in skeletal muscle. Patients with cardiac AL have higher levels of serum NT-ProBNP than patients with ATTR, either wild-type or hereditary. This is remarkable, given the fact that patients with ATTR have a greater wall thickness, higher LV mass, and a lower LV ejection fraction (EF) than patients with AL. This thought to represent a toxic effect of the amyloidoigenic LCs on the myocardium.

The Mayo 2004 staging for AL amyloidosis defines prognosis based on cardiac biomarkers, revised in 2012 to include the LC burden. Cardiac biomarkers have also been incorporated into a ATTRwt risk model.

**Diagnostic Evaluation**

The diagnosis of CA requires a positive biopsy for Congo red staining coupled with typing of the protein associated with the deposit. Although EMB is the gold standard for diagnosis of CA, it may rarely result in complications. Owing to advanced

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**Figure 1.** A, Parasternal long-axis view demonstrates thinning and scarring of the mid anterior septum (arrow) because of previous myocardial infarction. The basal septum measures 12 mm and posterior wall 18 mm. B, Parasternal short-axis view: thinned and scarred anterior wall (') with thickening of the posterior wall (arrow). C, Apical long-axis view, Mayo format: demonstrates thinned and scarred anterior septum (') with thickening of the inferior-lateral wall (arrow). D, Global longitudinal strain is markedly reduced at −5% but does not demonstrate the typical bull’s eye pattern of cardiac amyloidosis because of anterior-apical infarction. Courtesy of Martha Grogan, MD, Mayo Clinic, Rochester, MN.

**Figure 2.** Cardiac magnetic resonance imaging of patient with cardiac amyloidosis. A, Early gadolinium phase. Note the thickened heart walls. B, Diffuse late gadolinium enhancement of the myocardium.
imaging and the use of cardiac biomarkers, more easily accessible tissues should be sampled first (Figure 4). Subcutaneous fat pad aspirate is positive in almost half of the patients although the yield is higher in AL>ATTRm>ATTRwt (80% versus 67% versus 14%, respectively). When a monoclonal protein is found in blood/urine studies or if the serum free LC assay is abnormal, suggesting AL amyloidosis, a bone marrow biopsy performed for the evaluation of plasma cell dyscrasia is an additional tissue source for Congo red staining, and when coupled with fat aspirate, is diagnostic in 85% to 90%. When these tissues fail to demonstrate amyloid deposits, EMB is a rational approach, but other soft tissue sources can still be biopsied (lip, rectum) if EMB is deemed unsafe. If EMB is attempted, measurement of right heart pressure and the pulmonary capillary wedge pressure should be performed, as this may help in the cardiac management.

After biopsy confirmation of amyloid deposits, amyloid typing is required as treatment is type-specific. Traditionally, typing was done by immunohistochemistry using commercial antibodies against the suspected precursor protein. However, false-positive and false-negative results occur, and rare amyloid types cannot be identified by this method. Today, the gold standard is mass spectrometry, a proteomic analysis that sequences the amino acid composition of the proteins present in the deposit to allow identification of the amyloidogenic protein. This technique has 100% specificity and 98% sensitivity. Mass spectrometry requires a trained and equipped laboratory. If not available, amyloid typing can be done by immunohistochemistry or immunoelectron microscopy, but should be cross-validated with clinical and laboratory data. If ATTR (wild-type or mutant) is suspected based on clinical grounds or is proven by amyloid typing,

**Figure 3. Nuclear imaging in cardiac amyloidosis.** A. A planar whole-body image using 99mTc-labeled pyrophosphate (99mTc-PYP), demonstrating grade 3 cardiac uptake, characteristic of transthyretin cardiac amyloidosis. B. Single-photon emission computed tomography image showing increased uptake in the heart. The uptake here is equivalent to that seen in bone.
DNA analysis of the TTR gene is required to identify a potential TTR mutation. In the event of confirmed ATTRm, genetic counseling is indicated for siblings and children.

After tissue diagnosis and amyloid typing, the extent of involvement should be sought. Patients with ATTRwt usually do not have additional visceral involvement outside the heart, but 5% of patients present with noncardiac organ damage. In ATTRm and in AL amyloidosis, up to 40% of patients may have extracardiac disease in ≥2 organs.

**Prognosis**

AL amyloidosis carries the poorest prognosis among systemic amyloidosis syndromes. In the absence of treatment, the median survival is 6 months\(^{22}\) compared with 24 to 66 months in ATTR CA.\(^{23}\) This survival difference might be a result of the direct cardiotoxicity effect of the LCs, or the more widespread involvement associated with AL amyloidosis.

**Treatment**

The goal of treatment is to halt production of the pathogenic protein and hope for organ recovery. This should translate into an improvement in the quality of life and longer survival. Recently, however, targeting the deposits themselves has been introduced. As many patients are frail as a result of advanced disease, age, or comorbidities, treatment selection should be made to avoid significant therapy-related toxicity and treatment interruptions. This is best accomplished in specialized centers and requires multidisciplinary care. Cardiac supportive care is essential to manage ongoing symptoms and treatment toxicity.

**Heart Failure Medications**

Most medications used for heart failure management are not well tolerated by patients with CA. Angiotensin-converting enzyme inhibitors and angiotensin receptor II blockers often lead to profound hypotension, even in modest doses. \(β\)-blockers and calcium channel blockers may aggravate hypotension because of the fixed stroke volume and need for a higher heart rate to maintain cardiac output. Loop diuretics and aldosterone antagonists remain the mainstay of treatment, requiring monitoring for changes in creatinine and electrolytes. The choice of loop diuretics remains unanswered. Torsemide has better bioavailability than furosemide and a longer half-life. Care should be taken to avoid excessive diuresis as this may invoke a fall in filling pressures and result in systemic hypoperfusion.

For tachyarrhythmia rate control, digoxin use is limited as the drug can bind to amyloid fibrils, increasing the risk of digoxin toxicity. Amiodarone may be considered, but has not been proven to be beneficial and can cause significant thyroid dysfunction in patients with amyloidosis.\(^{24a}\) \(β\)-blockers may be used cautiously for this purpose.

**Device Therapy**

SCD accounts for approximately one third of early deaths in AL amyloidosis.\(^{24}\) The rate in ATTR is under-reported but presumably is less. Although fatal ventricular arrhythmias are encountered, most SCDs are attributed to electromechanical dissociation. Our experience suggests that an internal cardiac defibrillator (ICD) does not result in a survival advantage, although appropriate patient selection may increase the benefit.\(^{25}\)

LV assist devices have emerged as a treatment modality for refractory heart failure. However, its use in CA has been reported predominantly in non-AL amyloidosis, reflecting strict patient selection as a result of serious adverse events associated with the device.\(^{26}\) Its use should be restricted to patients with CA and no extracardiac involvement. The thickened heart walls with small LV chamber in CA is a major limitation to implantation.

**Therapeutic Options for AL Amyloidosis**

From an organ recovery and survival standpoint, a complete (or near-complete) reduction in the amyloid precursor is required. If this cannot be achieved within 2 to 3 months of initial treatment, an alternative regimen is warranted. Overview of the array of treatment options in AL amyloidosis and its comparison to ATTR amyloidosis can be viewed in Figure 5.

**Conventional Chemotherapy**

Most patients with AL amyloidosis cannot tolerate high-dose chemotherapy because of safety. Even with the standard chemotherapy, treatment should be individualized. The optimal duration of treatment with conventional chemotherapy is unknown. In most trials, treatment spans over 6 to 12 cycles, depending on the rate of LC reduction and whether a plateau has been achieved. Melphalan and dexamethasone combination is an effective regimen, with responses seen in up to two thirds of patients.\(^{26}\) This regimen is ineffective in advanced cardiac disease. Bortezomib, a proteasome inhibitor, has shown remarkable results when combined with alkylator (melphalan or cyclophosphamide) and dexamethasone. The 3 drug combination bortezomib–melphalan–dexamethasone has a higher response rate than melphalan and dexamethasone although a survival advantage has not been reported.\(^{27}\) Bortezomib can increase cardiac symptoms. We prefer a once-weekly schedule, which is better tolerated compared with a twice-weekly schedule.\(^{30}\) In patients with advanced cardiac disease, we initiate bortezomib at a lower dose (0.7–1 mg/\(m^2\)) and increase to the standard dose (1.3 mg/\(m^2\)) as tolerated. As high-dose steroids can aggravate heart failure, lower dosing is warranted in advanced cardiac disease.

Immunomodulatory drugs (IMiDs) are another drug class with antiplasma cell activity. IMiDs include the parent drug thalidomide and its more potent derivatives, lenalidomide and pomalidomide. IMiDs are poorly tolerated in patients with AL amyloidosis. Recently, however, targeting the deposits themselves has been introduced. As many patients are frail as a result of advanced disease, age, or comorbidities, treatment selection should be made to avoid significant therapy-related toxicity and treatment interruptions. This is best accomplished in specialized centers and requires multidisciplinary care. Cardiac supportive care is essential to manage ongoing symptoms and treatment toxicity.

**Autologous Stem Cell Transplantation**

The depth and durability of response achieved with autologous stem cell transplantation has not been duplicated with any conventional chemotherapy. Therefore, our treatment approach is dependent on whether the patient is a stem cell candidate or not. Autologous stem cell transplantation has a considerable morbidity, mainly in patients with cardiac and multiorgan involvement. Transplant-related death is as low as ≈2% in experienced centers. The Mayo eligibility criteria for autologous stem cell transplantation are reported.\(^{25}\) It is reasonable in patients with poor organ function to initiate induction chemotherapy in anticipation of improvement in organ function, which then might restore eligibility to autologous stem cell transplantation. Stem cell mobilization can be challenging in patients with AL amyloidosis. Complications may include fluid overload, cardiac arrhythmias, hypotension, and rarely cardiopulmonary collapse.

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amyloidosis compared with patients with myeloma and should be given at lower doses. Because thalidomide has a modest effect in patients with AL with significant toxicity, lenalidomide or pomalidomide are usually a better choice. IMiDs should be combined with corticosteroid (±alkylator) because single-agent activity is limited. IMiD-treated patients frequently experience a rise of NT-proBNP/BNP, which is usually asymptomatic, but was reported to be associated with a shortened survival. It is unclear whether the biomarker rise indicates direct cardiac toxicity, fluid retention, or impaired renal clearance.

Monoclonal Antibodies

Antiplasma Cell Antibody

Daratumumab is an IgGκ monoclonal antibody, targeting CD38, a cell surface antigen ubiquitously expressed on plasma cells. It has remarkable single-agent activity in heavily pre-treated patients with myeloma. Apart from infusion-related reactions, which subside with subsequent doses, it is well tolerated and does not require dose modifications because of organ impairment. Thus, it is an appealing agent for AL amyloidosis. A phase I/II trial of single-agent daratumumab is expected to open this year.

Monoclonal Antibodies Targeting the Amyloid Deposits

Three antiamyloid monoclonal antibodies are in clinical trials. The first targets serum amyloid P, a glycoprotein that is part of all amyloid deposits, and contributes to fibril stabilization and proteolytic resistance. A phase I trial using a single anti-serum amyloid P infusion showed a reduction in amyloid deposits, mainly hepatic, in those who received a higher antibody dose. Patients with CA were excluded from participation.

Another monoclonal antibody, NEOD001, targets the misfolded LCs. In a phase I/II trial, patients who achieved at least partial response to chemotherapy, but had persistent organ dysfunction, received monthly infusion of the antibody. Cardiac response was achieved in 57%, with no organ progression seen. A phase 3 trial is currently recruiting, evaluating the efficacy and safety of NEOD001 plus standard chemotherapy versus placebo and standard chemotherapy in untreated AL amyloidosis with cardiac involvement.

11-1F4 is a chimeric antibody, targeting anther epitope on the misfolded light chains. It is currently investigated in phase I/II clinical trial among relapsed/refractory AL patients.

Orthotopic Heart Transplantation

Orthotopic heart transplantation (OHT) is infrequently used because of organ shortage, involvement of organs other than the heart, and the risk of amyloid recurrence in the transplanted organ. Studies demonstrate an inferior outcome for OHT for AL amyloidosis compared with non-AL indications. In a single-center report on OHT in AL amyloidosis, the median overall survival was 3.1 years. Survival was impacted by response to amyloid-directed therapy. Patients who achieved a complete response had a longer survival (median, 10.8 years) than those achieving less than complete response (median, 5.4 years) or nonresponders/nonevaluable (median, 1.2 years). Therefore, a combined chemotherapy/transplant approach is warranted. In most instances, OHT will precede antiamyloid therapy, but low-intensity, nonmyelosuppressive treatment can be initiated while waiting for a heart. A major limitation to the expanded use of OHT in patients with AL is death of patients on the waiting list compared with non-AL patients. The major predictor for survival from waiting list to OHT is low body mass index.

There has been a decline in OHT use for AL amyloidosis, but with the availability of more effective antiplasma cell treatment and higher rates of complete response, OHT should be reconsidered in those patients with single organ involvement.

Tetramer Stabilizers

Stabilization of TTR in its tetrameric form will halt amyloidogenesis. Two tetramer stabilizers, structurally related, are...
available: diflunisal in the United States and tafamidis in Europe/Japan. Both were shown in randomized placebo-controlled trials to slow neurological progression and improve quality of life, but data on cardiac response were limited. Tafamidis was assessed in 21 patients with ATTRm CA treated >12 months. Four patients had an increase in septal wall thickness ≥2 mm over the study period, and the remaining patients had an unchanged septal thickness. Increased cardiac toxicity was not found. Diffusional, unlike tafamidis, is a nonsteroidal anti-inflammatory drug. It is tolerated in patients with cardiac TTR, with no change in cardiac function/biomarkers. Close monitoring is warranted for volume overload and change in renal function.

**Doxyecycline and Tauroursodeoxycholic Acid**

In ATTR, doxycycline was shown to disrupt amyloid fibrils and facilitate tissue clearance. In a mouse model, doxycycline in combination with TUDCA (tauroursodeoxycholic acid) was shown to be more effective in amyloid removal than either agent alone. This combination was assessed in a phase II study and reported stable disease >12 months with no major toxicity.

**Small Interfering RNA: Antisense-Based Approach**

This novel approach utilizes small interfering RNA to silence hepatocyte expression of TTR mRNA. Liver drug delivery is enhanced by a lipid or N-acetylgalactosamine-conjugate given parenterally. Data from a mouse model have shown that the degree of TTR knockdown correlated with the reduction of tissue TTR deposits. In human studies, >80% TTR knockdown is seen. Currently, there are 2 phase 3 trials that completed accrual and will be reported in 12 to 18 months.

**Monoclonal Antibodies**

Anti–serum amyloid P and NEOD001 antibodies have a potential role in all forms of amyloidosis, as the target is not protein specific. Its evaluation in ATTR has not been reported. There are several reports on monoclonal antibodies targeting misfolded TTR monomers or TTR amyloid fibrils; none has reached a clinical trial phase.

**Orthotopic Liver Transplantation**

This treatment is designed for ATTRm as a method to replace serum amyloidogenic TTR with a more stable wild-type tetramer. As organ improvement after orthotopic liver transplantation (OLT) is not the rule, early transplantation is preferred. A report on 1940 patients showed a 20-year overall survival of 55%. Independent negative survival predictors were lower modified body mass index, late-onset disease, non-V30M mutations and longer disease duration before OLT. Importantly, 22% of the deaths were cardiac compared with 9% in patients undergoing OLT for end-stage liver disease. 

Cardiac progression can still occur after OLT, particularly in non-V30M. Post-OLT analysis of the cardiac deposits demonstrates both mTTR and wtTTR, suggesting that pre-existing mutant-derived deposits serve as a nidus for wtTTR codeposition. Combined heart-liver transplant may overcome this barrier.

**Cardiac Sarcoidosis**

Sarcoidosis is a multisystem inflammatory disorder of unknown cause characterized by the presence of T lymphocytes, mononuclear phagocytes, and noncaseating granulomas in involved tissues. It frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltrates, uveitis, or skin lesions. The heart, liver, spleen, nervous system, bone marrow, kidneys, bones, joints, muscles, and other organs may also be involved. Sarcoidosis commonly affects young and middle-aged adults, but children and the elderly may be affected.

**Epidemiology**

The incidence and prevalence of sarcoidosis remains unclear but seem to vary according to geographic region, race/ethnicity, sex, and age. The disease can also aggregate in families. Scandinavians have the highest reported incidence rate of sarcoidosis at 50 to 60 cases per 100000. Likewise, a high incidence of sarcoidosis and death due to cardiac sarcoidosis have been reported in Japan. In the United States, the incidence rate of sarcoidosis has been reported to be 10.9 cases per 100000 in whites and 35.5 per 100000 blacks. Sarcoidosis is more common in women than in men. Among the women enrolled in the Nurse Health Study II, the average annual incidence rate was 11 per 100000. The incidence rate increased with age from 9 per 100000 in women aged <35 years to 15 per 100000 in women aged ≥55 years. The prevalence and incidence of sarcoidosis was highest among black women (43 cases per 100000 and 519 per 100000, respectively).

In a study of newly diagnosed sarcoidosis cases in Detroit, MI, black women aged 30 to 39 years were at the greatest risk, with an annual incidence of 107 per 100000.

Only a small minority of patients with sarcoidosis are diagnosed with cardiac involvement. Of the >700 patients enrolled in ACCESS (A Case Control Etiologic Study of Sarcoidosis), only 2.5% had documented CS. Other smaller studies have reported that cardiac involvement in patients with sarcoidosis is as high as 5%. The detection rate of cardiac sarcoidosis has improved, in part because of the advances in the diagnostic techniques.

According to 2 autopsy series of patients with systemic sarcoidosis, however, the rate of CS was ~25%. Although systemic sarcoidosis is more common in women, CS has been reported to be more common in men. The reasons for these sex differences remain unclear, but may be related to the effects of sex steroid hormones and their receptors on the myocardium.

**Cause and Pathophysiology**

Despite extensive research efforts, the cause of sarcoidosis remains elusive. The prevailing hypothesis is that sarcoidosis is an inflammatory disease that results from exposure of genetically susceptible hosts to specific environmental agents.

The role of inflammation in the pathogenesis of sarcoidosis is discussed by Trachtenberg and Hare in another paper in this Compendium. Results from ACCESS indicate that exposure to insecticides, pesticides, moldy environments, and microbial bioaerosols are associated with increased risk of sarcoidosis. Occupations associated with sarcoidosis include metal machining, firefighting, the US military, and working in agriculture or the lumber industry.

Mycobacteria and other infectious organisms have been implicated in the pathogenesis of sarcoidosis. Because of the histological similarity between Mycobacterium tuberculosis and sarcoidosis, numerous studies have investigated a possible link between these 2, but no convincing evidence has yet been found. Elucidating the exact environmental antigen(s) responsible for sarcoidosis remains an important issue, as identifying specific, a disease-specific treatment target is urgently needed.
Genetics

The role of genetic factors in sarcoidosis is supported by familial clustering, increased concordance in monozygotic twins, and varying incidence and disease presentation among different ethnic groups. Studies have shown that certain human leukocyte antigen and non–human leukocyte antigen alleles have been consistently associated with sarcoidosis susceptibility, although these associations may vary according to race and ethnicity. A genome scan in blacks reported linkage to chromosome 5,65 whereas a scan in German families reported linkage to chromosome 6.66 Genome-wide association studies have found the butyrophilin-like 2 (BTNL2), annexin A11, and RAB23 genes to be associated with sarcoidosis. An association between sarcoidosis and angiotensin-converting enzyme genotypes in certain subgroups of patients, including blacks and Finns, has also been postulated. There have been no studies to date that have identified genes specifically associated with increased susceptibility for CS. Because of ongoing advances in the field of genetics, however, the identification of genetic markers for CS remains promising.

Clinical Manifestations

Asymptomatic cardiac involvement is fairly common. The primary site of involvement is the myocardium, clinically manifesting with conduction defects and arrhythmias. As diagnostic imaging techniques have advanced, patients with extra-cardiac sarcoidosis are increasingly being diagnosed with CS before onset of symptoms. Among patients with symptomatic CS, clinical signs and symptoms tend to vary according to the extent and location of granulomatous inflammation. Granulomas most frequently infiltrate the LV myocardium, but any area of the heart including the RV, atria, papillary muscles, valves, pericardium, and coronary arteries may be involved. The most common presentation is heart failure, but patients may present with syncope, palpitations, dyspnea, fatigue, chest pain, or SCD. Cardiac involvement may precede, occur concurrently, or follow lung or other organ involvement. Clinicians should thus consider the possibility of CS in patients with known extra-cardiac sarcoidosis who develop cardiac symptoms, ECG changes, or abnormal findings on cardiac imaging. Clinicians should also consider the diagnosis of CS in otherwise healthy young or middle-aged patients who present with cardiac symptoms, arrhythmias, or heart failure without a preceding diagnosis of extra-cardiac sarcoidosis.

Diagnostic Criteria

Currently, there is no reliable reference standard to diagnose CS. Several diagnostic criteria for CS have been proposed, but none have been validated by randomized controlled trials or prospective data. The most commonly used criteria are the Japanese Ministry of Health and Welfare (JMHW) criteria and the Heart Rhythm Society (HRS) expert consensus statement (Table 2).

The JMHW criteria, originally published in 1999 and updated in 2006, are the most commonly used and cited. These criteria include the presence of noncaseating granulomas on EMB and either positive extracardiac biopsy or clinical diagnosis based on major and minor criteria as listed. These criteria have been criticized for including certain ECG, echocardiographic, and nuclear imaging findings that are relatively insensitive and nonspecific as clinical criteria. The 2006 update added the presence of LGE on CMR and the presence of perfusion defects on nuclear scintigraphy as clinical criteria, but did not incorporate fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging as a diagnostic criterion. In addition, the JMHW has provided no explanation as to how they decided which imaging findings were included as major versus minor criteria. Most importantly, these guidelines have not been clearly validated against a reference standard.

Similar to the JMHW criteria, the 2014 HRS expert consensus statement provides a histological pathway using myocardial tissue and a clinical pathway for diagnosing CS. The HRS clinical pathway not only contains criteria somewhat comparable to those of the JMHW including advanced heart block, VT, a positive gallium-67 cardiac scan, and decreased LVEF but also includes 18FDG-PET imaging and cardiomyopathy or heart block responsive to corticosteroid therapy as additional diagnostic criteria. In addition, the HRS criteria require a positive biopsy from either myocardial or extracardiac tissue, indicating that the diagnosis of CS cannot be made simply on clinical criteria as the JMHW criteria allows. Finally, the HRS criteria specify that “it is probable that there is CS,” that is, a clinical diagnosis of CS can be established, if there is histological diagnosis of extra-cardiac sarcoidosis and ≥1 clinical criterion are met. Despite the inclusion of more contemporary imaging and clinical criteria for the diagnosis of CS in the HRS criteria, this set of criteria also lacks validation. A systemic study to compare the diagnostic accuracy of the JMHW and HRS criteria is warranted.

Diagnostic Evaluation: Noninvasive Testing

ECG

An ECG should be performed in every patient with sarcoidosis to detect subtle or overt conduction or repolarization abnormalities. The ECG is usually abnormal in patients with clinically active CS but is abnormal in <10% of patients with clinically silent disease. Complete heart block and right bundle branch block are the most common presenting conduction abnormalities, but all types of conduction abnormalities may occur. AV block may be the presenting sign of CS in patients aged <60 years. VT is the most common presenting arrhythmia, but supraventricular arrhythmias, frequent premature ventricular contractions, and ventricular fibrillation also occur before diagnosis.

Holter Monitor

A 24-hour Holter monitor test should be obtained in patients with suspected CS to document conduction and rhythm disturbances that may be missed on ECG, including intermittent high-grade AV block, supraventricular arrhythmias, excessive premature ventricular contractions, and nonsustained VT.

Echocardiography

Echocardiography is often the first imaging screening test for CS and is extremely useful for assessing left and right ventricular systolic and diastolic function and estimating pulmonary artery pressures. Echocardiography, however, has low sensitivity for detecting early CS. Newer echo technologies, including speckle-tracking imaging, show promise in the early diagnosis of CS and may predict clinical outcomes (Figure 6). A recent study compared 35 patients with diagnosed sarcoidosis and normal cardiac function with 35 controls and found that LV GLS was reduced in
the former. Impaired LV GLS was also significantly associated with clinical outcomes. Another study compared 31 patients with biopsy-proven extra-cardiac sarcoidosis with normal LVEF and LGE on CMR with 31 patients without LGE. In this study, LGE was associated with reduced GLS and GLS magnitude inversely correlated with LGE burden. These studies suggest that reduced LV GLS may represent an early marker of myocardial involvement in patients with CS and that the magnitude of reduction in LV GLS may be associated with worse clinical outcomes.

Late abnormalities suggestive of CS detected on transthoracic echocardiography imaging include basilar septal wall thinning, aneurysms, and regional wall motion abnormalities in a non-coronary artery distribution (Figure 6). Nonspecific findings supportive of the diagnosis of CS include increased myocardial wall thickness and LV chamber dilatation, decreased LV systolic function, and LV diastolic dysfunction. RV dilatation and decreased systolic function may be present, but these findings are more common because of pulmonary hypertension secondary to pulmonary sarcoidosis. RV aneurysms are occasionally observed.

**Nuclear Imaging**

Although gallium-67 imaging is considered to be a major clinical criterion for the diagnosis of CS per the JMHW guidelines, its use is currently of limited value because of low sensitivity in comparison with other imaging modalities. Perfusion defects seen on rest perfusion imaging using single-photon emission computed tomography are one of the JMHW minor clinical criteria. Perfusion defects may improve with stress; this phenomenon is not specific to CS. The spatial resolution of single-photon emission computed tomographic imaging is much lower than that of PET. Because of the relatively low sensitivity and specificity of gallium-67 and single-photon emission computed tomographic imaging, these techniques should only be used when FDG-PET or CMR is not available.

**Fluorodeoxyglucose-Positron Emission Tomography**

Cardiac FDG-PET has been utilized increasingly for the diagnosis and management of CS because of its high spatial resolution. Cardiac PET imaging for CS involves 2 different scans: one scan to assess resting myocardial perfusion and areas of fibrosis or scar using 

$^{82}$Rb or $^{13}$N-ammonia and another scan to image inflammation using FDG (Figure 7). Both scans are acquired in a single PET session and should be interpreted together to diagnose CS and determine the stage of the disease. In early stages of the disease, focal areas of increased FDG uptake are present and resting perfusion defects may be seen. In advanced CS, resting perfusion defects may be seen in the absence of FDG uptake, indicating the presence of scar without inflammation. Resting perfusion defects and areas of inflammation may either coincide or occur in different locations of the myocardium.

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**Table 2. Comparison of Current Diagnostic Criteria for Cardiac Sarcoidosis**

<table>
<thead>
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<tbody>
<tr>
<td><strong>Histological diagnosis (definite CS)</strong></td>
<td>EMB: noncaseating granulomas and Histological or clinical diagnosis of extra-cardiac sarcoidosis</td>
<td>EMB: noncaseating granulomas AND No alternative cause identified</td>
</tr>
<tr>
<td><strong>Clinical diagnosis</strong></td>
<td></td>
<td></td>
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<tr>
<td>Extra-cardiac sarcoidosis per histological or clinical criteria plus</td>
<td>Probable CS</td>
<td></td>
</tr>
<tr>
<td>≥2 major clinical criteria for CS or 1 major plus ≥2 minor criteria for CS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical criteria</strong></td>
<td></td>
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<tr>
<td>Major</td>
<td></td>
<td></td>
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<tr>
<td>Advanced AV block</td>
<td>Mobitz type II second-degree heart block or third-degree heart block</td>
<td></td>
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<tr>
<td>Thinning of basal IV septum</td>
<td>Positive gallium-67 uptake in heart</td>
<td></td>
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<tr>
<td>Positive gallium-67 uptake in heart</td>
<td>Unexplained LVEF &lt;40%</td>
<td></td>
</tr>
<tr>
<td>LVEF &lt;50%</td>
<td>ECG: unexplained sustained (spontaneous or induced) VT</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG: VT, multifocal or frequent PVCs, complete RBBB, axis deviation or Q waves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo: RWMA, aneurysm, wall thickening</td>
<td>Cardiomyopathy or heart block responsive to corticosteroid therapy</td>
<td></td>
</tr>
<tr>
<td>Nuclear: perfusion defects on thallium-201 or technetium-99 m SPECT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMR: LGE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMB: &gt;moderate interstitial fibrosis or monocyte infiltration</td>
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</table>

CMR indicates cardiac magnetic resonance imaging; CS, cardiac sarcoidosis; EMB, endomyocardial biopsy; FDG-PET, fluorodeoxyglucose-positron emission tomography; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; PVC, premature ventricular contraction; RBBB, right bundle branch block; RWMA, regional wall motion abnormality; SPECT, single-photon emission computed tomography; and VT, ventricular tachycardia.
Whole-body FDG imaging, typically from the orbits to the midthigh level, is increasingly being used to evaluate for extracardiac sarcoidosis during the same PET session at which dedicated cardiac perfusion and FDG imaging occurs (Figure 7). Clinicians may find this useful for identifying extracardiac metabolically active areas that may be amenable for biopsy and to help discern whether or not immunosuppressive therapy is indicated.

Cardiac PET imaging for CS requires patient preparation to suppress physiologic myocardial glucose uptake and shift metabolism to fatty acid utilization because both normal myocytes and inflammatory cells take up glucose. Standardized patient preparation protocols are lacking, but current approaches include eating a high-fat, low-carbohydrate diet followed by fasting, eating a low-carbohydrate diet followed by fasting >18 hours without previous diet restrictions, and administration of intravenous unfractionated heparin. Patients should avoid strenuous exercise for 24 hours prior to FDG-PET scanning.

FDG-PET is very accurate for diagnosing CS. In a meta-analysis of 7 studies including 164 patients, pooled estimates for FDG-PET yielded a sensitivity and specificity of 89% and 78%, respectively. Diagnostic yields may potentially be increased by adding quantification using specific uptake values (SUVs) of FDG. This technique is currently limited due to lack of standardization of SUV analysis across different PET systems, protocols and institutions, but may become more promising in the future.

Baseline FDG-PET scans may also have prognostic value in patients with CS. In a series of 118 consecutive patients referred for evaluation of known or suspected CS, 60% had abnormal cardiac PET findings. Over a median follow-up of 1.5 years, the presence of both a perfusion defect and focal FDG abnormality on baseline imaging was a strong predictor of death or VT. Focal RV uptake also portended a worse prognosis.

Serial FDG-PET scans may play a role in assessing therapeutic response in patients with CS. Several small studies have shown that change in degree of inflammation assessed by serial FDG-PET scans correlate with change in symptoms, conduction abnormalities, arrhythmias burden and LVEF. Use of serial FDG-PET imaging may thus help guide decisions regarding immunosuppressive therapy in patients with CS.

**Cardiac Magnetic Resonance Imaging**

CMR is the gold standard for assessing LV and RV chamber size and EF and has emerged as a useful tool in the diagnosis of CS. Although CMR images may show thinned walls, aneurysms, and segmental wall motion abnormalities in a noncoronary distribution, the principal method for detecting CS by CMR relies on identifying areas of LGE, usually in a subepicardial or transmural distribution (Figure 8). During the acute inflammatory stage, CMR may demonstrate regional wall motion abnormalities and increased wall thickness. During more advanced stages of the disease, CMR may show myocardial
wall thinning or aneurysm and increased signal on LGE images, suggesting fibrosis and scarring.

The presence of increased T2-weighted signal, which indicates increased water content, may also be used to identify areas of inflammation. This technique, however, remains technically challenging and has not been systematically studied in patients with CS. Newer T2 mapping techniques may overcome some of the limitations of current techniques and provide an additional method to identify and quantify myocardial inflammation.

Similar to FDG-PET, the accuracy of CMR for detecting CS is high. In 1 study of 58 patients with suspected CS, LGE had a sensitivity of 100% and a specificity of 78% compared with the JMWH criteria. The low specificity likely reflects the poor sensitivity of the JMWH criteria and the ability of CMR to detect small areas of scarring. LGE burden on baseline CMR may have prognostic value. One study revealed that among 81 patients with extra-cardiac sarcoidosis, the presence of LGE on baseline CMR resulted in a 9-fold higher rate of major adverse events and an 11.5-fold higher rate of cardiac death as compared with patients without LGE. A more recent study of 155 patients with suspected CS revealed that patients with LGE had >30-fold increased risk of death, aborted SCD, or appropriate ICD shocks compared with patients without LGE. Several small studies suggest that serial CMR scans may be useful for monitoring disease progression and response to therapy.

Figure 7. Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography imaging in a patient with cardiac and extracardiac sarcoidosis (maximum intensity projection). A. Multiple focal sites of increased FDG activity in the heart, peribronchovascular, portocaval, periportal, mesenteric, pelvic and inguinal lymph nodes, liver, spleen, and bones can be noted. B. After 6 mo of immunosuppression, no focal hypermetabolic lesions are detected.

Figure 8. Cardiac magnetic resonance imaging of patient with cardiac sarcoidosis. A. Noncontrast image shows left ventricular chamber dilatation with marked thinning of the interventricular septum (arrows). B. Postcontrast image shows focal transmural late gadolinium enhancement involving the entire interventricular septum (arrows).
to assess response to corticosteroid treatment, but further studies are needed to validate these findings.

Hybrid PET-CMR imaging systems, which promise to combine the unique strengths of FDG-PET and CMR, are emerging. The CMR scan provides accurate assessment of cardiac morphology and function as well as identification of fibrosis or scar, whereas the FDG-PET portion of the scan assesses degree of inflammation. These systems may prove to be especially helpful in the future to assess response to immunosuppressive therapy, but need to be systematically studied before routine use in clinical practice is indicated.

**Biomarkers**

Numerous biomarkers to aid in diagnosis and to follow disease activity have been proposed, but none have been validated. Serum angiotensin-converting enzyme, lysozyme, high-sensitivity troponin, and BNP are often elevated in patients with CS, but have poor sensitivity and specificity. Additional sarcoidosis biomarkers currently being investigated include serum AA, micro-RNAs, the transforming growth factor-β pathway, tumor necrosis factor-α and related proteins, vitamin D metabolism, lipid metabolism, and metabolomics.

**Diagnostic Evaluation**

**Coronary Angiography**

Coronary angiography is useful in excluding the diagnosis of atherosclerotic coronary artery disease when noninvasive testing reveals regional wall motion abnormalities. As previously noted, sarcoidosis may rarely cause granulomatous vasculitis of the coronary arteries.

**Electrophysiological Study**

In cases of suspected or confirmed CS, an electrophysiological study may be helpful for risk stratification for SCD. Although data are limited, studies have shown that in patients with CS who have inducible VT or ventricular fibrillation but no other established indications for ICD implantation have higher risk of ventricular arrhythmias and appropriate ICD shocks than those patients without inducible ventricular arrhythmias.54,79

**Endomyocardial Biopsy**

Identifying noncaseating granulomas in myocardial tissue is the gold standard for diagnosing CS. However, because of the patchy nature of CS, the sensitivity of EMB for detecting granulomatous disease in patients with CS is <20%.80 In patients with extra-cardiac sarcoidosis, lymph node or lung biopsy is generally attempted before EMB because of higher yield and decreased procedural risk. In cases of negative extracardiac biopsy or isolated CS, EMB may be warranted. To increase EMB yield, electroanatomic mapping or CMR versus PET image-guided biopsies are now recommended.54 These techniques may increase EMB diagnostic yield up to 50%.81 Infectious causes for granuloma formation should always be excluded by the use of special stains and cultures of biopsy specimens to exclude microorganisms.

**Diagnostic Evaluation for Isolated CS**

Neither the JMHW nor the HRS criteria include a pathway for diagnosing patients with isolated CS. This is problematic, as it is been estimated that at least 25% of patients with CS may have isolated CS and that patients with isolated CS may present with more advanced heart disease than patients with systemic sarcoidosis with cardiac involvement.82–86 Current data suggest a combined diagnostic approach using FDG-PET and CMR may provide complementary data to identify inflammation and scar or fibrosis, respectively.54 This combined approach may not only facilitate earlier diagnosis but also improve diagnostic accuracy. Also, by utilizing whole-body imaging, FDG-PET may serve as a useful screening technique for possible extracardiac involvement in cases of suspected isolated CS.

**Screening**

Data regarding the sensitivity and specificity of screening for CS in patients with extra-cardiac sarcoidosis is limited. Mehta and colleagues84 interviewed 62 patients with extra-cardiac sarcoidosis for clinical symptoms who were then referred for ECG, Holter monitoring, and TTE. Those with symptoms or abnormal test results were studied with either CMR or PET scanning. The diagnosis of CS was based on abnormalities detected either by CMR or PET. The authors found that the presence of 1 abnormal screening test and/or cardiac symptoms had a high specificity and sensitivity for diagnosing CS (87% and 100%, respectively). Based on the findings of this study, the authors of the HRS expert consensus statement on the diagnosis and management of arrhythmias associated with CS outlined recommendations on initial screening for cardiac involvement in patients with biopsy-proven extra-cardiac sarcoidosis.64 Class I recommendations include asking patients about unexplained syncope, presyncope and significant palpitations and obtaining an ECG. Class II recommendations indicate that an echocardiogram and a CMR or FDG-PET (at a center with experience in CS imaging protocols) can be useful. Patients who are asymptomatic and have no abnormalities on ECG or echocardiography should not undergo CMR or FDG-PET imaging (class III recommendation).

A key clinical question left unanswered is when to rescreen patients with normal baseline screening. The HRS guidelines do not address this question and there are no published studies to provide guidance. It seems reasonable for physicians to consider repeating an ECG and echocardiogram in patients with extra-cardiac sarcoidosis if they develop new signs or symptoms of cardiac disease.

The utility of screening patients without biopsy-proven extra-cardiac sarcoidosis has not been studied, but it seems reasonable to consider screening for CS in patients <60 years with unexplained high grade atrioventricular block or sustained ventricular tachycardia or any patient with unexplained cardiomyopathy.

**Management**

**Heart Failure Medications**

Guideline-directed medical therapy for heart failure, including angiotensin-converting enzyme inhibitors or angiotensin receptor II blockers, diuretics and aldosterone inhibitors should be initiated in patients with reduced LVEF. B-blockers should be used with caution in patients without pacemakers because of the risk of high-grade AV block. The role of these heart failure medications in patients with CS with normal LVEF is...
uncertain. Digoxin should be avoided in the acute stage of CS because of the risk for heart block and arrhythmias in the setting of active inflammation.

**Antiarrhythmic Therapy**

Granulomatous lesions and active inflammation are substrates for ventricular arrhythmias in patients with CS. Amiodarone may be useful, but long-term use is typically avoided because of potential lung toxicity. Catheter radiofrequency ablation may be useful in some CS patients with VT, but results have been mixed. Current HRS guidelines state that catheter ablation can be useful in patients with CS and ventricular arrhythmias that are refractory to immunosuppressive and antiarrhythmic therapy. VT recurrences are common. Repeat ablation with concomitant antiarrhythmic therapy in these patients may be useful.

**Immunosuppression**

Currently, there are no Food and Drug Administration–approved therapies for sarcoidosis in general or CS in particular. Although corticosteroids are the mainstay treatment for patients with CS, there is a paucity of data to support the effectiveness of this therapy. A systematic review of corticosteroid therapy for treatment of CS showed that corticosteroid therapy led to improvement in AV conduction recovery, but the data were not strong enough to draw conclusions on the utility of corticosteroids for other outcomes.

There are no clear guidelines regarding when to initiate corticosteroid therapy. Most experts agree immunosuppression should be considered in symptomatic patients with CS with evidence of active myocardial inflammation and any of the following: (1) reduced LVEF, (2) high-grade AV block, (3) frequent premature ventricular contractions or frequent non-sustained VT, or (4) sustained VT or ventricular fibrillation. It remains uncertain whether asymptomatic patients with CS should be treated.

Steroid-sparing agents are often used for refractory cases or when patients experience adverse effects from steroid therapy. Antimetabolites such as methotrexate, azathioprine, leflunomide, mycophenolate mofetil, and cyclophosphamide have been used as second-line agents. If the disease progresses despite use of glucocorticoids and a second-line agent, tumor necrosis factor-α inhibition with either infliximab or adalimumab should be considered. Our institution has used rituximab, a monoclonal antibody directed against the CD20 antigen on the surface of B-lymphocytes, to treat patients with refractory CS with some success.

Some centers, including the Mayo Clinic, have routinely introduced a steroid-sparing agent when corticosteroid therapy is initiated rather than waiting to determine responsiveness to steroid therapy before adding a second agent, allowing a more rapid steroid taper so as to minimize the potential for steroid-induced weight gain, diabetes, and osteoporosis. The steroid-sparing agent is typically continued for at least 6 to 12 months after prednisone has been discontinued.

Concomitant levofloxacin, ethambutol, azithromycin, and rifampin (CLEAR) has been reported as effective in treating cutaneous and pulmonary sarcoidosis. The rational for use of CLEAR is based on evidence that some cases of sarcoidosis may be caused by an unidentified mycobacterium and that fluoroquinolones and macrolides both have anti-inflammatory properties. Due to potential toxicities, the CLEAR regimen is generally reserved for patients who have failed other less potentially toxic therapies. The efficacy of CLEAR therapy in patients with CS has not been reported.

**Device Therapy**

As many patients with CS present with high-grade AV block, pacemaker implantation is frequently indicated per standard device guidelines. The 2014 HRS expert consensus recommendations on device therapy for conduction abnormalities in patients with CS indicate that device implantation can also be useful for patients with CS with an indication for pacing even if the AV block is transient and that ICD implantation can be considered in patients with CS who have an indication for permanent pacing.

ICD implantation is indicated in patients who have history of spontaneous sustained ventricular arrhythmias, including SCD, or who have LVEF ≤35% despite optimal medical therapy and a period of immunosuppression if inflammation is present (class I recommendation). ICD implantation can be useful for patients with unexplained syncope or near-syncope and inducible sustained ventricular arrhythmias (class IIa recommendation). Finally, ICD implantation can be considered in patients with LVEF 36% to 49% and or an RVEF <40% despite optimal heart failure medical therapy and a period of immunosuppression if inflammation is present (class IIb recommendation).

**Mechanical Circulatory Support**

LV assist device (LVAD) implantation is occasionally indicated in patients with CS because of advanced heart failure symptoms refractory to medical management. Several studies have reported that a small number of patients are diagnosed with isolated CS based on analysis of LV core samples obtained at the time of LVAD implantation for previously unexplained cardiomyopathy. Histopathologic analysis may assist in identifying patients who either have the potential to improve to the point where mechanical support can be discontinued or may require urgent heart transplant.

**Orthotopic Heart Transplantation**

OHT is occasionally indicated for patients with CS who experience intractable arrhythmias or end-stage heart failure. The outcomes, including intermediate and long-term survival, for these patients with CS are better than for patients undergoing OHT for all other diagnoses. Rarely, sarcoidosis may recur in the transplanted heart, particularly in patients on no or low-dose steroid treatment.

**Prognosis**

The natural history and prognosis of patients with CS remains uncertain. The extent of LV dysfunction seems to be the most important predictor of survival. Several studies have examined the prognosis of clinically silent CS with varying results. Many patients with clinically silent CS have a benign clinical course, but some of these patients present with SCD. Larger and more contemporary studies on the prognosis of both symptomatic and asymptomatic patients with CS are warranted. Clinicians...
are advised to closely monitor patients with CS for disease progression and development of symptoms or arrhythmias so as to optimize management to prevent potentially devastating complications.

Cardiac Hemochromatosis

Hereditary hemochromatosis (HH) is caused by increased absorption of dietary iron, which accumulates in various organs, leading to their dysfunction. Several mutations in genes involving iron absorption and metabolism can cause HH and influence clinical manifestations, severity of disease, and response to therapy. Almost all mutations are inherited in an autosomal recessive fashion. The predominant gene mutation causing the disease is HFE C282Y. The prevalence for homozygosity in Western Europe and the United States is estimated at 1 per 200 individuals.98 However, disease penetrance is incomplete and homozygosity for C282Y does not necessarily result in clinical disease or iron overload.

The clinical manifestations of HH are broad and include fatigue, hepatopathy (ranging from hepatomegaly, elevated liver enzymes to frank cirrhosis, and risk of hepatocellular carcinoma), skin hyperpigmentation (bronze skin), arthralgia, diabetes mellitus, and other endocrinopathies, male hypogonadism, cardiac conduction defects, and cardiomyopathy. Increased risk for several infectious organisms (V. vulnificus, L. monocytogenes, and Yersinia enterocolitica) is another hallmark of the disease.

Cardiac involvement is less common than liver, diabetes mellitus, or skin involvement, occurring in 15% to 20% of patients with HH.99 Typically, early-stage CH manifests as a typical RCM with a nondilated LV and restrictive LV filling pattern. As the disease progresses, the ventricles dilate and biventricular systolic dysfunction occurs, sometimes with rapid deterioration to acute decompensated heart failure. In addition to heart failure, CH can cause variety of conduction disturbances as well as atrial and ventricular bradyarrhythmias and tachyarrhythmias. Echocardiography aids in confirming myocardial abnormalities, but there are no characteristic findings to specifically suggest CH. CMR imaging (utilizing T2* relaxation times) has become a valuable tool because it can be used to quantify heart and liver iron.100 This often obviates the need to perform organ biopsy to quantify organ iron overload.

CH is usually suspected in the face of characteristic extra-cardiac features of the disease in a patient with heart failure and arrhythmia or conduction disorders. However, isolated cardiac involvement does not exclude HH, and CH should be considered in the presence of unexplained heart failure. Screening with serum ferritin and transferrin saturation is the first step, and if either result is elevated (transferrin saturation ≥45%, serum ferritin above normal, adjusted for sex), genetic studies should be pursued.101

Diagnosis is made by mutational analysis for HH, which is usually completed for the 2 most common HFE gene mutations, C282Y and H63D. If these tests are negative, mutational analysis for rarer genotypes can be pursued and evaluation for iron overload from other causes including iron-loading anemias, repeated blood transfusions, and chronic liver disease. EMB is usually not required because of the availability of genetic analysis and the use of CMR-T2* to establish liver and cardiac iron overload, but may sometimes be helpful in select patients.99

The treatment of choice for symptomatic CH in nonanemic patients is therapeutic phlebotomy. Treatment improves cardiac function, but benefit is inversely correlated with the degree of cardiac dysfunction, emphasizing the need for early diagnosis. Phlebotomy may occur every week or other week, adjusted according to the patient tolerance. Patients with cardiac dysfunction may require a less aggressive phlebotomy plan with a less frequent schedule and reduced amount of blood collection per phlebotomy. Phlebotomy is generally repeated until serum ferritin falls <50 ng/mL and transferrin saturation <50%.102 A subsequent maintenance phlebotomy schedule is required, usually consisting of 1 unit of blood quarterly. The use of iron chelating agents is usually not required and is poorly tolerated compared with phlebotomy. Chelation can be considered in patients with significant anemia or poor tolerance to phlebotomy because of low blood pressure or symptomatic hypovolemia not corrected with fluid management. Cardiac function generally improves with iron stores decrease. Heart transplant or heart/liver transplant is rarely necessary, but can be considered in patients with advanced disease unamenable to medical treatment. The prognosis of HH is driven by the presence of liver disease and its complications, particularly cirrhosis and hepatocellular carcinoma. Death from cardiac causes has been reported to occur in ≈20% of patients with HH.103

Patients with HH should be advised to maintain a normal diet with no need to exclude foods containing iron. Iron supplements, as well as vitamin C supplements, should be avoided, however. Excessive alcohol intake can also adversely affect iron stores and should be discouraged.

Summary

RCM is a relatively rare form of cardiomyopathy with diverse inherited and acquired causes and manifestations. A high index of suspicion is essential to recognize early-stage RCM so that effective treatment can be initiated and prognosis potentially improved.

CA is heterogeneous not only between the different types of precursor proteins but also within each type. In AL amyloidosis, cardiac involvement dominates the clinical picture and drives prognosis. Cardiac involvement in AL amyloidosis can be seen without thickened walls, so awareness for amyloidosis and screening for serum free LCs is required when seeing a patient with heart failure and preserved LVEF, regardless of wall thickness. Once a diagnosis is established, typing is essential before treatment. Therapeutic advances have occurred in the past decade in all types of CA.

CS is a rare manifestation of multisystem inflammatory disease with an as yet undetermined cause. Heightened suspicion for cardiac involvement in patients with known sarcoidosis and for the presence of CS in patients aged <60 years with unexplained high-grade AV block or unexplained RCM is required. Evaluation for CS includes history, ECG, 24-hour Holter monitoring, and cardiac imaging using echocardiography, FDG-PET,
CMR, and biopsy. Treatment of CS includes guideline-directed medical and device therapy for management of heart failure, conduction disorders, and arrhythmias. Immunosuppression may be helpful, but effects have not been systematically studied.

Patients with CH usually present with typical extracardiac involvement before cardiac involvement develops, but typical cardiac signs or symptoms may be the first manifestation of iron overload and should prompt screening for HH. Conduction abnormalities, heart failure, and arrhythmias may all occur. Therapeutic phlebotomy enables reversal of cardiac damage in most cases.

References


Restrictive Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy
Eli Muchtar, Lori A. Blauwet and Morie A. Gertz

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