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35th Anniversary

Inflammatory cardiomyopathy

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ESC REPORT

Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

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Introduction

- Inflammatory cardiomyopathy is defined as myocarditis accompanied by cardiac dysfunction, which may result dilated cardiomyopathy (DCM)
- Myocarditis is an inflammatory disease of cardiac muscle that is caused by a variety of infectious and noninfectious conditions
- Definition:
  - Myocarditis is an inflammatory disease of the myocardium. The World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) definition specifies diagnosis by established histological (Dallas criteria), immunological and immunohistochemical criteria
- Majority of patients with clinical manifestations of myocarditis do not undergo endomyocardial biopsy, thus definitive diagnosis is not established

Definitions

Myocarditis (WHO /ISFC[1]):

Inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria**.*

**N.B. established histological Dallas criteria[12] defined as follows: 'histological evidence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of non-ischaemic origin [12]'.*

***N.B. unspecified immunohistochemical criteria[1], we propose an abnormal inflammatory infiltrate to be defined as follows: '≥ 14 leucocytes/mm^2 including up to 4 monocytes/mm^2 with the presence of CD 3 positive T-lymphocytes ≥ 7 cells/mm^2'.[15,18,19]*

Inflammatory Cardiomyopathy (WHO /ISFC[1]):

Myocarditis in association with cardiac dysfunction.

N.B. Inflammatory cardiomyopathy, involved in the pathogenesis of DCM, includes idiopathic, autoimmune and infectious subtypes.[1]

Dilated Cardiomyopathy (ESC[13]; WHO /ISFC[1]):

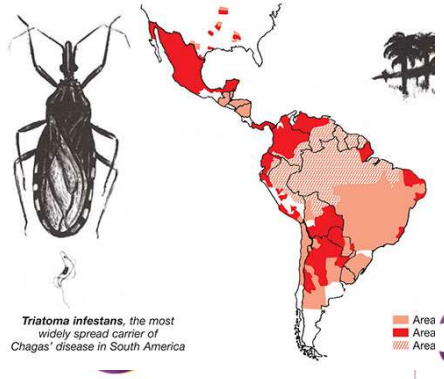
DCM is a clinical diagnosis characterized by dilation and impaired contraction of the left or both ventricles that is not explained by abnormal loading conditions or coronary artery disease.

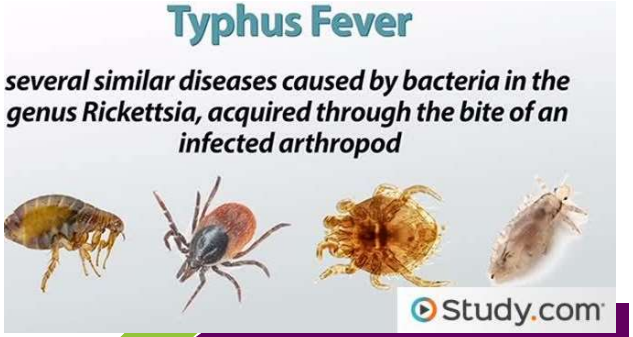
N.B. DCM includes idiopathic, familial/genetic, viral and/or immune, alcoholic/toxic subtypes.[1]

Table 1 Causes of myocarditis/inflammatory cardiomyopathy

1. Infectious myocarditis

Bacterial	*Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Meningococcus*, *Gonococcus*, *Salmonella*, *Corynebacterium diphtheriae*, *Haemophilus influenzae*, *Mycobacterium* (tuberculosis), *Mycoplasma pneumoniae*, *Brucella*
Spirochaetal	*Borrelia* (Lyme disease), *Leptospira* (Weil disease)
Fungal	*Aspergillus*, *Actinomyces*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Histoplasma*, *Mucormycoses*, *Nocardia*, *Sporothrix*
Protozoal	*Trypanosoma cruzi*, *Toxoplasma gondii*, *Entamoeba*, *Leishmania*
Parasitic	*Trichinella spiralis*, *Echinococcus granulosus*, *Taenia solium*
Rickettsial	*Coxiella burnetii* (Q fever), *R. rickettsii* (Rocky Mountain spotted fever), *R. tsutsugamuschi*
Viral	RNA viruses: Coxsackieviruses A and B, echoviruses, polioviruses, influenza A and B viruses, respiratory syncytial virus, mumps virus, measles virus, rubella virus, hepatitis C virus, dengue virus, yellow fever virus, Chikungunya virus, Junin virus, Lassa fever virus, rabies virus, human immunodeficiency virus-1 DNA viruses: adenoviruses, parvovirus B19, cytomegalovirus, human herpes virus-6, Epstein-Barr virus, varicella-zoster virus, herpes simplex virus, variola virus, vaccinia virus





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2. Immune-mediated myocarditis	
Allergens	Tetanus toxoid, vaccines, serum sickness
	Drugs: penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyldopa, thiazide diuretics, amitriptyline
Alloantigens	Heart transplant rejection
Autoantigens	Infection-negative lymphocytic, infection-negative giant cell
	Associated with autoimmune or immune-oriented disorders: systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki's disease, inflammatory bowel disease, scleroderma, polymyositis, myasthenia gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, Wegener's granulomatosis, rheumatic heart disease (rheumatic fever)
3. Toxic myocarditis	
Drugs	Amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hemetine, interleukin-2, trastuzumab, clozapine
Heavy metals	Copper, iron, lead (rare, more commonly cause intramyocyte accumulation)
Miscellaneous	Scorpion sting, snake, and spider bites, bee and wasp stings, carbon monoxide, inhalants, phosphorus, arsenic, sodium azide
Hormones	Phaeochromocytoma, vitamins: beri–beri
Physical agents	Radiation, electric shock

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Clinical manifestation

- Highly variable, ranging from fatigue, chest pain, HF, cardiogenic shock, arrhythmias, and sudden death
- Lack of a safe and sensitive noninvasive diagnostic test that can confirm the diagnosis.
- Myocardial inflammation may be focal or diffuse, involving any or all cardiac chambers. Severe, diffuse myocarditis can result in acute dilated cardiomyopathy

Circulation

ORIGINAL RESEARCH ARTICLE

Clinical Presentation and Outcome in a Contemporary Cohort of Patients With Acute Myocarditis

Multicenter Lombardy Registry

METHODS: A total of 684 patients with suspected AM and recent onset of symptoms (<30 days) were screened between May 2001 and February 2017. Patients >70 years of age and those >50 years of age without coronary angiography were excluded. The final study population comprised 443 patients (median age, 34 years; 19.4% female) with AM diagnosed by either endomyocardial biopsy or increased troponin plus edema and late gadolinium enhancement at cardiac magnetic resonance.

RESULTS: At presentation, 118 patients (26.6%) had left ventricular ejection fraction <50%, sustained ventricular arrhythmias, or a low cardiac output syndrome, whereas 325 (73.4%) had no such complications. Endomyocardial biopsy was performed in 56 of 443 (12.6%), and a baseline cardiac magnetic resonance was performed in 415 of 443 (93.7%). Cardiac

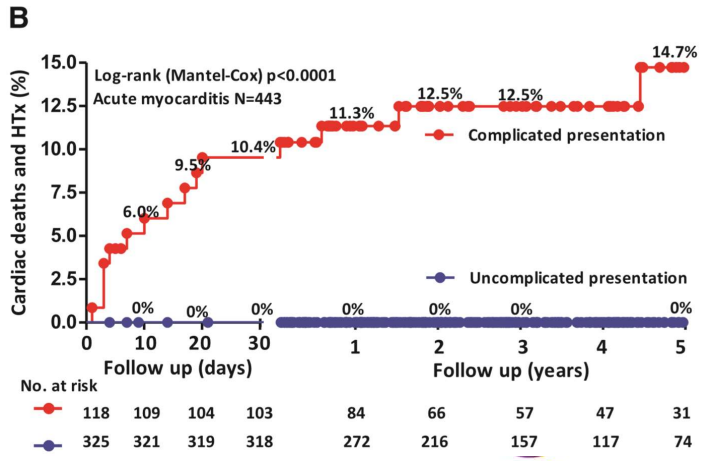
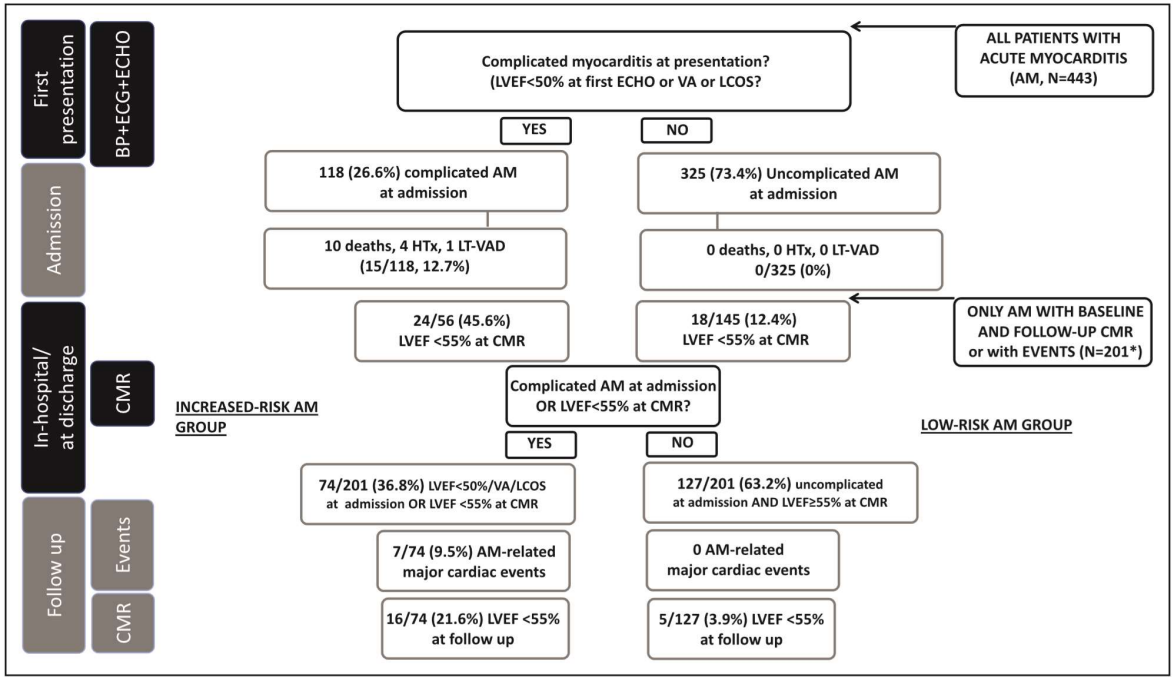


Table 1. Clinical Presentation and Initial Diagnostic Findings in 443 Patients Admitted With Clinically Suspected AM

	Patients With Available Data, n	AM			*P* Value
		All	Complicated Presentation	Uncomplicated Presentation	
n		443	118	325	
Age, median (Q1–Q3), y	443	34 (24–42)	35 (22–45)	33 (24–42)	0.46
Age <15 y, n (%)		14 (3.2)	7 (5.9)	7 (2.2)	0.06
Female, n (%)	443	86 (19.4)	37 (31.4)	49 (15.1)	0.0002
White, n (%)	443	407 (92.1)	104 (88.1)	303 (93.2)	0.11
Clinical presentation, n (%)					
Dyspnea	437	84 (19.2)	64 (55.7)	20 (6.2)	<0.0001
Chest pain	437	379 (86.7)	68 (59.1)	311 (96.6)	<0.0001
Syncope	437	27 (6.2)	19 (16.5)	8 (2.5)	<0.0001
Fulminant presentation*	443	38 (8.6)	38 (32.2)	0 (0)	<0.0001
Fever, n (%)	437	282 (64.5)	73 (63.5)	209 (64.9)	0.82
Prodromal symptoms, n (%)	437	352 (80.5)	94 (81.7)	258 (80.1)	0.78
Sore throat, n (%)	437	161 (36.8)	44 (38.3)	117 (36.3)	0.74
Respiratory tract infection, n (%)	437	10 (2.3)	6 (5.2)	4 (1.2)	0.02
Gastrointestinal disorders, n (%)	437	126 (28.8)	36 (31.3)	90 (28.0)	0.55
Patients with associated autoimmune disorders,† n (%)	430	31 (7.2)	18 (15.4)	13 (4.2)	0.0002
Previous myocarditis, n (%)	443	5 (1.1)	2 (1.7)	3 (0.9)	0.61
ECG at admission, n (%)	426				
Normal		61 (14.3)	8 (7.6)	53 (16.5)	<0.0001
ST-segment elevation		245 (57.5)	45 (42.9)	200 (62.3)	
Other abnormal ST-T segment		100 (23.5)	39 (37.1)	61 (19.0)	
Bundle-branch block		20 (4.7)	13 (12.4)	7 (2.2)	
Any AV block, n (%)	427	13	10 (9.6)	3 (0.9)	<0.0001
Laboratory findings, n (%)					
Increased CRP at admission	414	333 (80.4)	89 (84.0)	244 (79.2)	0.32
Increased troponin T/troponin I/CK-MB at admission	437	434 (99.3)	111 (99.1)	323 (99.4)	1
Echocardiography at admission, n (%)	431	431 (97.3)	112 (94.9)	319 (98.2)	0.09
LVEF (Q1–Q3), %	428	55 (50–60)	35 (20–45)	60 (55–60)	<0.0001
LVEDD, median (Q1–Q3) (only patients ≥15 y old), mm	246	49 (46–52)	50 (46–55)	48 (46–50)	0.050
RV-TAPSE <18 mm or evidence of visual dysfunction, n (%)	259	22 (8.5)	19 (30.6)	3 (1.5)	<0.0001
Presence of pericardial effusion, n (%)	397	102 (25.7)	41 (38.7)	61 (21.0)	0.0007
Coronary angiography or CT angiography performed, n (%)	434	203 (46.8)	57 (50.0)	146 (45.6)	0.45
No evidence of CAD	203	203 (100)	57 (100)	146 (100)	…

Table 3. Events That Occurred in 443 Patients Admitted With Clinically Suspected AM

	AM			
	All	Complicated at Presentation	Uncomplicated at Presentation	*P* Value
n	443	118	325	
In-hospital events, n (%)				
Overall deaths	10 (2.3)	10 (8.5)	0 (0)	<0.0001
Cardiac deaths	10 (2.3)	10 (8.5)	0 (0)	<0.0001
Noncardiac deaths	0 (0)	0 (0)	0 (0)	…
HTx	4 (0.9)	4 (3.4)	0 (0)	0.005
VAD	5 (1.1)	5 (4.2)	0 (0)	0.001
Va-ECMO	18 (4.1)	18 (15.3)	0 (0)	<0.0001
Lost after discharge, n (%)	5 (1.1)	2 (0.8)	3 (0.9)	
Postdischarge events, n (%)				
n	428	106	322	
Overall deaths	7 (1.6)	6 (5.7)	1 (0.3)	0.001
Cardiac deaths	2* (0.5)	2* (1.9)	0 (0)	…
Noncardiac deaths	5 (1.2)	4 (3.8)†	1 (0.3)†	0.014
HTx	2 (0.5)	2 (1.9)	0 (0)	…
SVT treated with shock/ ablation	4 (0.9)	4 (3.8)	0 (0)	0.004
CRT implantation	1 (0.2)	1 (0.8)	0 (0)	…
Other events, n (%)				
ICD implantation	9 (2.0)	8 (6.8)	1 (0.3)‡	<0.0001
Recurrence of AM	11 (2.6)	1 (0.9)	10 (3.1)	0.31
STEMI	2 (0.5)	0 (0)	2 (0.6)	…



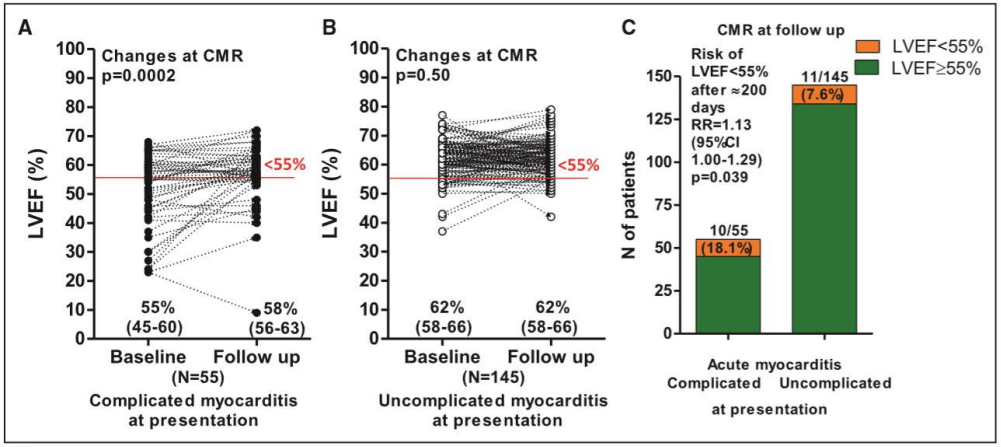


Figure 4. Changes in left ventricular (LV) ejection fraction (EF) between baseline and follow-up (median time, 196 days) cardiac magnetic resonance (CMR).

Table 3 **Clinical presentations of patients with biopsy-proven inflammatory heart muscle disease**

(1) Acute coronary syndrome-like

(a) Acute chest pain

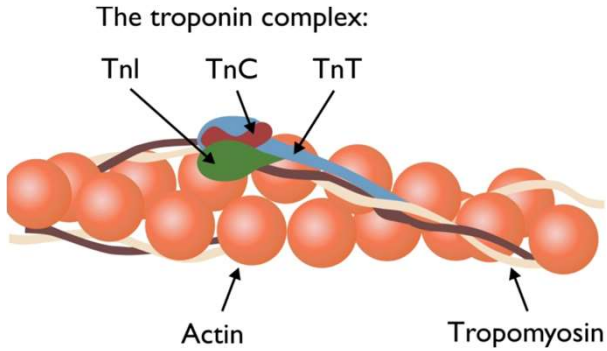
- Frequently starting within 1–4 weeks of a respiratory or gastrointestinal infection
- Frequently associated with severe and recurrent symptoms
- In the absence of angiographic evidence of CAD

(b) ST/T wave changes

- ST-segment elevation or depression
- T-wave inversions

(c) With or without normal global or regional LV and/or RV dysfunction on echocardiography or CMR

(d) With or without increased TnT/TnI that may have a time course similar to acute myocardial infarction or a prolonged and sustained release over several weeks or months



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(2) New onset or worsening heart failure in the absence of CAD and known causes of heart failure

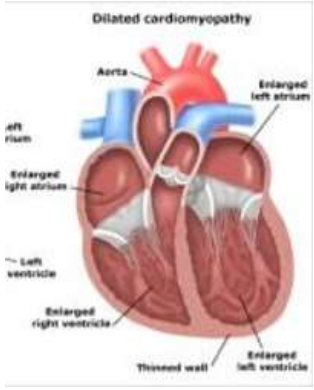
(a) New onset or progressive heart failure over 2 weeks to 3 months

- Dyspnoea
- Peripheral oedema
- Chest discomfort
- Fatigue

(b) Impaired systolic LV and/or RV function, with or without an increase in wall thickness, with or without dilated LV and/or RV on echocardiography or CMR

(c) Symptoms possibly started after a respiratory or gastrointestinal infection, or in the peri-partum period

(d) Non-specific ECG signs, bundle branch block, AV-block, and/or ventricular arrhythmias



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(3) Chronic heart failure in the absence of CAD and known causes of heart failure (see point 2 above)

(a) Heart failure symptoms (with recurrent exacerbations) of >3 months duration

(b) Fatigue, palpitation, dyspnoea, atypical chest pain, arrhythmia in an ambulant patient

(c) Impaired systolic LV and/or RV function on echocardiography or CMR suggestive of DCM or non-ischaemic cardiomyopathy

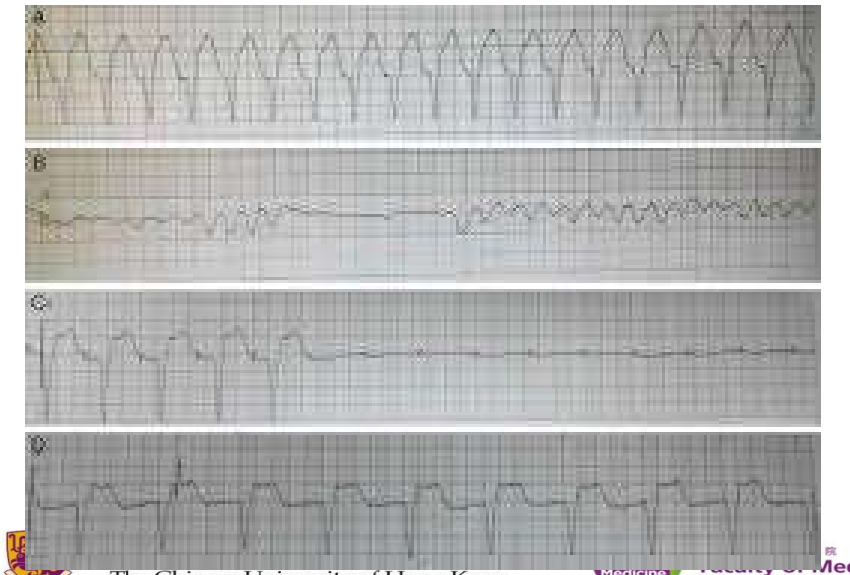
(d) Non-specific ECG signs, sometimes bundle branch block and/or ventricular arrhythmias and/or AV-block

(4) 'life-threatening condition', in the absence of CAD and known causes of heart failure comprising

(a) Life-threatening arrhythmias and aborted sudden death

(b) Cardiogenic shock

(c) Severely impaired LV function



Representative ECGs (lead II) in patient with fulminant myocarditis. Various arrhythmias and of pacemaker recorded by the ECG monitor during hospitalization. (A) Ventricular tachycardia; (B) ventricular fibrillation; (C) high-degree atrioventricular block; (D) ventricular pacing by temporary pacemaker.

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CASE REPORT

An unusual case of fulminant myocarditis closely mimicking ST-segment elevation myocardial infarction and presenting as refractory cardiogenic shock complicated by multiple life-threatening arrhythmias

Zhi-quan Wang*, Yi-Gang Li

Diagnosis of myocarditis

- Definitive diagnosis of myocarditis — A definitive diagnosis of myocarditis is based upon identification of diagnostic findings on EMB, including histology (Dallas criteria) as well as immunohistochemical stains.

- Diagnosis of clinically suspected myocarditis — A combination of clinical presentation and noninvasive diagnostic findings including typical CMR abnormalities may be used to make a diagnosis of "clinically suspected" myocarditis. While histology remains the gold standard for establishing the diagnosis of myocarditis, low-risk patients may be diagnosed with "clinically suspected myocarditis" on the basis of a compatible clinical presentation.

Clinically suspected myocarditis

- The 2013 ESC position statement suggested selective coronary angiography +/- EMB in all patients with clinically suspected myocarditis
- To provide a clinical diagnosis for patients who do not have one indication for EMB or who have undergone EMB with nondiagnostic results
- In this setting, a diagnosis of "clinically suspected myocarditis" is generally not sufficient to serve as a basis for immunosuppressive therapy but may be helpful to guide other aspects of management (eg, exercise recommendations)

Table 4 **Diagnostic criteria for clinically suspected myocarditis**

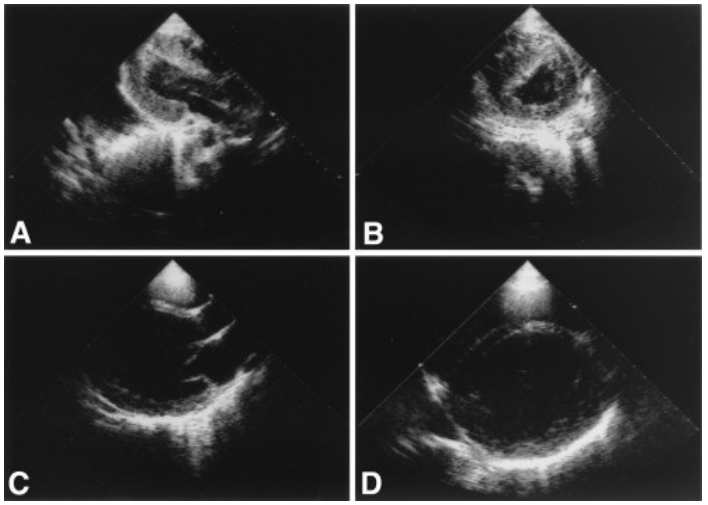
Clinical presentations[a]
Acute chest pain, pericarditic, or pseudo-ischaemic
New-onset (days up to 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
Subacute/chronic (>3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death
Unexplained cardiogenic shock
Diagnostic criteria
I. ECG/Holter/stress test features
Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia
II. Myocardiocytolysis markers
Elevated TnT/TnI
III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)
New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi
IV. Tissue characterization by CMR
Oedema and/or LGE of classical myocarditic pattern (see text)

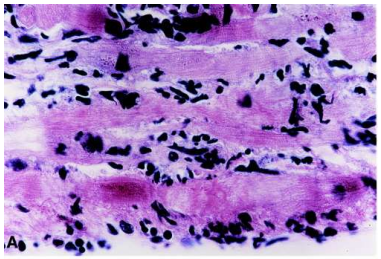
Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis ≥ 50%); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.) (see text). Suspicion is higher with higher number of fulfilled criteria.

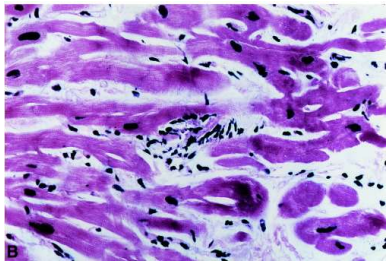
[a]If the patient is asymptomatic ≥2 diagnostic criteria should be met.

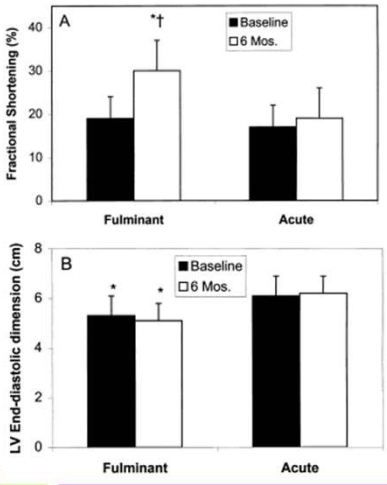
Role of echocardiography

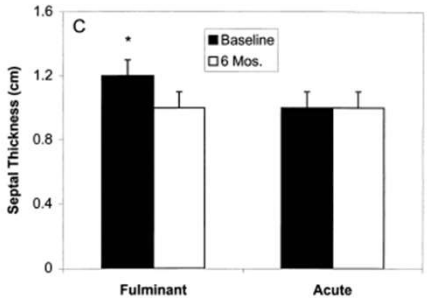
- Findings include LV dilation, changes in LV geometry to more spheroid shape, and wall motion abnormalities. The systolic dysfunction is generally global, but may be regional or segmental
- Fulminant and acute myocarditis are associated with
  - LV dilation and systolic dysfunction
  - Fulminant myocarditis typically have near-normal LV diastolic dimensions and mildly increased interventricular septal thickness
  - Acute myocarditis have relatively normal diastolic dimensions and septal thickness







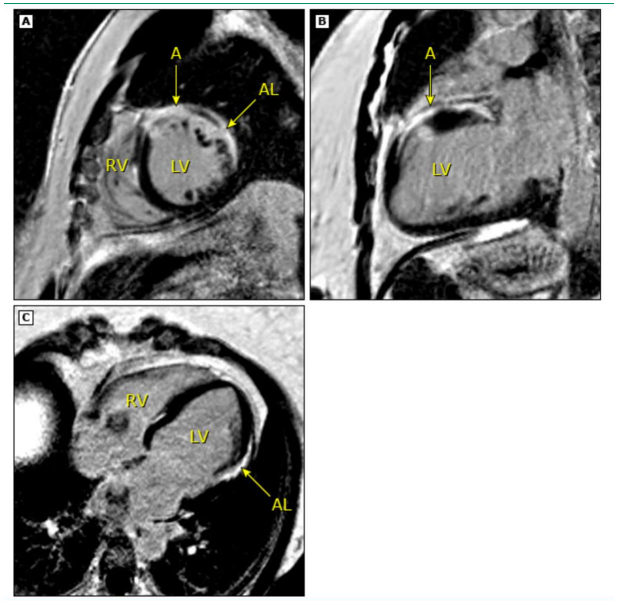




Role of Cardiac MRI (Lake Louise criteria)

CMR findings consistent with myocarditis if at least two out of three criteria are present:

- ● Evidence of myocardial edema with regional or global myocardial signal intensity increase in T2-weighted images.
- ● Early gadolinium enhancement (GE) suggestive of hyperemia and capillary leakage with an increased signal intensity ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images
- ● LGE defined as at least one focal lesion with nonischemic regional distribution, typically involving the subepicardium or midwall with infrequent involvement of subendocardium, often multifocal) in inversion recovery prepared gadolinium-enhanced T1-weighted images obtained at least five minutes after gadolinium contrast injection.
- ** LGE suggestive of myocardial injury or scar in myocarditis can generally be distinguished from that in ischemic cardiomyopathy. In ischemic cardiomyopathy, LGE reflects the distribution of MI, which typically involves the endocardium with variable extension into the mid-myocardium and epicardium.



Diagnostic Performance of CMR Imaging Compared With EMB in Patients With Suspected Myocarditis

METHODS One hundred thirty-two consecutive patients with suspected AMC (defined by symptoms ≤14 days; n = 70) and CMC (defined by symptoms >14 days; n = 62) were included. Patients underwent cardiac catheterization with left ventricular endomyocardial biopsy and CMR, including T_2-weighted imaging for assessment of edema, T_1-weighted imaging before and after contrast administration for evaluation of hyperemia, and assessment of late gadolinium enhancement. CMR results were considered to be consistent with the diagnosis of myocarditis if 2 of 3 CMR techniques were positive.

RESULTS Within the total population, myocarditis was the most common diagnosis on endomyocardial biopsy analysis (62.9%). Viral genomes were detected in 30.3% (40 of 132) of patients within the total patient population and significantly more often in patients with AMC than CMC (40.0% vs. 19.4%; p = 0.013). For the overall cohort of patients with either suspected AMC or CMC, the diagnostic sensitivity, specificity, and accuracy of CMR were 76%, 54%, and 68%, respectively. The best diagnostic performance was observed in patients with suspected AMC (sensitivity, 81%; specificity, 71%; and accuracy, 79%). In contrast, diagnostic performance of CMR in suspected CMC was found to be unsatisfactory (sensitivity, 63%; specificity, 40%; and accuracy, 52%).

Table 4. Extent and Localization of LGE on CMR Images

	All Patients	Group 1 (Symptoms ≤14 Days)	Group 2 (Symptoms >14 Days)	Group 1 vs. 2, p Value
Presence of LGE	84 (63.6)	45 (64.3)	39 (62.9)	0.99
Extent				
Epicardial	42 (50.0)	25 (55.6)	17 (43.6)	0.35
Intramyocardial	28 (33.3)	13 (28.9)	15 (38.5)	0.52
Endocardial	6 (7.1)	1 (2.2)	5 (12.8)	0.1
Transmural	8 (9.5)	6 (13.3)	2 (5.1)	0.28
Localization				
Anterior	31 (23.5)	20 (28.6)	11 (17.7)	0.16
Septal	40 (30.3)	17 (24.3)	23 (37.1)	0.13
Lateral	60 (45.5)	38 (54.3)	22 (35.5)	0.04
Inferior	61 (46.2)	34 (48.6)	27 (43.5)	0.6

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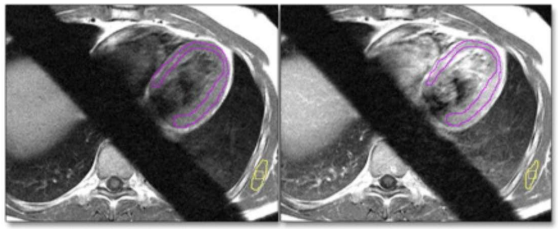

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Figure 3. T_1-Weighted MR Imaging and Assessment of Myocardial Hyperemia

Pre-contrast **(left)** and post-contrast **(right)** axial T_1-weighted spin echo images of the same slice used to calculate global relative enhancement from the mean signal intensities within the manually outlined borders around the left myocardium **(purple contour)** and right erector spinae muscle **(yellow contour)**. An additional saturation section is positioned across the atria to reduce signal from slow-flowing blood. In this patient, image analysis revealed a global relative enhancement ratio >4, indicating myocardial hyperemia/inflammation.

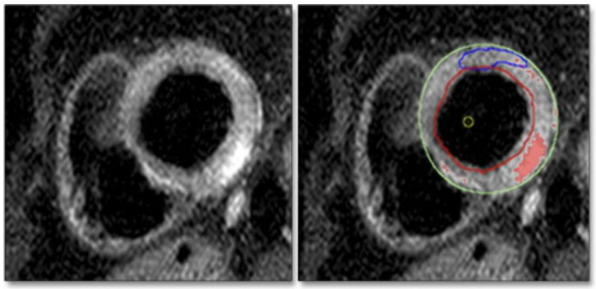

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Figure 2. T_2-Weighted Imaging and Assessment of Focal Myocardial Edema

T_2-weighted magnetic resonance (MR) imaging in a patient with focal areas of visually apparent high signal intensity (SI) (short-axis slice, **[left]**). Semi-quantitative assessment detects a focal subepicardial high SI (SI >2 SDs above the SI of normal myocardium, **blue contour**) **(red overlay)**, indicating regional myocardial edema in this patient **(right)**.

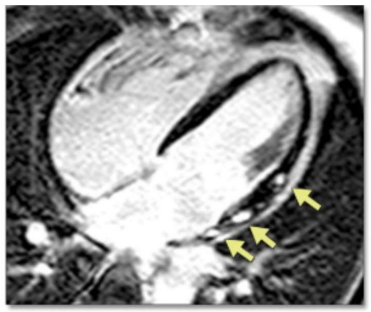

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Figure 4. Assessment of Myocardial Fibrosis/Necrosis/Scarring by Visualization of Late Enhancement on MR

Late gadolinium enhancement imaging of a patient with active myocarditis on endomyocardial biopsy shows focal late gadolinium enhancement **(arrows)** within the lateral wall of the left ventricle (long-axis view). Abbreviation as in Figure 1.

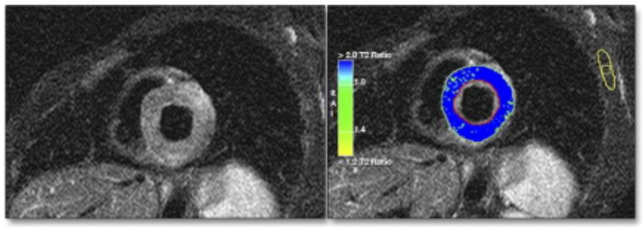

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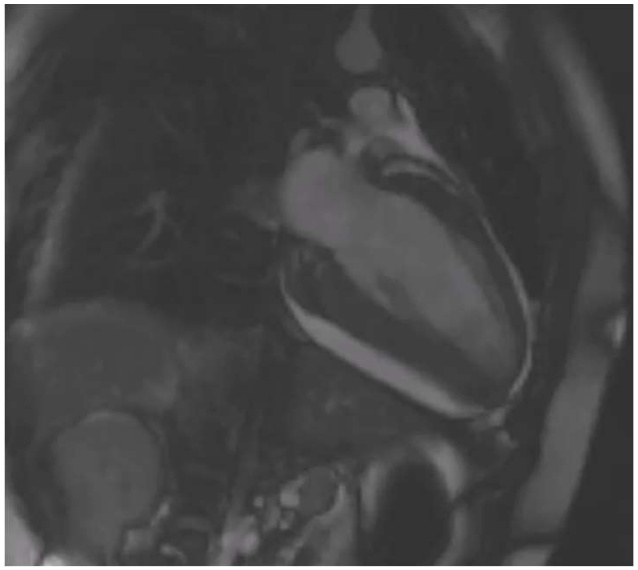
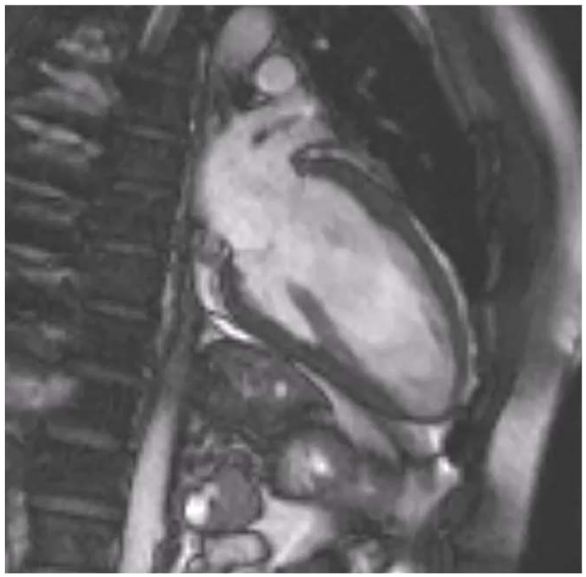
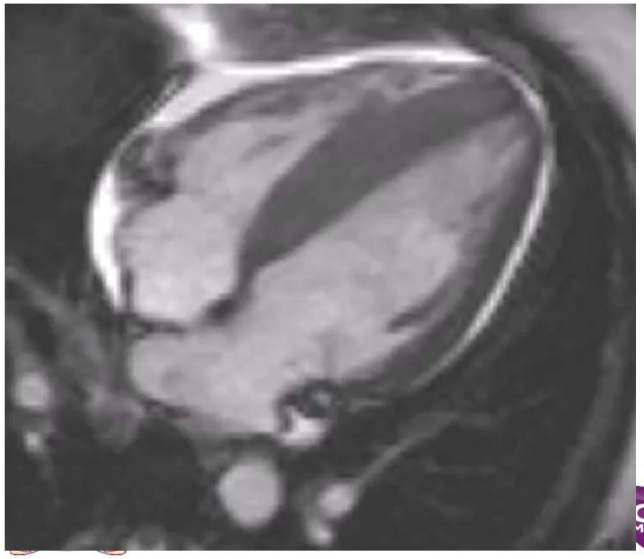
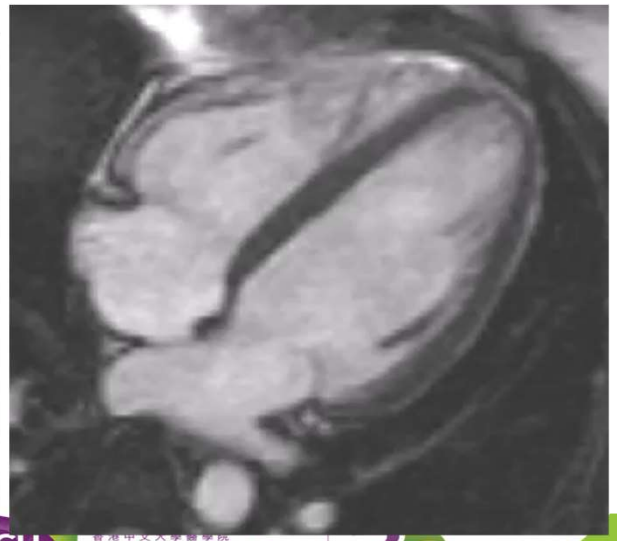
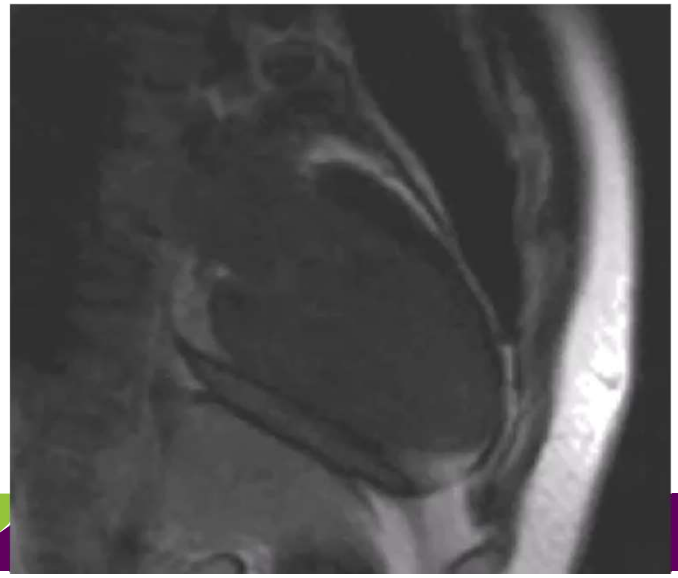
Figure 1. T_2-Weighted MR Imaging and Assessment of Global Myocardial Edema

(Left) T_2-weighted magnetic resonance (MR) images demonstrating global myocardial edema in a patient with acute myocarditis (short-axis slice). **(Right)** Computer-aided signal intensity (SI) analysis of the T_2-weighted images with color-coded display of relative SI normalized to skeletal muscle **(blue** indicates an SI ratio of myocardium/skeletal muscle >1.9, indicating edema; **green/yellow** indicates normal ≤1.9). The **yellow** contour marks the region of interest for SI assessment of the skeletal muscle.

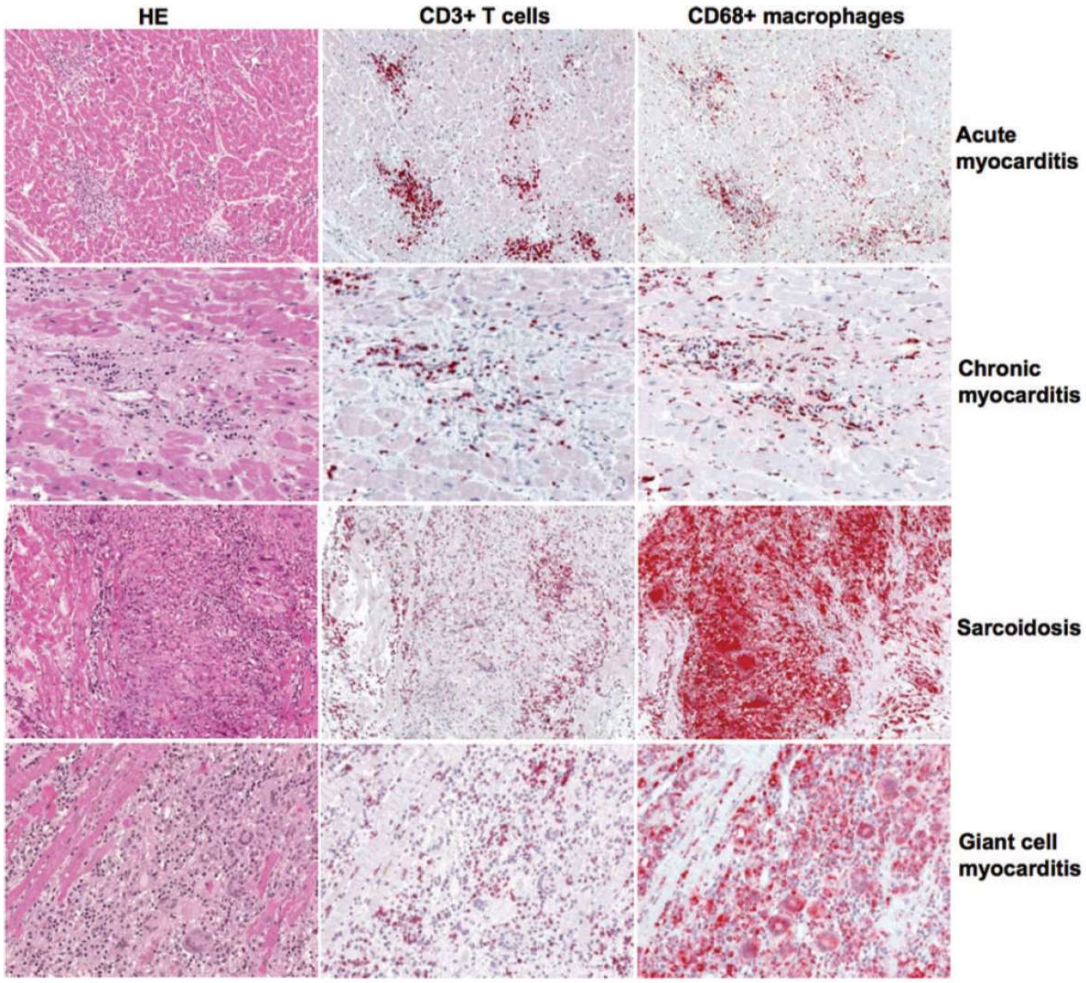




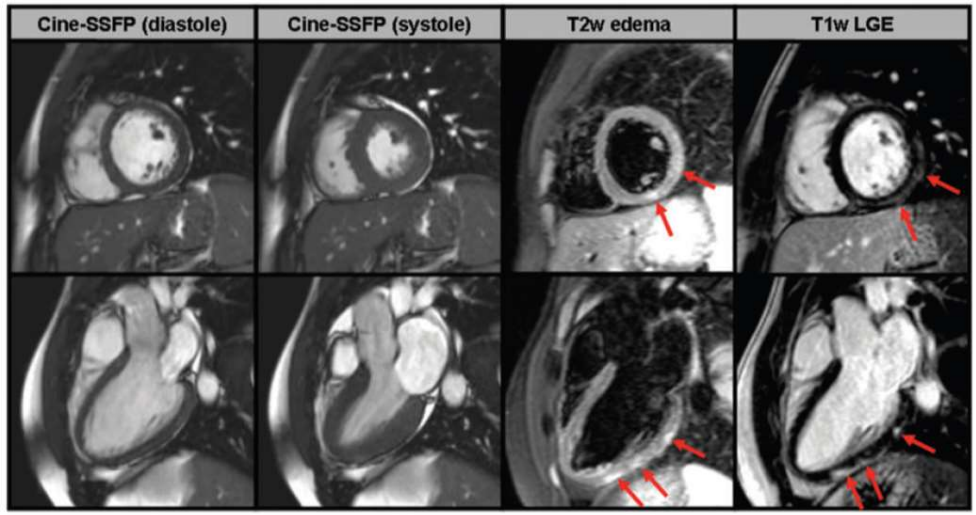
Endomyocardial biopsy (EMB)

- For patients with unexplained fulminant HF
  - new onset HF of less than two weeks duration associated with hemodynamic compromise
- Unexplained new onset HF of two weeks to three months duration associated with a dilated LV and new ventricular arrhythmias, Mobitz type II second-degree AV block, third-degree AV block, or failure to respond to usual care within one to two weeks.

Scenario number	Clinical scenario	Class of recommendation (I, IIa, IIb, III)	Level of evidence (A,B,C)
1	New onset heart failure of **less than 2 weeks** duration associated with a normal size or dilated left ventricle and hemodynamic compromise	I	B
2	New onset heart failure of **2 weeks to 3 months** duration associated **with** a dilated left ventricle, and new ventricular arrhythmias, second or third degree heart block, or failure to respond to usual care within 1 to 2 weeks	I	B
3	Heart failure of **greater than 3 months** duration associated **with** a dilated left ventricle and new ventricular arrhythmias, second or third degree heart block, or failure to respond to usual care within 1 to 2 weeks	IIa	C
4	Heart failure associated with a dilated cardiomyopathy of any duration associated with suspected allergic reaction and/or eosinophilia	IIa	C

The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Circulation 2007; 116:2216.





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Prognosis of myocarditis

The NEW ENGLAND JOURNAL of MEDICINE

Underlying Causes and Long-Term Survival in Patients with Initially Unexplained Cardiomyopathy

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BACKGROUND

Previous studies of the prognosis of patients with heart failure due to cardiomyopathy categorized patients according to whether they had ischemic or nonischemic disease. The prognostic value of identifying more specific underlying causes of cardiomyopathy is unknown.

METHODS

We evaluated the outcomes of 1230 patients with cardiomyopathy. The patients were grouped into the following categories according to underlying cause: idiopathic cardiomyopathy (616 patients); peripartum cardiomyopathy (51); and cardiomyopathy due to myocarditis (111), ischemic heart disease (91), infiltrative myocardial disease (59), hypertension (49), human immunodeficiency virus (HIV) infection (45), connective-tissue disease (39), substance abuse (37), therapy with doxorubicin (15), and other causes (117). Cox proportional-hazards analysis was used to assess the association between the underlying cause of cardiomyopathy and survival.

TABLE 3. ASSOCIATION BETWEEN CLINICAL VARIABLES AND SURVIVAL.*

VARIABLE	UNADJUSTED ANALYSIS		MULTIVARIATE ANALYSIS	
	HAZARD RATIO FOR DEATH (95% CI)	P VALUE	HAZARD RATIO FOR DEATH (95% CI)	P VALUE
Cause				
Idiopathic cardiomyopathy†	1.00		1.00	
Peripartum cardiomyopathy	0.14 (0.05–0.44)	0.001	0.31 (0.09–0.98)	0.05
Cardiomyopathy due to hypertension	0.69 (0.35–1.35)	0.28	0.74 (0.36–1.52)	0.42
Cardiomyopathy due to myocarditis	0.74 (0.49–1.10)	0.13	1.05 (0.67–1.61)	0.82
Cardiomyopathy due to other causes	1.21 (0.85–1.72)	0.28	1.30 (0.89–1.91)	0.18
Cardiomyopathy due to connective-tissue disease	1.44 (0.85–2.43)	0.18	1.75 (1.02–3.01)	0.04
Cardiomyopathy due to substance abuse	1.45 (0.88–2.38)	0.15	1.41 (0.79–2.53)	0.25
Cardiomyopathy due to ischemic heart disease	2.01 (1.46–2.77)	<0.001	1.52 (1.07–2.17)	0.02
Cardiomyopathy due to doxorubicin therapy	2.64 (1.35–5.17)	0.005	3.46 (1.67–7.18)	0.001
Cardiomyopathy due to HIV infection	4.00 (2.80–5.74)	<0.001	5.86 (3.92–8.77)	<0.001
Cardiomyopathy due to infiltrative myocardial disease	4.79 (3.36–6.81)	<0.001	4.40 (3.04–6.39)	<0.001

General approach to myocarditis

- NSAID should be avoided, given the risk of HF exacerbation and possible risk of increase mortality
- Alcohol consumption should be restricted
  - since heavy alcohol intake may enhance the severity of the myocarditis
- Exercise should be restricted during the acute phase of myocarditis
  - three to six months abstinence from competitive sports after myocarditis.

Clinical and Demographic Predictors of Outcomes in Recent Onset Dilated Cardiomyopathy

Results of the IMAC (Intervention in Myocarditis and Acute Cardiomyopathy)-2 Study

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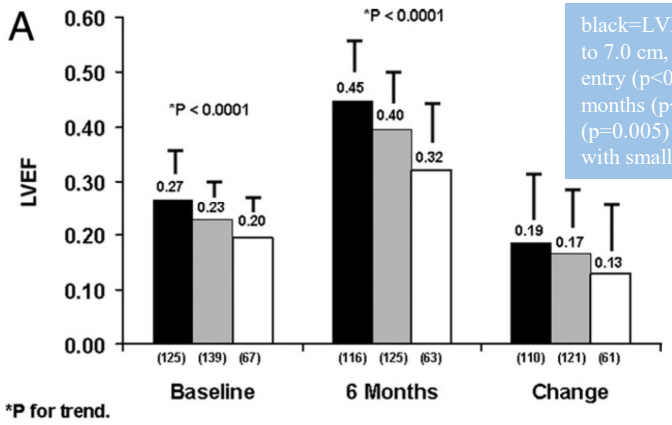
Pittsburgh, Hershey, and Philadelphia, Pennsylvania; Cleveland, Ohio; Rochester, Minnesota; Tampa, Florida; and Boston, Massachusetts

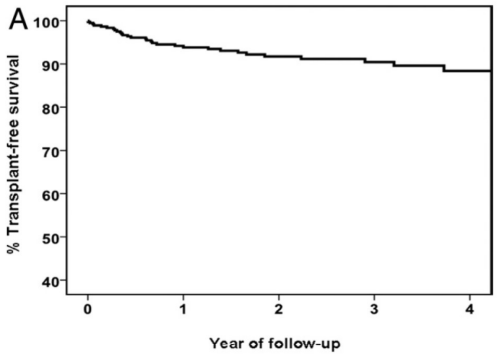


black=LVEDD<6.0cm, gray 6.0 to 7.0 cm, white>7.0 cm, LVEF entry (p<0.0001), LVEF six months (p<0.0001), LV change (p=0.005) all significantly greater with smaller LVEDD.

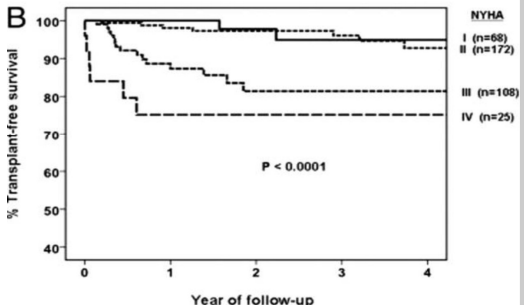
Methods In the multicenter IMAC (Intervention in Myocarditis and Acute Cardiomyopathy)-2 study, subjects with a left ventricular ejection fraction (LVEF) of ≤0.40, fewer than 6 months of symptom duration, and an evaluation consistent with idiopathic dilated cardiomyopathy or myocarditis were enrolled. LVEF was reassessed at 6 months, and subjects were followed up for 4 years. LVEF and event-free survival were compared by race, sex, and clinical phenotype.

Results The cohort of 373 persons was 38% female and 21% black, with a mean age of 45 ± 14 years. At entry, 91% were receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and 82% were receiving beta-blockers, which increased to 92% and 94% at 6 months. LVEF was 0.24 ± 0.08 at entry and 0.40 ± 0.12 at 6 months (mean increase: 17 ± 13 ejection fraction units). Transplant-free survival at 1, 2, and 4 years was 94%, 92%, and 88%, respectively; survival free of heart failure hospitalization was 88%, 82%, and 78%, respectively. In analyses adjusted for sex, baseline LVEF, and blood pressure, LVEF at 6 months was significantly lower in blacks than in nonblacks ($p = 0.02$). Left ventricular end-diastolic diameter at presentation was the strongest predictor of LVEF at 6 months ($p < 0.0001$).

Conclusions Outcomes in ROCM are favorable but differ by race. Left ventricular end-diastolic diameter by transthoracic echo at presentation was most predictive of subsequent myocardial recovery. (Genetic Modulation of Left Ventricular Recovery in Recent Onset Cardiomyopathy; NCT00575211) (J Am Coll Cardiol 2011;58:1112–8) © 2011 by the American College of Cardiology Foundation



Year of follow-up



Immunosuppressive therapy

- Immunosuppressive therapy is suggested for specific autoreactive disorders
  - Giant cell myocarditis (GCM)
  - Sarcoidosis
  - Noninfectious eosinophilic myocarditis
  - Extra-cardiac autoimmune disease (eg, lupus myocarditis).
  - Biopsy-proven, virus-negative lymphocytic myocarditis refractory to standard heart failure (HF) therapy

- A systematic review of 8 RCTs: glucocorticoid therapy did not reduce mortality or improve functional status in patients with viral myocarditis

Immunosuppressive therapy

- No benefit from immunosuppressive therapy was found in acute myocarditis of unspecified etiology. In RCT of Myocarditis Treatment Trial, 111 patients with a histopathologic diagnosis of myocarditis of unspecified etiology with LVEF<45% were randomly assigned to receive conventional therapy alone or immunosuppression with either cyclosporine or azathioprine for 28 weeks
  - In all patients, the LVEF improved from 25 to 34% and the mortality rate was 20% at one year and 56% at 4.3 years. There was no difference in outcome in the two treatment groups.

- The Tailored Immunosuppression in Inflammatory Cardiomyopathy [TIMIC] study) compared outcomes with immunosuppressive treatment (glucocorticoid plus azathioprine) as compared with placebo in a chronic stable DCM population.
  - Of 512 patients with LVEF ≤45 percent who were screened with EMB, 85 subjects without viral genomes by PCR were assigned to either azathioprine and prednisone or placebo for six months. The immunohistologic criteria were the presence of >14 CD45 or >2 CD3 positive T cells per high power field. The presence of circulating anti-heart antibodies was not required for enrollment. The LVEF improved by >10 percent in 38 of 43 patients treated with immunosuppression, compared with none of the patients treated with placebo. The placebo-treated patients' mean LVEF declined from 27.8 percent to 19.7 percent after six months. Clinical improvement in the immunosuppression treated subjects was reflected in significantly lower average New York Heart Association functional class (table 1) at six months.

Intravenous immunoglobulin (IVIG)

- Intravenous immune globulin (IVIG) has antiviral and immunomodulatory effects, suggesting that it may play a role in the treatment of viral myocarditis but systematic review showed insufficient data to recommend routine IVIG therapy in patients with acute myocarditis

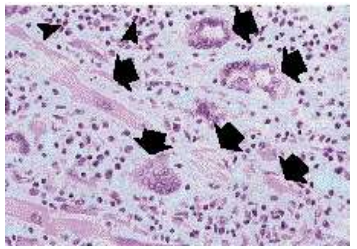
- RCT of IMAC trial with 62 patients with recent-onset (≤6 months of symptoms) DCM with LVEF ≤40% given either IVIG (1 g/kg per day for two days) or placebo. 17% of patients had "Dallas criteria" positive myocarditis.
  - At one year, both groups LVEF increased from 25% at baseline to 42% in follow up. Transplant-free survival at one and two years was 92 and 88%. Imp: IVIG does not augment the improvement in LVEF.

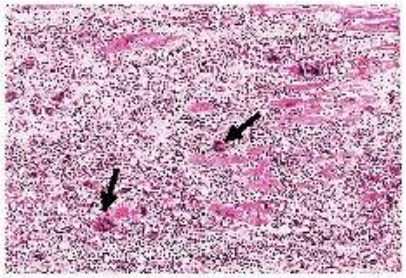
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idiopathic Giant-Cell Myocarditis — Natural History and Treatment

Leslie T. Cooper, Jr., M.D., Gerald J. Berry, M.D., and Ralph Shabetai, M.D. for the Multicenter Giant Cell Myocarditis Study Group Investigators*



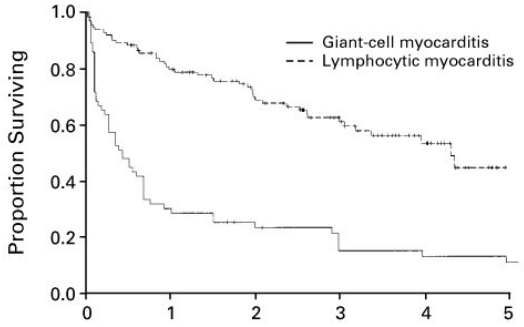


RESULTS

The patients consisted of 33 men and 30 women with an average age of 42.6 years; 88 percent were white, 5 percent were black, 5 percent were Southeast Asian or Indian, and 2 percent were Middle Eastern. Most presented with congestive heart failure (47 patients, or 75 percent), ventricular arrhythmia (9 patients, or 14 percent), or heart block (3 patients, or 5 percent), although in some cases the initial symptoms resembled those of acute myocardial infarction (4 patients). Nineteen percent had associated autoimmune disorders. The rate of survival was worse than among 111 patients with lymphocytic myocarditis in the Myocarditis Treatment Trial ($P<0.001$); among our patients, the rate of death or cardiac transplantation was 89 percent, and median survival was only 5.5 months from the onset of symptoms. The 22 patients treated with corticosteroids and cyclosporine, azathioprine, or both therapies survived for an average of 12.3 months, as compared with an average of 3.0 months for the 30 patients who received no immunosuppressive therapy ($P = 0.001$). Of the 34 patients who underwent heart transplantation, 9 (26 percent) had a giant-cell infiltrate in the transplanted heart and 1 died of recurrent giant-cell myocarditis.

CONCLUSIONS

Giant-cell myocarditis is a disease of relatively young, predominantly healthy adults. Patients usually die of heart failure and ventricular arrhythmia unless cardiac transplantation is performed. Despite the possibility of fatal disease recurrence, transplantation is the treatment of choice for most patients.



A

Patient Group	No. of Patients	Median Survival from Symptom Onset (mo)	P Value*
No immunosuppression	30	3.0	—
Corticosteroids alone	11	3.8	0.68
Corticosteroids plus azathioprine	11	11.5	0.025
Cyclosporine combination therapy†	10	12.6	0.003
All treatment groups except corticosteroids alone	22‡	12.3	0.001
All treatment groups including corticosteroids alone	33	8.2	0.014

*P values are for the comparison of median survival with that in the group that received no immunosuppressive therapy, by the log-rank test.

†Cyclosporine was combined with corticosteroids (three patients), with corticosteroids and azathioprine (five patients), or with corticosteroids, azathioprine, and muromonab-CD3 (OKT3, two patients).

Conclusion

- Inflammatory cardiomyopathy is defined as myocarditis accompanied by cardiac dysfunction. Myocarditis is an inflammatory disease of cardiac muscle that is caused by a variety of infectious and noninfectious conditions
  - Manifest similar to ACS, heart failure, cardiogenic shock or acute arrhythmia
- Cardiovascular imaging: Echo and especially CMR play an important role in diagnosis, EMB is still the gold standard which allows precise immunohistological dx (Dallas criteria)
- Immunosuppressive agents is suggested in specific autoreactive disorders e.g. giant cell myocarditis, lupus myocarditis