

JACC REVIEW TOPIC OF THE WEEK

# Management of Patients With Giant Cell Myocarditis

## JACC Review Topic of the Week



Vigyan Bang, MD,<sup>a,\*</sup> Sarju Ganatra, MD,<sup>a,\*</sup> Sachin P. Shah, MD,<sup>a</sup> Sourbha S. Dani, MD,<sup>a</sup> Tomas G. Neilan, MD, MPH,<sup>b</sup> Paaladinesh Thavendiranathan, MD, SM,<sup>c</sup> Frederic S. Resnic, MD,<sup>a</sup> Thomas C. Piemonte, MD,<sup>a</sup> Ana Barac, MD,<sup>d</sup> Rushin Patel, MBBS,<sup>a</sup> Ajay Sharma, MD,<sup>a</sup> Rohan Parikh, MD,<sup>a</sup> Ghulam M. Chaudhry, MD,<sup>a</sup> Mark Vesely, MD,<sup>e</sup> Salim S. Hayek, MD,<sup>f</sup> Monika Leja,<sup>f</sup> David Venesy, MD,<sup>a</sup> Richard Patten, MD,<sup>a</sup> Daniel Lenihan, MD,<sup>g</sup> Anju Nohria, MD,<sup>h</sup> Leslie T. Cooper, MD<sup>i</sup>

### ABSTRACT

Giant cell myocarditis is a rare, often rapidly progressive and potentially fatal, disease due to T-cell lymphocyte-mediated inflammation of the myocardium that typically affects young and middle-aged adults. Frequently, the disease course is marked by acute heart failure, cardiogenic shock, intractable ventricular arrhythmias, and/or heart block. Diagnosis is often difficult due to its varied clinical presentation and overlap with other cardiovascular conditions. Although cardiac biomarkers and multimodality imaging are often used as initial diagnostic tests, endomyocardial biopsy is required for definitive diagnosis. Combination immunosuppressive therapy, along with guideline-directed medical therapy, has led to a paradigm shift in the management of giant cell myocarditis resulting in an improvement in overall and transplant-free survival. Early diagnosis and prompt management can decrease the risk of transplantation or death, which remain common in patients who present with cardiogenic shock. (J Am Coll Cardiol 2021;77:1122-34) © 2021 by the American College of Cardiology Foundation.

**A** 59-year-old white male with no significant past medical history presented with 2 days of low-grade fever and unheralded syncope. His electrocardiogram (ECG) showed normal sinus rhythm with bifascicular block. Cardiac troponin I (cTnI) (11.23 ng/ml) and brain natriuretic peptide (2,166 pg/ml) levels were elevated. Other laboratory tests were unremarkable. Paroxysmal high-grade

atrioventricular (AV) block was noted on telemetry. An echocardiogram demonstrated normal biventricular size and systolic function and no evidence of structural heart disease. Coronary angiography revealed no obstructive coronary artery disease. He was discharged after permanent pacemaker placement. However, he continued to be febrile and felt unwell. A few days after the index event, cTnI levels



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From the <sup>a</sup>Department of Cardiovascular Medicine, Lahey Hospital & Medical Center, Burlington, Massachusetts, USA; <sup>b</sup>Cardiovascular Imaging Research Center (CIRC) and Cardio-Oncology Program, Massachusetts General Hospital, Boston, Massachusetts, USA; <sup>c</sup>Division of Cardiology and Joint Division of Medical Imaging, Peter Munk Cardiac Center, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada; <sup>d</sup>Department of Cardiology, MedStar Washington Hospital Center, MedStar Heart and Vascular Institute, Washington, DC, USA; <sup>e</sup>Department of Cardiovascular Medicine, University of Maryland Medical Center, Baltimore, Maryland, USA; <sup>f</sup>Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan, USA; <sup>g</sup>Division of Cardiovascular Medicine, Department of Medicine, Washington University, St. Louis, Missouri, USA; <sup>h</sup>Division of Advanced Heart Failure, Department of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; and the <sup>i</sup>Department of Cardiovascular Medicine, Mayo Clinic, Jacksonville, Florida, USA. \*Drs. Bang and Ganatra contributed equally and are co-first authors.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Manuscript received September 2, 2020; revised manuscript received November 20, 2020, accepted November 24, 2020.

## HIGHLIGHTS

- Diagnosis of GCM requires a high index of suspicion given its often rapid and potentially fatal course.
- EMB is the cornerstone of diagnosis. If nondiagnostic but the clinical scenario strongly suggests GCM, repeating EMB with LV sampling should be considered.
- Immunosuppression together with GDMT for heart failure and arrhythmias, have improved the prognosis of patients with GCM.
- MCS and cardiac transplantation have an evolving role in the management of patients with GCM.

remained elevated and a second echocardiogram revealed moderately reduced left ventricular (LV) systolic function with basal to mid-segmental hypokinesis in a noncoronary distribution. A right ventricular endomyocardial biopsy (EMB) demonstrated nonspecific changes. Given the heightened clinical suspicion for acute myocarditis or sarcoidosis, <sup>18</sup>fluorodeoxyglucose positron-emission tomography (FDG-PET) imaging computed tomography (CT) scan was performed, which revealed increased uptake in the interventricular septum and right ventricular free wall (peak specific uptake value 13.8). Given the concern for sampling error, EMB was repeated and revealed giant cell myocarditis. He was started on a multidrug immunosuppressive regimen and evaluated for heart transplantation.

## INTRODUCTION

Giant cell myocarditis (GCM) was first described in a young man with acute heart failure (HF) by Saltykow in 1905 (1). It is a rare, often rapidly progressive, and potentially fatal disease that commonly affects young and middle-aged adults, without a sex predominance (2). Historically, the diagnosis was often made at autopsy until transvenous EMB became widely available in the 1970s. The diagnosis of GCM can often be challenging due to its nonspecific clinical presentation, potential overlap with other cardiovascular diseases, and a general lack of awareness regarding this entity. The annual detection rate of 0.13 cases per 100,000 persons likely underestimates the true disease burden, given the short window for antemortem diagnosis (3). The pathogenesis of GCM is commonly attributed to T-lymphocyte-mediated inflammation

of the myocardium (2). All GCM cases were either fatal or required cardiac transplantation until GCM was successfully treated with immunosuppression using prednisone and azathioprine in 1987 (4). Heightened awareness has increased early diagnosis and accelerated access to a management strategy involving multidrug immunosuppression, advanced hemodynamic support, and cardiac transplantation, when necessary.

## INCIDENCE AND RISK FACTORS

The reported incidence of GCM based on autopsy case series from India, England, and Japan is between 0.007% and 0.051% (5).

GCM typically affects young and middle-aged individuals. Based on various single and multicenter international registries, the mean age of affected individuals is 42.6 to 60 years (2,4,6). In the multicenter GCM registry, 4 of 63 (6%) cases occurred in patients below the age of 19 years. No sex predominance has been reported (2).

GCM primarily affects healthy individuals; however, noncardiac autoimmune disorders (inflammatory bowel disease, thyroiditis, and thymoma) have been reported in approximately 20% of cases (1). Recently, GCM has also been described in cancer patients treated with immune checkpoint inhibitors (7); however, in general, giant cells are not seen in biopsy specimens from patients with immune checkpoint inhibitor-associated myocarditis (8,9).

## CLINICAL PRESENTATION AND OUTCOMES

The clinical characteristics of GCM vary widely at the time of presentation. A multicenter international registry of 63 patients with GCM revealed that 75% presented with HF, 14% with ventricular tachycardia (VT), 6% mimicked acute myocardial infarction, and 5% had complete heart block (CHB) (2). In contrast, in another single-center study of 51 patients, only 39% presented with HF, while high-grade heart block (27%) and ventricular arrhythmias (22%) were more frequent (6). Importantly, HF is the most common presentation of GCM and rapidly progressive HF, with or without arrhythmias, that does not respond to usual therapy within 1 to 2 weeks, warrants consideration of GCM.

In the multicenter international registry, nearly one-half of GCM patients experienced sustained or symptomatic VT during the course of their illness.

## ABBREVIATIONS AND ACRONYMS

- AV** = atrioventricular
- CMR** = cardiac magnetic resonance
- CS** = cardiac sarcoidosis
- cTn** = cardiac troponin
- EF** = ejection fraction
- EMB** = endomyocardial biopsy
- FDG-PET** = fluorodeoxyglucose positron-emission tomography
- GCM** = giant cell myocarditis
- GDMT** = guideline-directed medical therapy
- HF** = heart failure
- ICD** = implantable cardioverter-defibrillator
- LV** = left ventricle
- MCS** = mechanical circulatory support
- TFS** = transplant-free survival
- VT** = ventricular tachycardia

Eventually, many patients experienced dilated cardiomyopathy, refractory HF, and/or cardiogenic shock requiring immunosuppressive therapy, mechanical circulatory support (MCS), and cardiac transplantation. Additionally, 62% of patients received an implantable cardioverter-defibrillator (ICD) (6). Historically, death or transplantation occurred in 89%, with a median survival from symptom onset to death or transplantation of 5.5 months (2). However, with combination immunosuppressive therapy and guideline-directed medical therapy (GDMT), this has improved to 11 months (10).

### **PATHOGENESIS**

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The pathogenesis of GCM is incompletely understood. Both human and animal models of GCM are characterized by inflammatory infiltration of the myocardium by T-lymphocytes and macrophages (11). In experimental GCM, interferon- $\gamma$  is produced by CD4-positive T cells, which stimulates macrophages to produce nitric oxide and tumor necrosis factor (11). The proposed mechanism of underlying hemodynamic deterioration in GCM includes up-regulation of inducible nitric oxide synthase and production of nitrite free-radicals (12). Immunochemical studies have demonstrated dislocation of the desmosomal protein, plakoglobin, at cell-junctions in myocardial samples from patients with GCM compared with those with lymphocytic myocarditis and normal control tissues, likely due to increased expression of interleukin-17 and tumor necrosis factor- $\alpha$  in patients with GCM (13).

In addition to up-regulation of the immune response, proteomic analysis has also identified differential regulation of classic and alternative complement pathways, plasmin signaling, and the Slit-Robo pathway in patients with GCM compared with noninflammatory dilated cardiomyopathy, lymphocytic myocarditis, and normal control serum (14). Specifically, the Slit-Robo signaling pathway has been found to play a role in heart morphogenesis and was up-regulated in GCM when compared to lymphocytic myocarditis (14).

While autoimmune disorders and viral myocarditis have been implicated in the pathogenesis of GCM, the evidence is limited and derived primarily from case reports (1).

### **DIAGNOSIS**

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The diagnosis of GCM can be challenging and is often missed until transplantation or autopsy. GCM should be considered in the differential for all patients with

new-onset nonischemic cardiomyopathy complicated by rapidly progressive HF despite GDMT, ventricular arrhythmias, and/or high-degree heart block.

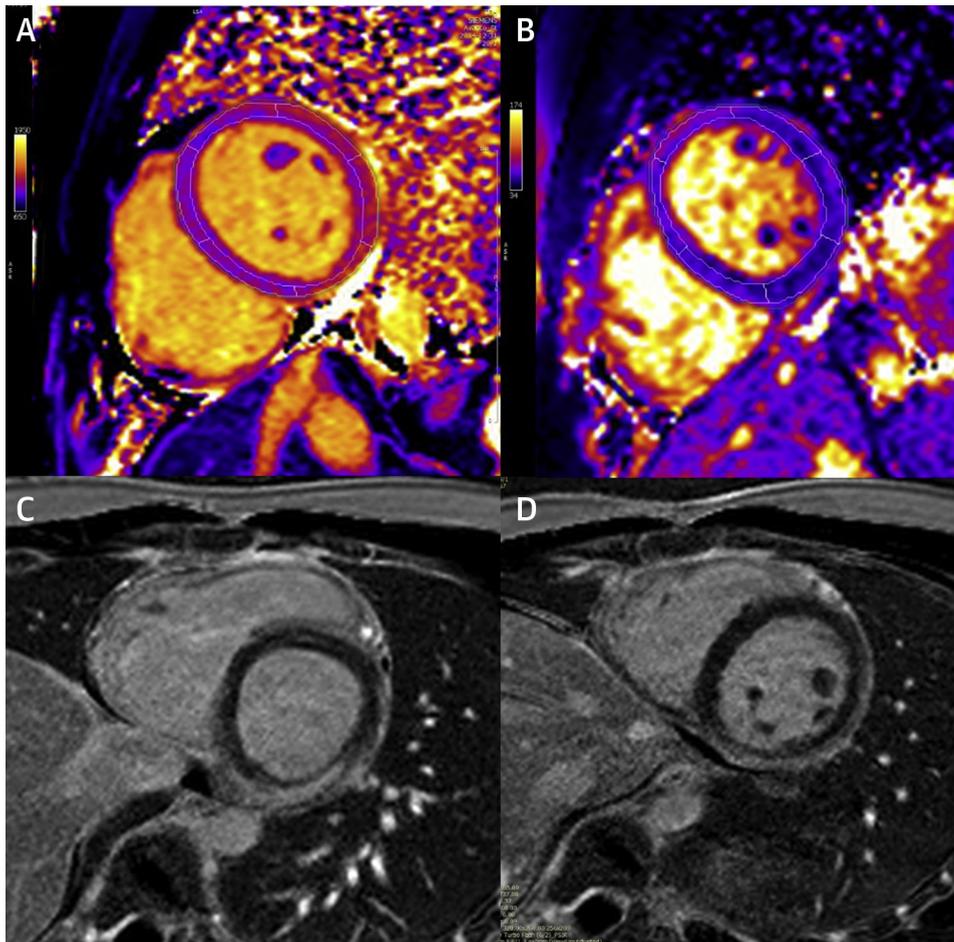
**ELECTROCARDIOGRAM.** An ECG may show nonspecific findings, such as sinus tachycardia, PR/QRS/QT prolongation, Q waves, local or diffuse ST-segment elevation, diffuse T-wave inversion, high-grade AV block, and/or ventricular arrhythmias (1). Although ECG abnormalities are found in most patients at the time of presentation, a normal ECG does not rule out GCM.

**CARDIAC BIOMARKERS.** Biomarkers suggestive of myocardial injury, such as troponin, cannot be relied upon to make the diagnosis of GCM. In a small case series of 6 patients with GCM, the peak cTnI level at presentation varied from undetectable to >20 ng/ml, with no correlation with time to presentation or histological severity of myocardial necrosis (15). These findings are consistent with a report from the Myocarditis Treatment trial showing that only 34% of patients with myocarditis had an elevation in cTnI (16). Significant elevations in cTnI in the absence of coronary occlusion should raise the suspicion of acute myocarditis. Although not specific for the diagnosis of myocarditis, elevated brain natriuretic peptide levels, indicative of decompensated heart failure, have been consistently associated with adverse outcomes, notably cardiac death or transplantation (10). In general, dramatic elevations in biomarkers should prompt close monitoring for decompensation and the potential need for MCS.

**CARDIAC IMAGING.** Data on the features of noninvasive imaging modalities in GCM are limited. Echocardiographic findings are nonspecific and variable. Depending on the acuity of presentation, an echocardiogram can be normal or can demonstrate LV systolic dysfunction, increased LV wall thickness (due to myocardial edema), LV dilatation, or aneurysm formation with mural thrombus. In a series of 51 patients with GCM, the mean LV ejection fraction (EF) was 41%: 72% had LVEF <50%, and 52% had LVEF <35%. LV dilatation was absent in 72%. On follow-up, LVEF <35% was associated with reduced transplantation-free survival (TFS), where each 5% decrement in LVEF was associated with a 13% increase in the need for cardiac transplantation (17). Among patients with acute myocarditis, a decline in longitudinal or circumferential strain may be diagnostic and prognostic, independent of EF (18).

Reports describing cardiac magnetic resonance (CMR) findings in GCM are limited because cardiogenic shock and malignant arrhythmias often make CMR impractical. Extrapolating from data in patients with

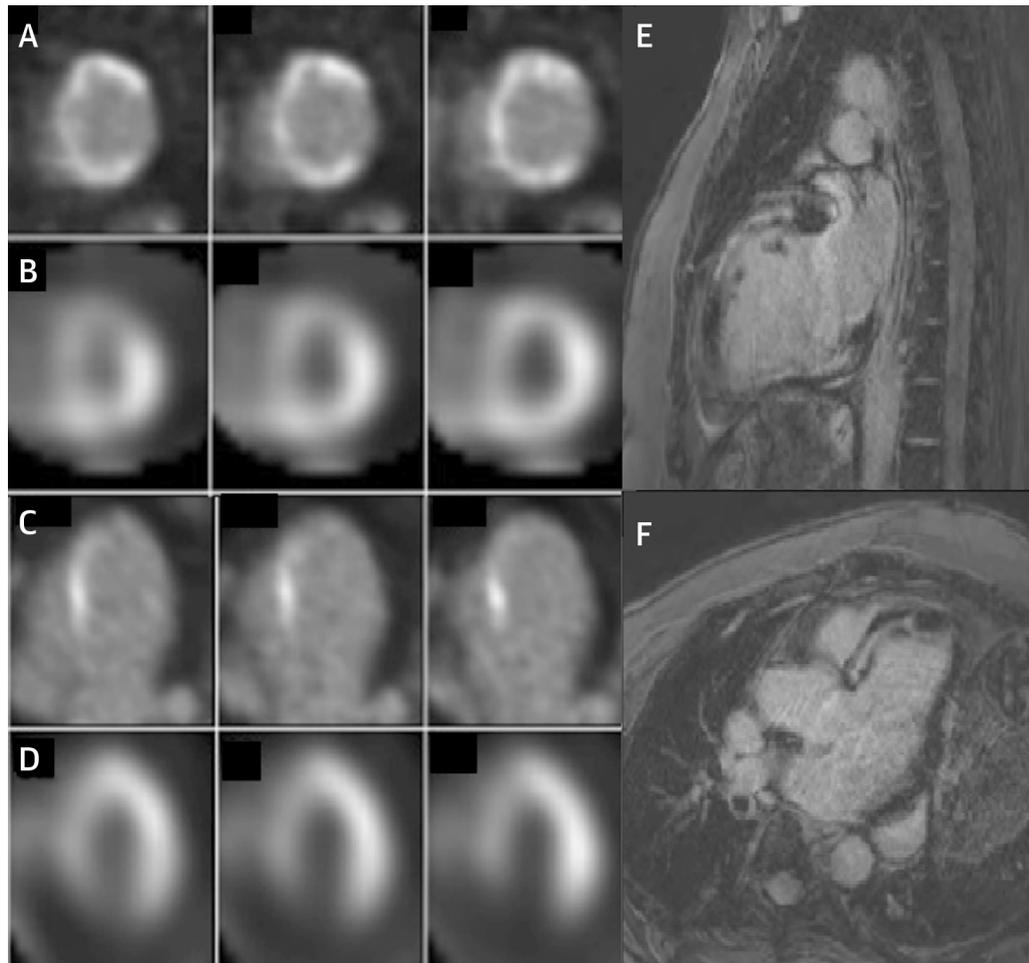
**FIGURE 1** Myocardial Relaxometry and LGE Imaging in a Patient With Giant Cell Myocarditis



**(A)** T<sub>1</sub> map of a mid short-axis view demonstrates significant elevated T<sub>1</sub> values on a 1.5-T Siemens magnet (site and scanner specific normal 1,006 ± 24 ms). Segments 7 to 12 based on the American Heart Association model: 1,142, 1,121, 1,161, 1,182, 1,029, and 1,057 ms. **(B)** T<sub>2</sub> mapping in the same patient at the mid short-axis view with significantly elevated values (site- and scanner-specific normal 52 ± 3 ms) Segments 7 to 12 based on the AHA model: 71.1, 58.2, 58.5, 54.5, 59.8, and 63.3 ms. **(C)** Late gadolinium enhancement (LGE) images shows subepicardial enhancement in the basal inferior and inferior-lateral walls, and **(D)** mid inferior and inferior lateral walls. For measurement of T<sub>1</sub> and T<sub>2</sub> values, the endocardial and epicardial borders were first drawn, then a 10% offset was applied to move the contours toward each other to minimize partial volume effects.

myocarditis, using the combination of T<sub>2</sub>-weighted imaging (to detect edema), T<sub>1</sub>-weighted imaging before and early after gadolinium contrast injection (to detect hyperemia), and late gadolinium enhancement (LGE) imaging (more indicative of necrosis/replace- ment fibrosis), CMR has a sensitivity of 78% to 80% and specificity of 87% to 88% for diagnosing myocarditis within a few weeks of symptom onset (19,20). Para- metric mapping to obtain quantitative T<sub>1</sub> and T<sub>2</sub> relaxation times adds significantly to the sensitivity and specificity of CMR in the diagnosis of myocarditis (Figures 1A and 1B) (21). Furthermore, tissue

characterization with CMR, particularly the location, pattern, and extent of LGE, on initial imaging and on follow-up, has been shown to be an effective tool for risk stratification and prognostication in myocarditis (22). In a single-center case series of GCM, LGE was present in 96% (24 of 25) of patients, and its distribu- tion correlated with histology (6). LGE tended to be widespread, involving all layers of the myocardium, due to extensive underlying inflammation and/or fibrosis (23). As an important caveat, our understand- ing of the use of CMR for risk stratification and prog- nostication stems from patients with myocarditis in

**FIGURE 2** FDG-PET and Sestamibi Perfusion Scan in a Patient With Giant Cell Myocarditis

(**A and C**)  $^{18}\text{F}$ fluorodeoxyglucose (FDG) positron-emission tomography (PET) images with increased activity most predominantly involving the basal to mid anterior wall, interventricular septum, and inferior wall. (**B and D**) Sestamibi perfusion imaging with decreased myocardial perfusion in the areas of increased FDG uptake. (**E and F**) Cardiac magnetic resonance delayed enhancement images with prominent mid myocardial enhancement involving the basal to mid-anterior and inferior wall and the interventricular septum.

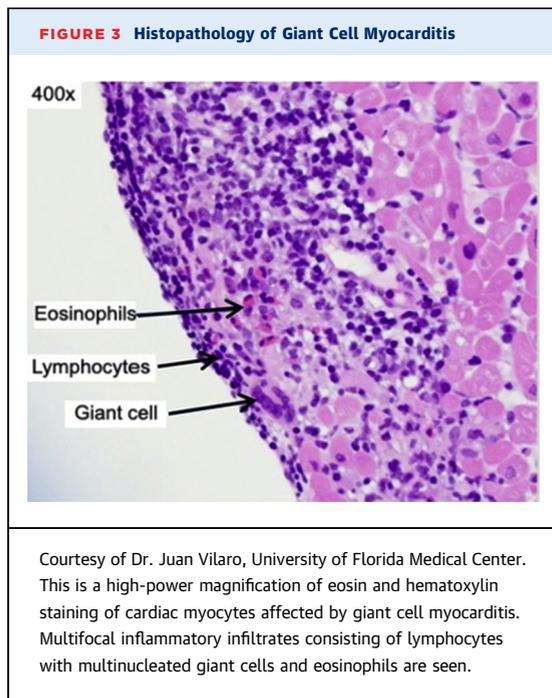
general, and is not specific to GCM. Last, CMR could be useful to guide EMB by identifying areas of the LV or interventricular septum that would have the highest yield for EMB (Figures 1C and 1D), especially when the initial EMB is unrevealing.

FDG-PET imaging can assess metabolic activity (active inflammation) to help make the diagnosis of myocarditis and provide anatomic localization to guide EMB (Figure 2). In a single-center cohort, 15 of 51 patients with GCM underwent cardiac FDG-PET. The majority of patients (93%) had enhanced focal uptake of  $^{18}\text{F}$ -FDG, principally in the septum, and among these the majority had abnormal SPECT colocalized to a perfusion defect (Figure 2) (6).

Additionally, FDG-PET can be helpful in identifying lymph nodes as a target site for biopsy to rule out cardiac sarcoidosis (CS), with which there can be substantial clinical overlap.

**ENDOMYOCARDIAL BIOPSY.** The diagnosis of GCM requires EMB. EMB should be strongly considered in patients with new-onset cardiomyopathy and ventricular arrhythmias and/or infranodal AV block (24). A total of 5 to 6 samples should be obtained from more than 1 region of the RV septum.

The pathognomonic histological features of GCM are diffuse or multifocal inflammatory infiltrates that consist of lymphocytes with multinucleated giant cells and associated myocyte damage (Figure 3). The



giant cells are typically associated with intact or degranulated eosinophils and usually extend to the edges of inflammation (25). Fibrosis is usually mild if present. Although poorly formed granulomas may be seen in GCM, well-organized follicular granulomas containing central giant-cells exclude the diagnosis (25). Special stains for non-viral organisms should be negative.

EMB has reasonably high sensitivity, particularly in severe cases of GCM. However, in up to 20% of cases, EMB can yield a false-negative result (26). The reported sensitivity of EMB is significantly lower in patients with milder forms of GCM, possibly due to patchy myocardial involvement (27). If the clinical suspicion is high, imaging-guided EMB, either from the interventricular septum or LV, should be considered. No comparative studies exist for left versus right ventricular biopsy in GCM.

Electroanatomic mapping can be used to guide EMB by identifying low-voltage areas (electrogram amplitude 0.5 to 5 mV) with high sensitivity (70.4%) and specificity (100%) among patients with suspected myocarditis or CS (28).

**OVERLAP WITH OTHER INFLAMMATORY CARDIOMYOPATHIES.** The clinical and histological presentation of patients with GCM may mimic that of other inflammatory myocardial disorders, such as lymphocytic or eosinophilic myocarditis, immune checkpoint inhibitor-associated myocarditis, and

CS (1). There are subtle similarities, yet important differences, in the histopathological features of GCM and CS, which are crucial to recognize due to differences in the management and prognosis of these diseases.

Although patients with GCM and CS present at a similar age, CS is more prevalent in Blacks than Whites in the United States. The duration from symptom onset to presentation and diagnosis is greater for CS than GCM. Syncope, high-degree AV block, and permanent pacemaker implantation are more frequent in CS, whereas VT is equally prevalent in both (25).

On histopathology, noncaseating granulomas and fibrosis are suggestive of CS, whereas necrosis and eosinophilic infiltration are suggestive of GCM (25). It is important to note that the mere presence of giant cells does not distinguish these 2 entities, and differentiation can often be challenging.

## MANAGEMENT

Given its rarity, difficulty in diagnosis, and potentially life-threatening consequences, GCM has defied proper treatment trials. The recommendations made here are based upon the limited available evidence, derived largely from registry data (Table 1). Immunosuppressive therapy, management of HF and arrhythmias, hemodynamic support, and cardiac transplantation form the pillars of GCM management. We propose an algorithm for the diagnosis and management of GCM (Central Illustration).

**IMMUNOSUPPRESSIVE THERAPY.** The use of immunosuppressive therapy, together with guideline-directed medical management of HF and arrhythmias, has significantly altered the prognosis of GCM. Immunosuppressive therapy typically involves 2 or 3 drugs—most commonly corticosteroids and at least 1, and most often 2 additional immunosuppressive agents—cyclosporine + azathioprine, or mycophenolate mofetil + tacrolimus, and/or antithymocyte globulin (ATG) or muromonab CD3 antibody (no longer available in the United States) or alemtuzumab + cyclosporine (Table 2, Figure 4).

Historically, in patients with GCM, the rate of death or cardiac transplantation at 1 year without immunosuppressive therapy was 100%, with a median TFS of <3 months after symptom onset. TFS in patients treated with corticosteroids alone was similar to that in patients treated without immunosuppressive therapy. Combination immunosuppressive therapy that included cyclosporine improved median TFS from 3.0 to 12.4 months (2). In a prospective GCM registry, the first 11 patients treated with cyclosporine

**TABLE 1** Summary of Treatment Studies in Patients With Giant Cell Myocarditis

Study Design (Ref. #)	Patients Enrolled	Presentation, %	Treatment, n	Transplant, n	Overall Survival	Transplant-Free Survival	Comments
Retrospective multicenter registry (2)	63	HF, 75 VT, 14 MI mimic, 6 AV block, 5	No immunosuppression, 30 Immunosuppression, 33 • Corticosteroids alone, 11 • Corticosteroids + azathioprine, 11 • Cyclosporine combination therapy, 10	34	Median survival 3.0 months Median survival 12.3 months	Unknown	Higher proportion of transplants possibly due to less frequent and less intense immunosuppression used in the cohort
Prospective multicenter study (4)	11	Not available	Corticosteroids + cyclosporine, 11 and Muromonab-CD3, 9	2	90.9% at 1 yr	72.7% at 1 yr	Patients with fulminant myocarditis were excluded from the study
Retrospective single-center study (6)	51 (43 diagnosed by EMB or surgical biopsy, 8 on autopsy or transplant)	HF, 39 AV block, 27 VT/VF, 22 Other,* 12	42 patients treated with 2 to 4 drug immunosuppression • Corticosteroids, 42 • Azathioprine, 36 • Cyclosporine, 33 • Mycophenolate mofetil, 3 • Tacrolimus, 1 • Muromonab CD3, 2 • Gammaglobulin, 1 • Methotrexate, 1	19	86% at a median follow-up of 19 months	Unknown	80% received ICD 16% received pacemaker

\*MI mimic, nonspecific fatigue, frequent premature ventricular complexes.  
AV = atrioventricular block; EMB = endomyocardial biopsy; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; VF = ventricular fibrillation; VT = ventricular tachycardia.

and corticosteroids, with or without muromonab-CD3, had an overall survival of 91% at 1 year, with 1 death and 2 patients requiring transplantation within the first month (4). In another study of 26 patients, cyclosporine use was associated with a trend toward a lower likelihood of cardiac transplantation or death (29). The use of Muromonab-CD3, ATG, or alemtuzumab in addition to cyclosporine is supported by the mechanistic role of T cells in the pathogenesis of GCM. Along with improvement in overall survival, TFS rates improved significantly to 69% at 1 year, 58% at 2 years, and 52% at 5 years with combination immunosuppression (10).

A small prospective study also demonstrated that the extent of eosinophilic infiltration, giant cells, foci of lymphocytic myocarditis, and necrosis had decreased significantly between baseline and 4 weeks post-immunosuppression biopsy specimens. The same study also compared LVEF before and after immunosuppression. The mean LVEF was only mildly reduced ( $44 \pm 18\%$ ) at baseline and did not change significantly after 4 weeks of immunosuppression ( $47 \pm 15\%$ ;  $p = 0.60$ ) (4).

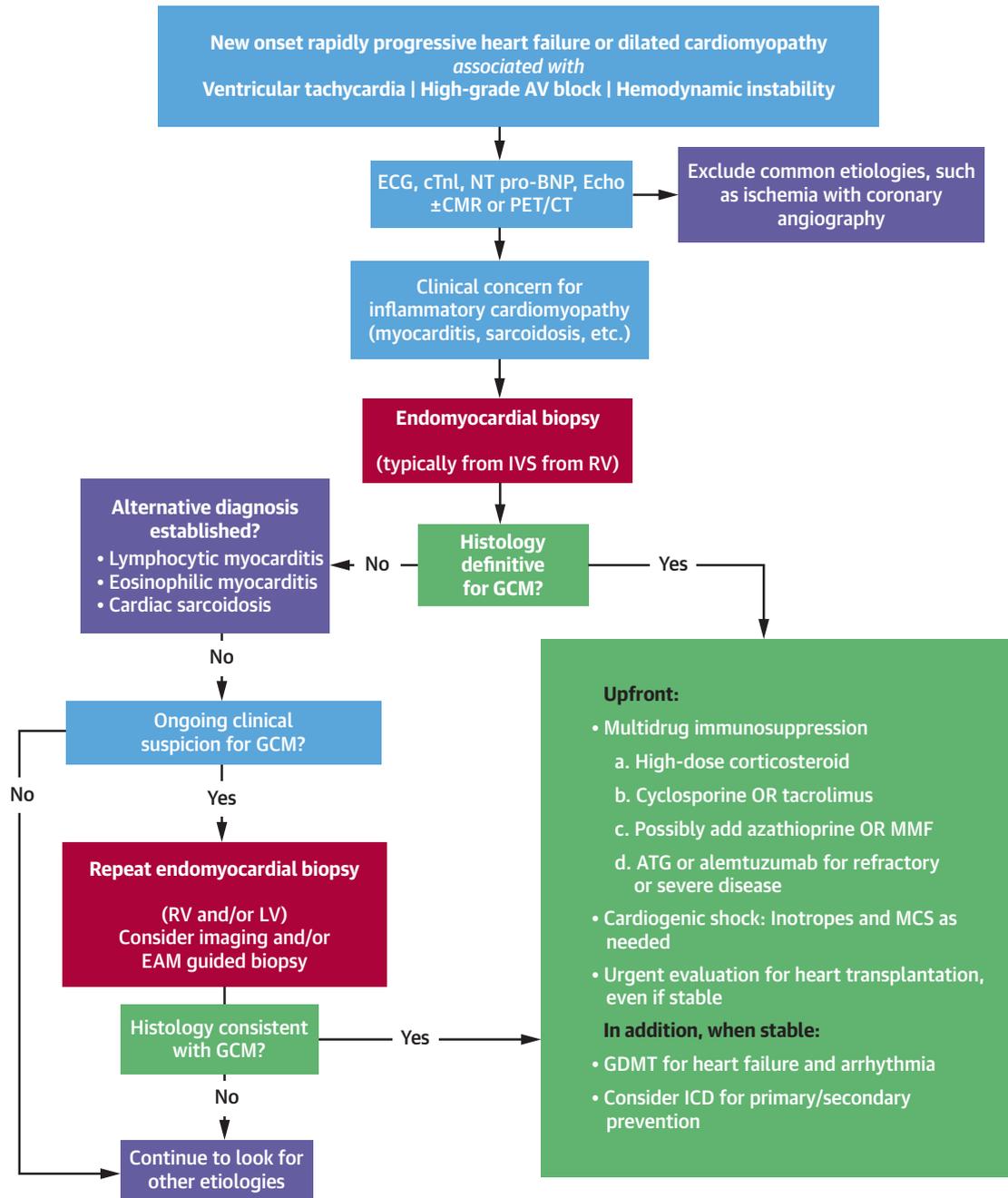
The usual regimen for GCM includes intravenous methylprednisolone 10 mg/kg (up to 1,000 mg/day) for the first 3 days, followed by a prednisone taper, with a starting dose of 40 to 60 mg/day and decreasing to 5 to 10 mg/day after 6 to 8 weeks (Figure 4). This is used in combination with either

ATG 100 mg intravenously daily for 3 days or alemtuzumab 15 mg intravenously daily for 2 days (or similar dosing regimens) and cyclosporine. Alternative regimens may include high-dose corticosteroids along with cyclosporine and azathioprine (1.5 to 2 mg/kg/day) (10).

Contemporary data in solid organ transplantation has demonstrated improved efficacy and safety with tacrolimus and mycophenolate mofetil compared with cyclosporine and azathioprine (30). As a result, some centers now use tacrolimus and mycophenolate mofetil, in addition to prednisone, for the treatment of GCM (Figure 4). However, a combination of either azathioprine or mycophenolate mofetil with tacrolimus or cyclosporine are acceptable. Typically, 1 year after initial treatment, azathioprine or mycophenolate is discontinued and prednisone may be tapered off slowly in patients with normalization of LV function. Cyclosporine or tacrolimus is often continued indefinitely.

Recurrence of GCM has been reported as late as 8 years after the initial diagnosis (29). Although there is no strong evidence supporting continuation of other immunosuppressive agents beyond 1 year, at least 1 immunosuppressant, usually a calcineurin inhibitor, is continued at a low dose for a minimum of 2 years, and often indefinitely, particularly in patients with persistent LV dysfunction. Alemtuzumab has been successfully used to treat a patient with recurrent post-cardiac transplant GCM, refractory to

**CENTRAL ILLUSTRATION Proposed Algorithm for Giant Cell Myocarditis Diagnosis and Management**



Bang, V. et al. J Am Coll Cardiol. 2021;77(8):1122-34.

This flow diagram illustrates stepwise evaluation and management strategies for patients presenting with a clinical scenario suggestive of giant cell myocarditis. We discuss the role of cardiac biomarkers, imaging tests, and endomyocardial biopsy in diagnosing giant cell myocarditis. This diagram also provides a brief overview of the management of giant cell myocarditis. ATG = antithymocyte globulin; AV = atrioventricular; CMR = cardiac magnetic resonance imaging; cTn = cardiac troponin; EAM = electroanatomic mapping; ECG = electrocardiogram; Echo = echocardiogram; GCM = giant cell myocarditis; GDMT = guideline directed medical therapy; HD = hemodynamics; HF = heart failure; ICD = implantable cardioverter defibrillator; ICU = intensive care unit; IVS = interventricular septum; LV = left ventricle/ventricular; MCS = mechanical circulatory support; MMF = mycophenolate mofetil; NT pro-BNP = N-terminal pro-brain natriuretic peptide; PET-CT = positron-emission tomography-computed tomography; RV = right ventricle/ventricular; VA = ventricular arrhythmia.

**TABLE 2 Immunosuppressive Medications Commonly Used for the Treatment of Giant Cell Myocarditis**

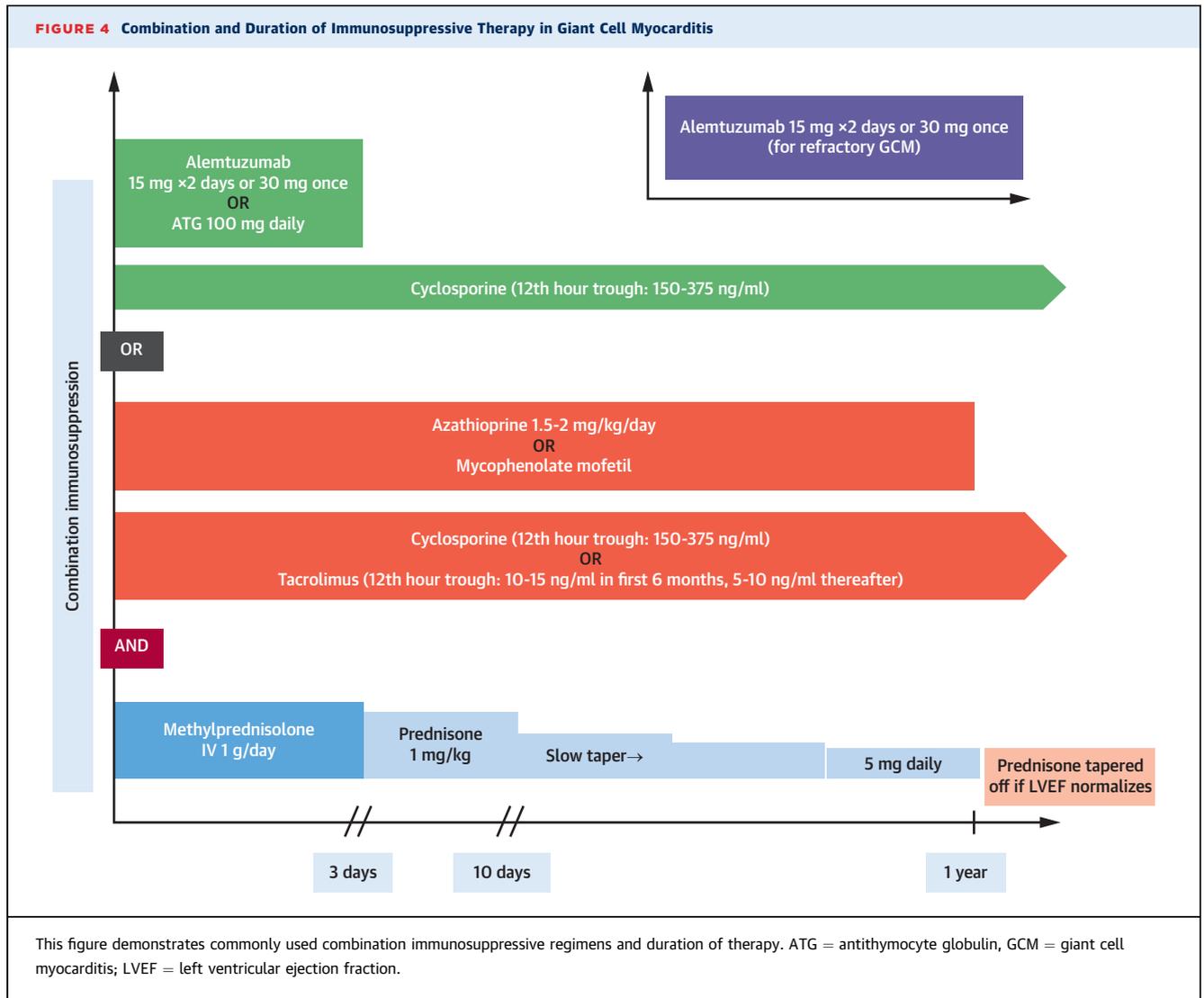
Drug	Mechanism of Action	Dose	Dose Monitoring	Duration	Adverse effects
Methylprednisolone followed by prednisone	Suppresses migration of leucocytes	1 g daily Followed by 1 mg/kg/day → tapered gradually, decreasing to 5-10 mg/day after 6-8 weeks	NA	3 days Slowly tapered off over 1 yr, then may stop or continue 5 mg/day indefinitely	Infection Hypertension Fluid retention Peptic ulcer Osteoporosis Encephalopathy Cataract
Cyclosporine	Inhibits IL-2-induced T-cell activation	Variable	12-h trough levels Goal: 75-300 ng/ml (150-300 ng/ml for the first 3 months, 100-150 ng/ml from month 4 through 12, 75-100 ng/ml thereafter)	Indefinite	Tremor Nephrotoxicity Hypertension Hirsutism Infection
Azathioprine	Inhibits purine synthesis, affecting DNA production in T and B cells	1.5-2 mg/kg/day	Temporarily withhold for WBC <3,000/ml or 50% of previous value	1 yr	Dose-dependent myelosuppression, particularly leucopenia Neoplasia Hepatotoxicity pancreatitis Infection
Tacrolimus	Inhibits calcineurin mediated T-cell activation	Variable	12-h trough levels Goal: 5-15 ng/ml (10-15 ng/ml in first 6 months, 5-10 ng/ml thereafter)	1 yr Possibly indefinite	Arrhythmias DVT Nightmares Encephalopathy Acne Dermatitis Diabetes mellitus Renal failure Bladder spasms Pancytopenia Hepatotoxicity Infection
Mycophenolate mofetil	Inhibits de novo purine synthesis, selectively affecting DNA production in T and B cells	1.5 g twice daily	Routine monitoring of levels not recommended but in patients with adverse effects, target trough levels 2-5 µg/ml	1 yr	Hypertension Hyperglycemia GI intolerance Electrolyte disturbances Hepatitis Pancytopenia Dyspnea Cough PML Infection
Antithymocyte globulin	Polyclonal anti-T-cell antibody	100 mg IV daily	Leucopenia and thrombocytopenia respond to dose reduction May need drug discontinuation for severe cases (WBC <2,000/ml or platelet count <50,000/ml)	3 days	Thrombocytopenia Leucopenia Chills Fever Headache Rash
Alemtuzumab	Monoclonal antibody that binds to CD-52 on B and T lymphocytes, macrophages, monocytes, and NK cells	30 mg IV once OR 15 mg IV daily × 2 days		1-2 days	Cytokine release syndrome* Severe and sustained lymphopenia Infection Autoimmune disorders (thyroid disease, ITP, anti-GBM nephropathy) Headache Skin rash

\*Treat cytokine release syndrome with supportive hemodynamic care, high-dose steroids, and possibly interleukin (IL)-6 monoclonal antibody (tocilizumab) (42).  
ANC = absolute neutrophil count; CBC = complete blood count; DNA = deoxyribonucleic acid; DVT = deep vein thrombosis; GBM = glomerular basement membrane; ITP = immune thrombocytopenia; IV = intravenous; LFT = liver function test; NA = not applicable; PML = progressive multifocal leukoencephalopathy, WBC = white blood cells.

intravenous methylprednisolone and ATG, with normalization of cTn and LV systolic function along with resolution of GCM on histology (31).

**NEUROHORMONAL THERAPY.** The utility of neurohormonal therapy in patients with GCM and LV systolic dysfunction is not well-established. In 1 registry, 85% of patients were on beta-blockers and 72% were

on angiotensin-converting enzyme inhibitors (16). Despite the lack of specific evidence, in patients with GCM who develop LV systolic dysfunction, maximally tolerated GDMT with beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or angiotensin receptor blocker-neprilysin inhibitors and aldosterone antagonists should be considered after hemodynamic stabilization (32).



**ANTIARRHYTHMICS AND IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR.** Many patients with GCM manifest VT or high-degree heart block. In general, the management of arrhythmias in patients with GCM is similar to that in other types of cardiomyopathies.

Patients with advanced conduction system disease may require temporary pacing, frequently followed by permanent pacemaker implantation due to persistent bradyarrhythmias despite immunosuppression. In a Finnish registry, 17% of patients received permanent pacemaker implantation. Ventricular fibrillation or hemodynamically unstable VT may require antiarrhythmic medications such as amiodarone and/or ICD for secondary prevention, if meaningful survival >1 year is expected. ICD implantation for primary prevention should be pursued in those patients with LVEF <35%, despite at least

3 months of GDMT, with consideration of wearable cardiac defibrillators in the interim. Although consensus guidelines provide a Class IIa recommendation for primary prevention ICD implantation in patients with CS and extensive LGE on CMR in the absence of other indications (33), there is no clear evidence supporting such an approach in GCM. However, extrapolating from the recommendations for CS, in the absence of typical indications, ICD implantation could be considered on a case-by-case basis in GCM patients with extensive LGE on CMR despite adequate immunosuppressive therapy, particularly those with ventricular arrhythmias or ectopy on presentation or on ambulatory rhythm monitoring or those with high-grade fibrosis on EMB. In the Finnish registry, 57% of patients with GCM received an ICD (46% for primary prevention; 11% for

secondary prevention) and 55% (17 of 31) received 1 or more appropriate therapies (ATP and/or shocks) for ventricular arrhythmias (6). Importantly, there were no reported device infections in the face of immunosuppression.

**EXERCISE LIMITATION.** Patients with GCM, like all forms of myocarditis, should be restricted from participation in competitive sports or similar activities for at least 3 to 6 months (34). Afterwards, patients with adequately treated and stable disease should undergo follow-up testing with cardiac biomarkers (cTn), an echocardiogram, ambulatory rhythm monitoring, and exercise tolerance testing. If the serum levels of cardiac biomarkers and LV systolic function have normalized, and there is no evidence of clinically relevant arrhythmias with either ambulatory rhythm monitoring or exercise testing, it may be reasonable to resume exercise gradually.

Although the presence of significant LGE on CMR has shown to be strongly predictive of major adverse cardiovascular events, particularly ventricular arrhythmia or sudden cardiac death (22), the majority of which occurred during exercise. This pertains to myocarditis in general, and not specifically to GCM. The role of repeat CMR assessment before resuming exercise is not well studied. However, extrapolating from the emerging evidence, it may be reasonable to perform follow-up CMR, in addition to other guideline-directed testing, to guide shared decision-making, particularly in those intending to return to competitive sports.

**INOTROPES, MECHANICAL CIRCULATORY SUPPORT, AND CARDIAC TRANSPLANTATION.** GCM may present with or progress to hemodynamic instability, either due to biventricular failure or ventricular arrhythmias, and hence may require inotropic therapy and/or temporary MCS (30). For patients with refractory shock, intra-aortic balloon pump placement, other forms of temporary MCS, or extracorporeal life support may be needed.

In a multicenter registry, 78% of patients were successfully bridged to transplant with MCS; this number is similar to that reported in the published data for other types of cardiomyopathies (35). Because GCM tends to involve both ventricles, it is not surprising that a significantly higher proportion of patients with GCM require biventricular mechanical circulatory support (MCS) before transplantation compared with patients with idiopathic dilated cardiomyopathy (IDCMP) (31% vs. 2%;  $p < 0.001$ ) (36-38). However, for reasons that are poorly understood, ventricular assist device (VAD) implantation has been

associated with a higher risk of GCM recurrence in the allograft (35).

Despite the risk of post-transplant recurrence in the allograft, transplantation is a reasonable option for medically refractory GCM. In the multicenter registry, approximately one-half (34 of 63) of the patients underwent cardiac transplantation, and 9 of these died during an average follow-up of 3.7 years after transplantation (2). The rate of cardiac transplantation was relatively high in this initial registry, likely due to less aggressive immunosuppression (2). The need for cardiac transplantation was significantly less (<20%) in 2 other studies where more intense immunosuppression was utilized upfront (4,10). United Network for Organ Sharing registry data demonstrated that patients with GCM present more acutely (44% listed as Status 1A, 2.8× more likely than IDCMP) and have increased rates of acute rejection compared with IDCMP patients (16% vs. 5.0%;  $p = 0.021$ ). The rate of pacemaker implantation, dialysis initiation, or stroke was similar to that observed in patients with other forms of myocarditis and IDCMP (38). Post-transplant survival in GCM patients was 94% at 1 year, 82% at 5 years, and 68% at 10 years, which was similar to other etiologies ( $p = 0.11$ ) (36).

Recurrent GCM after transplantation occurs in 20% to 25% of patients (39). Although patients may present with HF or other symptoms, the majority are asymptomatic, and GCM is typically detected on surveillance EMB. Currently, there is no guidance regarding routine EMB surveillance post-cardiac transplantation in asymptomatic patients; however, it is reasonable to consider EMB in patients with new-onset heart block, ventricular arrhythmias, or a decline in LV systolic function. The management of asymptomatic recurrent GCM with normal LV function is a steroid pulse, followed by a taper. Higher-dose corticosteroids and ATG are often used as a first-line therapy in patients with recurrent GCM and LV dysfunction. Although sirolimus and rituximab have been used with success (40,41), alemtuzumab may be more appropriate in refractory cases given its CD52-mediated effect on T cells (31).

## FUTURE DIRECTIONS

Substantial gaps exist in our current knowledge regarding the etiology, diagnosis, prognosis, and management of GCM. Although combination immunosuppressive therapy has changed the landscape of GCM treatment with improved outcomes, our understanding regarding the predictors of response in those treated with immunosuppressive therapy and

evidence regarding the most suitable agents, preferred combinations, and optimal duration is still limited. Similarly, our understanding regarding the role of unloading the ventricle with devices such as an intra-aortic balloon pump or axial flow pump, such as Impella (Abiomed, Danvers, Massachusetts), to lower the degree of inflammation and promote myocardial recovery (36) is sparse. Additionally, we need a better understanding of the use of MCS and concomitant immunosuppression in GCM and the trade-off between the risk of device infection and the likelihood of myocardial recovery and device explantation. Further studies, preferably prospective

trials, examining these knowledge gaps are required to enhance our understanding of GCM, its management, and prognosis.

#### FUNDING SUPPORT AND AUTHOR DISCLOSURES

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**ADDRESS FOR CORRESPONDENCE:** Dr. Sarju Ganatra, Department of Cardiovascular Medicine, Lahey Hospital & Medical Center, 41 Mall Road, Burlington, Massachusetts 01805, USA. E-mail: [Sarju.Ganatra@Lahey.org](mailto:Sarju.Ganatra@Lahey.org). Twitter: [@SarjuGanatraMD](https://twitter.com/SarjuGanatraMD).

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**KEY WORDS** cardiogenic shock, endomyocardial biopsy, giant cell myocarditis, heart block, heart failure, heart transplant, immunosuppression, left ventricular assist device, ventricular arrhythmia

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