Circulation: Heart Failure

ADVANCES IN HEART FAILURE

Management of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy

An Expert Consensus Document

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ABSTRACT: Myocarditis is an inflammatory disease of the heart that may occur because of infections, immune system activation, or exposure to drugs. The diagnosis of myocarditis has changed due to the introduction of cardiac magnetic resonance imaging. We present an expert consensus document aimed to summarize the common terminology related to myocarditis meanwhile highlighting some areas of controversies and uncertainties and the unmet clinical needs. In fact, controversies persist regarding mechanisms that determine the transition from the initial trigger to myocardial inflammation and from acute myocardial damage to chronic ventricular dysfunction. It is still uncertain which viruses (besides enteroviruses) cause direct tissue damage, act as triggers for immune-mediated damage, or both. Regarding terminology, myocarditis can be characterized according to etiology, phase, and severity of the disease, predominant symptoms, and pathological findings. Clinically, acute myocarditis (AM) implies a short time elapsed from the onset of symptoms and diagnosis (generally <1 month). In contrast, chronic inflammatory cardiomyopathy indicates myocardial inflammation with established dilated cardiomyopathy or hypokinetic nondilated phenotype, which in the advanced stages evolves into fibrosis without detectable inflammation. Suggested diagnostic and treatment recommendations for AM and chronic inflammatory cardiomyopathy are mainly based on expert opinion given the lack of well-designed contemporary clinical studies in the field. We will provide a shared and practical approach to patient diagnosis and management, underlying differences between the European and US scientific statements on this topic. We explain the role of histology that defines subtypes of myocarditis and its prognostic and therapeutic implications.

Key Words: cardiac magnetic resonance imaging ■ endomyocardial biopsy ■ inflammatory cardiomyopathy ■ myocarditis ■ viruses

DEFINITIONS, EPIDEMIOLOGY, AND PATHOPHYSIOLOGY

Myocarditis is an inflammatory disease of the heart that may occur as a consequence of infections, exposure to toxic substances, and immune system activation[1,2] and is included among secondary cardiomyopathies in the 1996 World Health Organization classification.[3] Myocarditis has a wide spectrum of clinical presentations and trajectories, with most cases resolving spontaneously. It is also a relatively common cause of sudden cardiac death (SCD) in young people (from 6% to 10% in autopsy-based series; Table I in the Data Supplement).[4,5,119–121] Furthermore, in some patients, inflammation may cause extensive scarring that triggers left ventricular (LV) remodeling, leading eventually to dilated cardiomyopathy (DCM)[6] or alternatively to

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Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
AM	acute myocarditis
CMRI	cardiac magnetic resonance imaging
CS	cardiac sarcoidosis
CTLA-4	cytotoxic T-lymphocyte antigen-4
DCM	dilated cardiomyopathy
EGPA	eosinophilic granulomatosis with polyangiitis
EM	eosinophilic myocarditis
EMB	endomyocardial biopsy
FM	fulminant myocarditis
GCM	giant cell myocarditis
HES	hypereosinophilic syndrome
HF	heart failure
HTx	heart transplantation
ICD	implantable cardiac defibrillator
ICI	immune checkpoint inhibitor
infl-CMP	inflammatory cardiomyopathy
LGE	late gadolinium enhancement
LV	left ventricle
LVEF	left ventricular ejection fraction
MCS	mechanical circulatory support
MTT	Myocarditis Treatment Trial
PD-1	programmed death receptor-1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PVB19	parvovirus-B19
SCD	sudden cardiac death

a predominant hypokinetic nondilated phenotype of cardiomyopathy. Myocarditis can be characterized according to etiology, phase, and severity of the disease, predominant symptoms, and pathological findings. Clinically, acute myocarditis (AM) implies a short time elapsed from the onset of symptoms and diagnosis (generally <1 month), while chronic inflammatory cardiomyopathy (infl-CMP) indicates myocardial inflammation with established DCM or hypokinetic nondilated phenotype generally with a longer duration of symptoms (>1 month; Figure 1). Based on the cell types infiltrating, myocarditis can be classified as eosinophilic, lymphocytic, giant cells, or granulomatous (Figure 2). Chronic myocarditis could represent an intermediate stage between AM and chronic infl-CMP in patients with persisting myocardial inflammation (Figure I in the Data Supplement). Due to evolving diagnostic criteria and differences in the conceptual view and interpretation of myocarditis within the medical community, definitions associated with myocarditis have changed over the last decades. A list of definitions used in this document is presented in Table 1.

The disease burden of myocarditis is difficult to define. Based on hospital discharge forms between 1990 and 2013, an incidence of 22 cases of 100 000 patients annually was estimated by the Global Burden of Disease Study.[10] However, this report did not distinguish between AM or chronic infl-CMP and other cardiomyopathies, with possible overestimation of myocarditis. Among patients presenting to the emergency department, AM was the second most common cardiac cause of chest pain (3%) in a French registry.[11] Furthermore, ≈33% of the patients initially labeled as myocardial infarction with nonobstructed coronary arteries are later diagnosed as AM.[12] According to contemporary registries, AM is a cardiac condition affecting relatively young patients (median age of onset ranges between 30 and 45 years in most of the series) and men more than women (male prevalence ranges between 60% and 80%; Table 2).[13–20] The absolute prevalence and relative proportion of different etiologies may vary over time and according to endemic diseases. For example, immune checkpoint inhibitor (ICI)–associated myocarditis is a recently recognized entity, whose rate of diagnosis has increased due to larger awareness and to the larger population of patients with cancer eligible for treatment with ICI.[21] On the other hand, AM and chronic infl-CMP may have a different incidence in specific geographic areas according to local epidemiology (such as Chagas disease in South America). Controversies still exist regarding the mechanisms that determine the transition from the initial trigger to myocardial inflammation and from acute myocardial injury to chronic dysfunction. To date, it is not known which viruses other than enteroviruses may cause direct tissue damage in humans or act mainly as triggers for autoimmunity-mediated damage or both.[22,23] It must be considered that the experimental evidences on murine models of viral myocarditis are based on infections with Coxsackie B viruses, whereas for the most common agent in virus-positive myocarditis patients, parvovirus-B19 (PVB19),[24,25] no animal models are available. A possible association between genetic abnormalities and susceptibility to inflammation has been suggested. In particular, patients with mutations responsible for arrhythmogenic cardiomyopathy may be at risk for AM and share clinical and pathological aspects with chronic infl-CMP,[26,27] although further studies are required to elucidate this association and understand its mechanistic underpinnings.

This review will try to summarize a shared and practical approach to patients presenting with AM or chronic infl-CMP, meanwhile pointing out the areas of controversies and uncertainties and the unmet clinical needs. Specific conditions such as pediatric myocarditis, including rheumatic carditis, Chagas disease, and HIV cardiomyopathy deserve separate discussion and are not addressed in this document.

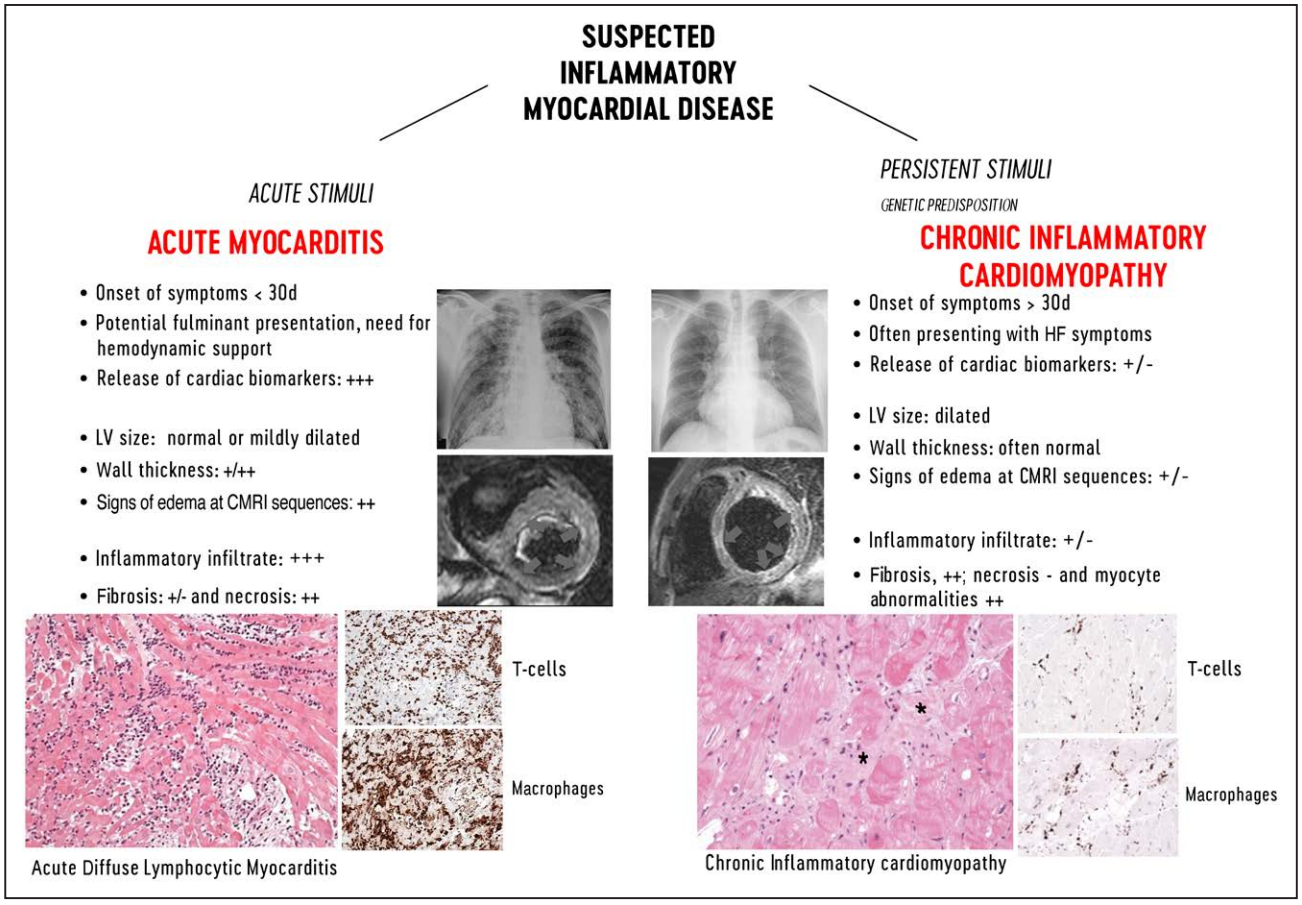

Figure 1. Characteristic features of lymphocytic acute myocarditis and chronic inflammatory cardiomyopathy. **Left**, Imaging features of acute myocarditis: chest radiograph of a patient admitted for chest pain and suspected acute myocarditis with no enlargement of the cardiac silhouette and cardiac magnetic resonance imaging (CMRI) showing normal left ventricular (LV) volume and significantly increased cardiac mass with diffuse high signal in T2-weighted images (arrows) suggesting diffuse edema. Histology shows acute lymphocytic myocarditis with myocyte necrosis and diffuse mononuclear cell infiltrates by hematoxylin-eosin and immunohistological stain on CD3+ T cells and CD68+ macrophages, compatible with an active myocarditis based on Dallas criteria (magnitude ×200). **Right**, Imaging features of chronic lymphocytic cardiomyopathy: chest radiograph of a patient admitted with heart failure (HF) symptoms, showing enlargement of cardiac silhouette; at CMRI, the LV is dilated, with normal thickness and focal areas of high signal intensity at T2-weighted images suggesting localized edema (arrows). At histology, chronic inflammatory cardiomyopathy typically presents fibrosis (*) within areas with inflammatory cellular infiltrates and myocyte abnormalities (magnitude ×200). CD indicates cluster of differentiation.

DIAGNOSTIC APPROACH TO AM AND INFL-CMP

AM: Symptoms and Signs

Patients with suspected AM are generally evaluated in the emergency room due to chest pain, dyspnea, fatigue, palpitations, or syncope.[1] Based on large registries, chest pain is the most frequent symptom (85%–95% of cases),[13–16,18] followed by dyspnea (19%–49% of cases),[13,16,17] whereas syncope occurs in about 6%.[13] Fever is common (about 65%),[13,15] while other prodromal manifestations, such as flu-like symptoms, gastrointestinal disorders, sore throat, or respiratory tract infections, may have preceded the acute phase by a few days or weeks, with a prevalence ranging from 18% to 80%.[13,14,18]

In a recent retrospective registry of 443 AMs, 26.6% had a presentation complicated by LV systolic dysfunction, ventricular arrhythmias, or cardiogenic shock (ie, fulminant myocarditis [FM] that accounted for 8.6% of total cases). On the other hand, the majority of AMs (73.4%) had no such complications (uncomplicated AM) and presented chest pain in 97% of cases and ST-segment elevation on ECG in 62.3% of cases, and they had no deaths or heart transplantation (HTx) at 5 years.[13] When collecting patient history, attention should focus on specific causes including recent exposure to drugs (eg, antibiotics, clozapine, ICI) or toxic substances (eg, cocaine or amphetamine)[2] or to infectious agents (eg, ingestion of raw meat suggesting helminthic infections,[39] travels to areas where viruses associated with AM, such as Dengue, are endemic). A proposed approach to AM is summarized in Figure 3.

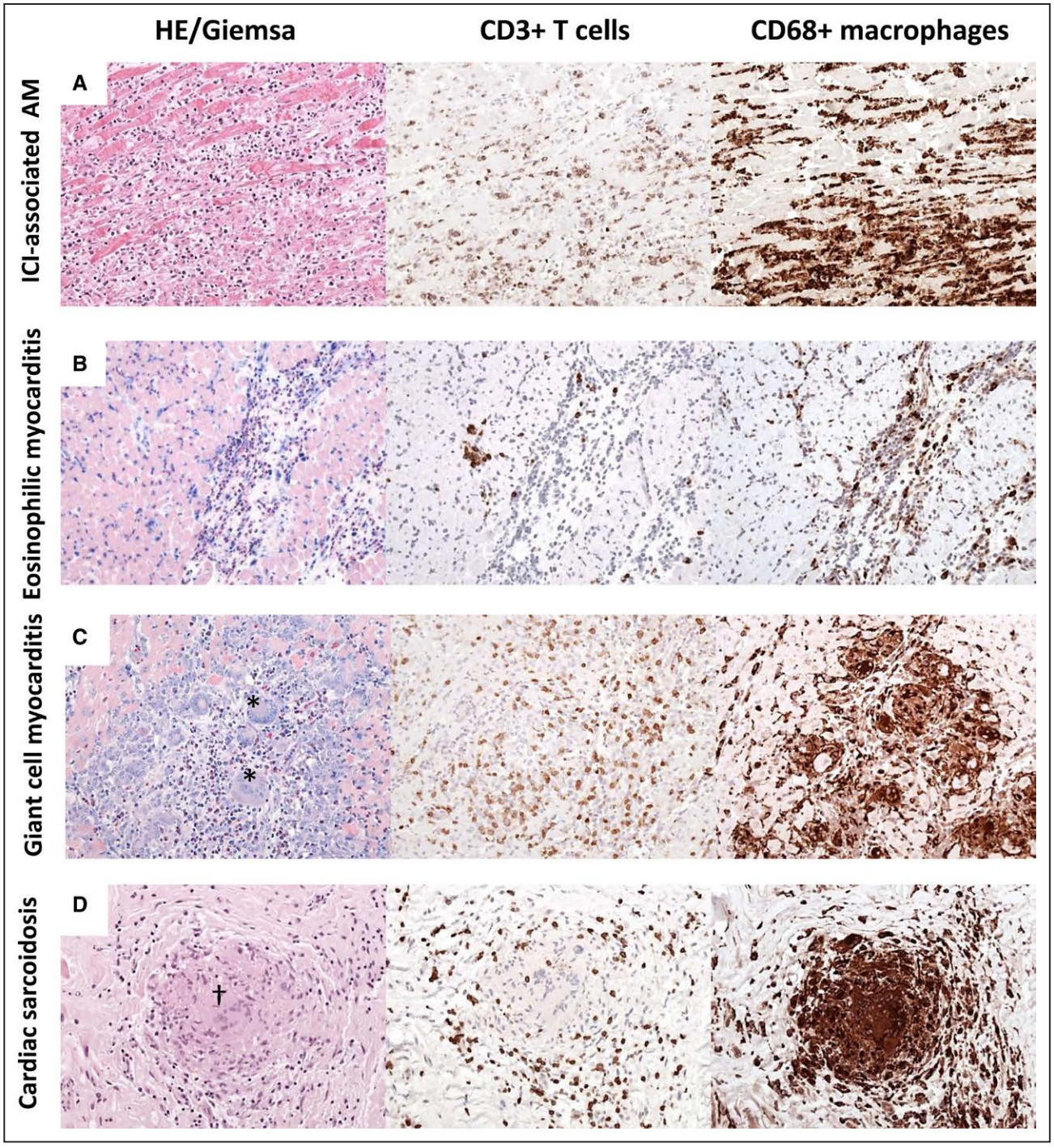

Figure 2. Different patterns of myocardial inflammation demonstrated by histological and immunohistological stainings on endomyocardial biopsy.

A, Immune checkpoint inhibitor (ICI)–associated acute myocarditis (AM) frequently reveals diffuse mononuclear infiltrates composed of CD3+ T cells and CD68+ macrophages. Based on hematoxylin-eosin (HE) and immunohistological stainings, ICI-associated myocarditis resembles a diffuse lymphocytic myocarditis. **B**, In eosinophilic myocarditis, prominent inflammatory cells are eosinophilic granulocytes (Giemsa) and macrophages. **C**, Giant cell myocarditis is characterized by large mononucleated infiltrates with the presence of giant cells (*) and eosinophils (Giemsa). **D**, Cardiac sarcoidosis can be differentiated from giant cell myocarditis by the presence of granuloma (†) and absence of necrotic myocytes (magnitude, ×200 in all pictures). CD indicates cluster of differentiation.

AM: ECG

The ECG is abnormal in about 85% of cases,[13,15] ST-segment elevation mimicking acute myocardial infarctions is the most frequent abnormality[13,15]; inferior and lateral leads are commonly involved. QRS width >120 ms, atrioventricular block, symptomatic bradycardia, or tachycardia and ventricular arrhythmias should increase the suspicion of AM and suggest high-risk forms.[38]

Table 1. Glossary of the Terms Used in this Document Regarding Myocarditis

Terms	Domain(s)				Definition
	Clinical Presentation	Time	Etiology, Pathophysiology	Pathology	
Active myocarditis*				X	On the basis of Dallas criteria, active myocarditis (versus borderline myocarditis or no myocarditis) indicates the presence of infiltrating inflammatory mononucleated cells and myocyte necrosis, with or without fibrosis, at routine light microscopy evaluation of EMB.[7]
Acute myocarditis*	X	X			Myocarditis with symptoms of recent onset (on average within ≈1 mo), generally with increased levels of high-sensitivity troponins, and evidence of edema on CMRI if performed within 4 wk or alternatively positive cardiac FDG-PET imaging (not suggested as routine diagnostic tool). Histologically is characterized by an active myocarditis. We propose the term acute presentation when medical attention occurs within 1 mo from the symptom onset compared with the previous 3-mo interval reported in ESC and AHA scientific statements. The term subacute myocarditis could be used to describe the interval between 1- and 3-mo interval from the symptom onset.
Borderline myocarditis†				X	On the basis of Dallas criteria, borderline myocarditis (versus active myocarditis or no myocarditis) indicates the presence of inflammatory mononucleated cell infiltrate, in the absence of myocytolysis, at routine light microscopy evaluation of EMB.[7] This term has been abandoned due to ambiguity and poor consistency among pathologists.
Clinically suspected myocarditis	X	X			Proposed definition in the ESC position statement[2] is the presence of (1) ≥1 clinical presentation (acute chest pain or new-onset dyspnea [days up to 3 mo] or in subacute/chronic dyspnea [>3 mo] or palpitations/ unexplained arrhythmia symptoms or unexplained cardiogenic shock) and (2) ≥1 diagnostic criteria from different categories (electrocardiographic features of cardiac injury, elevated markers of myocardial necrosis, functional/structural abnormalities on echocardiogram/angiogram or CMRI, tissue characterization by CMRI), in the absence of (a) angiographically detectable coronary artery disease (coronary stenosis, ≥50%) and (b) known preexisting cardiovascular disease or extracardiac causes that could explain the syndrome (eg, valve disease, congenital heart disease, hyperthyroidism). Suspicion is higher with higher number of fulfilled criteria. If the patient is asymptomatic, ≥2 diagnostic criteria should be met. The limitation of this overarching definition is that, for example, dyspnea associated to mild increase of troponin plus evidence of new evidence of electrocardiographic or echocardiographic changes can be enough for the suspect of myocarditis. Findings based on CMRI are probably more accurate than other diagnostic findings, even if it does not emerge from this definition.
Chronic inflammatory cardiomyopathy*	X	X		X	Indicates a persistent/chronic myocardial inflammatory condition (symptom onset >1 mo) with clinical phenotype of hypokinetic either dilated or non-DCM that can be associated with arrhythmogenic substrate. Histologically, it is generally characterized by myocyte abnormalities (eg, variations of myocyte diameter), focal or diffuse fibrosis with inflammatory infiltrates.
Chronic myocarditis*	X	X		X	Defines an ongoing inflammatory process with fibrosis but without myocyte necrosis or myocyte abnormalities. Chronic myocarditis could represent an intermediate stage between acute myocarditis and chronic infl-CMP in patients with persisting myocardial inflammation. This phenotype can be observed in nondilated or mild dilated arrhythmogenic cardiomyopathy or in the setting of an autoimmune disease or syndrome. There is some overlapping with the term subacute myocarditis.
Complicated acute myocarditis*	X				A working term aimed to identify high-risk patients, that is, those presenting with ≥1 of the following: LV dysfunction (LVEF <50% on first echocardiogram), sustained ventricular arrhythmias, advanced heart block, HF, low cardiac output syndrome, cardiogenic shock. Uncomplicated myocarditis defines a myocarditis without the above manifestations.
Drug-induced myocarditis*			X		Myocarditis caused by direct cytotoxic effect of the drug (ie, cocaine).
Eosinophilic myocarditis*				X	Myocarditis characterized by eosinophilic infiltrate at EMB. Peripheral eosinophilia at differential WBC count is suggestive, but it is not always present.

(*Continued*)

Table 1. Continued

Terms	Domain(s)				Definition
	Clinical Presentation	Time	Etiology, Pathophysiology	Pathology	
Fulminant myocarditis*	X	X		X	A working term indicating severe forms of acute myocarditis, with fast evolution and hemodynamic compromise (low-output syndrome or cardiogenic shock) requiring inotropes or MCS.[8] It is a form of acute myocarditis complicated by cardiogenic shock. When performed, EMB often (but not always) shows diffuse inflammatory infiltrates.
Giant cell myocarditis*				X	Myocarditis characterized by large multinuclear cells infiltrating the heart on histology (see text for details) in the absence of well-formed granuloma. It is usually associated with heart dysfunction and is often clinically fulminant.
Healing myocarditis†				X	A subacute myocarditis can be also defined as a healing myocarditis if there is evidence of a previous active myocarditis. In case of follow-up biopsies, the term healing myocarditis defines a partial resolution of a previous active myocarditis. It can be used as synonymous of subacute myocarditis.
Hypersensitivity myocarditis (or allergic myocarditis)*			X		Indicates that myocardial damage is caused by an abnormal reaction or overreaction with drugs (ie, clozapine) acting as stimuli/triggers. When performed, EMB demonstrates eosinophilic infiltrates. It is also called allergic myocarditis.
Immune checkpoint–associated myocarditis*			X		It is a specific form of immune-mediated myocarditis associated with the use of immune checkpoint inhibitor anticancer drugs. They can be also termed immune checkpoint–induced myocarditis.
Immune-mediated myocarditis*			X		Myocarditis caused by immune mechanisms (autoimmunity in most of the cases, although heart transplant rejection represents an example of myocarditis mediated by alloimmunity).
Infarct-like myocarditis†	X				Myocarditis presenting with chest pain and diffuse ST-segment elevation on the ECG that represents about 45.8% of admitted cases of acute myocarditis based on a contemporary registry. The term is misleading since this presentation can be associated with both normal or reduced LVEF, thus without a real prognostic utility. In fact, contrasting results are reported about the outcome of patients with infarct-like myocarditis. Instead, the term uncomplicated myocarditis is preferred to refer to patients with acute myocarditis presenting with chest pain and normal LVEF.
Infective myocarditis†			X		It refers to myocarditis definitely caused by infection targeting the heart and should be limited to viruses, protozoans, and bacteria that cause direct pathogen-mediated injury. Although the list of potential agents is long, a few of such cases are currently observed in immunocompetent subjects in Western countries or in infants (eg, enterovirus). The term can be misleading to define all types of virus-induced myocarditis or all virus-positive myocarditis/infl-CMP.
Lymphocytic myocarditis*				X	Myocarditis characterized by small mononuclear cells (CD3+ T lymphocytes) infiltrating the heart. It is the most frequent histological pattern and may or may not be associated with heart dysfunction. It is the histological subtype more often associated with virus-induced myocarditis and immune checkpoint–associated myocarditis.
Myopericarditis†	X				Inflammatory process of the heart involving both the pericardium and the myocardium, without systolic dysfunction. This term and perimyocarditis (see below) are frequently used as synonyms, although myocarditis with evidence of pericardial involvement would be preferable in both cases.
Myocarditis with pericardial involvement*	X				Inflammatory process of the heart involving both the pericardium and the myocardium, with or without systolic dysfunction. This term focuses the attention on the myocardium, as pericardium is often involved due to continuity; thus it is preferable to the terms of perimyocarditis/myopericarditis.
Perimyocarditis†	X				Inflammatory process of the heart involving both the pericardium and the myocardium, with evidence of systolic dysfunction (see above).
Postviral myocarditis†	X	X	X		Myocarditis that occurs shortly after an episode of possible/proven viral infection (eg, common cold, flu-like syndrome; see also Viral Myocarditis). It is often used in patients with prodromal symptoms without isolation of a specific virus.

(*Continued*)

Table 1. Continued

Terms	Domain(s)				Definition
	Clinical Presentation	Time	Etiology, Pathophysiology	Pathology	
Probable acute myocarditis*	X	X			A clinical syndrome, including HF of <3 mo duration, associated with an otherwise unexplained elevation in troponin or electrocardiographic features of cardiac injury. New wall motion abnormalities, a pericardial effusion on echocardiography, or characteristic tissue features on CMRI strengthen the diagnosis. This definition has been proposed by the AHA Scientific Statement on specific DCM.[9] The term is similar, to clinically suspected myocarditis proposed by the ESC position statement,[2] even if it appears too generic. Furthermore, proposed AM term is limited to acute forms compared with clinically suspected myocarditis that includes also chronic forms. The term probable acute myocarditis has a proposed time frame of 3 mo for acuity compared with the current proposal of 1 mo for acute myocarditis in this document.
Sarcoidotic myocarditis*			X	X	Patients presenting with an acute myocarditis associated with known or new systemic sarcoidosis. It can also be the clinical presentation of an isolated cardiac sarcoidosis. Sarcoidotic myocarditis is characterized by infiltration by activated macrophages, which in some cases can lead to chronic inflammation and fibrotic replacement with non-necrotizing granulomas.
Subacute myocarditis†	X	X		X	Persistent/ongoing myocardial damage due to persistent or recurrent stimulus for inflammation. There is some overlapping with chronic myocarditis, since time threshold has not been defined. A subacute myocarditis can be also defined as a healing myocarditis if there is evidence of a previous active myocarditis. The term can be also used to describe a myocarditis with symptom onset between 1- and 3-mo interval before diagnosis.
Viral myocarditis†	X				Myocarditis that occurs during the course of an episode of possible/proven viral infection or in patients with prodromal symptoms (eg, common cold, flu-like syndrome); it is often used as synonymous of postviral myocarditis in clinical practice.
Virus-induced myocarditis*			X	X	Myocarditis that is definitely or probably related to a viral infection. This term should be preferred over infective or viral myocarditis when referring to both virus-mediated and virus-triggered myocarditis (see below).
Virus-mediated myocarditis*			X	X	Myocarditis that is related to a viral infection via direct viral cytotoxicity at myocardial level (eg, coxsackie virus myocarditis). Demonstration of the virus in the myocardium is required.
Virus-positive (vs virus negative) myocarditis/chronic infl-CMP*				X	Biopsy-proven (more often lymphocytic) myocarditis or infl-CMP, with demonstration of the presence of viral genome in the myocardium by means of real-time PCR.[2] Note that type of viruses, number of viral genome copies, and techniques for their identification and measurements are not standardized.
Virus-triggered myocarditis*			X	X	Immune-mediated lymphocytic myocarditis that is triggered by common viruses (such as influenza and coronaviruses) in the absence of viral genome in the myocardium. Viral PCR on pharyngeal swabs in these patients can support the association between viral exposure and the onset of acute myocarditis. This myocarditis could be also termed postviral or viral myocarditis.

AHA indicates American Heart Association; CMRI, cardiac magnetic resonance imaging; DCM, dilated cardiomyopathy; EMB, endomyocardial biopsy; ESC, European Society of Cardiology; FDG-PET, fluorodeoxyglucose positron emission tomography; HF, heart failure; infl-CMP, inflammatory cardiomyopathy; LV, left ventricle; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; PCR, polymerase chain reaction; and WBC, whole blood cell.

*Terms that are suggested.

†Terms not suggested or have been abandoned due to ambiguity.

Second- or third-degree atrioventricular block is rarely observed in patients with normal LV ejection fraction (LVEF) >50%, except in cardiac sarcoidosis (CS), Lyme carditis, as well as ICI-associated myocarditis.[40]

AM: Laboratory Tests

Recommended laboratory tests for identification of patients with suspected AM are myocardial necrosis biomarkers (high-sensitivity troponins, creatinine kinase-MB). Only a weak correlation exists between troponin release and the severity of cardiac dysfunction.[41] Other laboratory tests routinely requested include markers of inflammation such as C-reactive protein that is positive in 80% to 95% in recent series.[13,14] Erythrocyte sedimentation rate is also commonly increased, but it is generally not available in the emergency department. A persistently increased erythrocyte sedimentation rate can suggest

Table 2. Principal Studies That Evaluated the Long-Term Outcome of Adult Patients With Myocarditis Based on Histology or Cardiac Magnetic Resonance Imaging Findings or the Combination of Both Published Since 1995

First Author	Years	Type of Study and Country	n	Age, y; Male Sex, %	Time Since the Onset of Symptoms	Histology	CMRI	Viral Search in the Heart	LVEF, %, and LV Dimension at Admission	Outcome
Grogan et al[28]	1979–1988	Retrospective monocentric; US	27	47 y; 59%	Median symptom duration, 3.5 mo	All based on EMB (all positive Dallas criteria: borderline or lymphocytic histology).	None	None	LVEF: 38%; LV dimension: not reported.	At 5 y: survival, 56%.
Mason et al[29]	1986–1994	Randomized trial, multicenter (n=31); US (treated with immunosuppression; all with LVEF <45%)	64	43 y; 58%	43% with symptom duration <30 d; 57% with symptoms above 30 d	All based on EMB (61% with positive Dallas criteria; all lymphocytic histologies).	None	None	LVEF: 24%; LV dimension: EDD, 64 mm.	At 4.3 y: survival, 44%. Independent predictors: reduced LVEF, extent of CD2+ cells in the myocardium.
Mason et al[29]	1986–1994	Randomized trial, multicenter (n=31); US (control group; all with LVEF <45%)	47	41 y; 32%	51% with symptom duration <30 d; 49% with symptoms above 30 d	All based on EMB (67% with positive Dallas criteria; all lymphocytic histologies).	None	None	LVEF: 24%; LV dimension: EDD, 64 mm.	At 4.3 y: survival, 44%. Independent predictors: reduced LVEF, extent of CD2+ T cells in the myocardium.
McCarthy et al[30]	1984–1997	Retrospective, monocentric; US (only FM)	15	35 y; 73%	Symptom duration, <1 y	All, based on EMB (only lymphocytic histology).	None	None	LVEF: not reported; LV dimension: not reported.	Median follow-up, 5.3 y: survival free of HTx, 93%.
McMarthy et al[30]	1984–1997	Retrospective, monocentric; US (only acute non-FM)	132	43 y; 64%	Symptoms duration, <1 y	All based on EMB (only lymphocytic histology).	None	None	LVEF: not reported; LV dimension: not reported.	Median follow-up, 5.7 y: survival free of HTx, 45%.
Magnani et al[31]	1978–2003	Retrospective monocentric (on inotrope, 51%); US	112	47 y; 60%	Symptom duration not specified, retrospective analysis based on EMB.	All based on EMB performed at the discretion of each patient's attending physician (lymphocytic histology, 55%; granulomatous, 10%; GCM, 6%; eosinophilic histology, 6%; borderline, 22%).	None	None	LVEF: 37%; LV dimension: not reported.	At 5 y: survival free of HTx, 56%. Independent predictors PCWP >15 mm Hg, type of histology (lymphocytic/granulomatous/GCM versus others).
Caforio et al[32]	1992–2005	Not specified whether prospective, monocentric; Italy	174	36 y; 63%	Symptom duration between 0 and 6 mo	All based on EMB (positive Dallas criteria), including all histologies (ie, GCM).	None	Viral PCR in the myocardium for all cardiotropic viruses (most frequently reported Enterovirus, 12.5%, and adenovirus, 5%).	LVEF: 43%; LV dimension: LVEDVi, 83 mL/m^2.	At 2 y: estimated survival free of HTx, 87%. Independent predictors: sign and symptoms of LV and RV failure. Lost at follow-up: 14%.
Kindermann et al[33]	1994–2007	Prospective, monocentric (excluded patients presenting with cardiogenic shock); Germany	181	42 y; 67%	Symptom duration not specified	All based on EMB (38% with positive and 62% negative for Dallas criteria). Immunohistological signs of inflammation, 50%. Not specified type of histology.	Unknown, the number of CMRI. Data not reported.	Viral PCR detected in 44%; PVB19, 29%; HHV6, 11%; enterovirus, 6%.	LVEF: 38%; LV dimension: LVEDDi, 36 mm/m^2, reported LV dilation in 51%.	Mean follow-up of ≈5 y: survival free of HTx, 78%. Independent predictors: NYHA III-IV, signs of inflammation at histology, lack of B-blocker therapy. Lost at follow-up: 8%.
Grun et al[19]	2002–2008	Not specified whether prospective, monocentric; Germany	203	52 y; 69%	Symptom duration not specified	All based on EMB (diagnosis: CD3+/CD68+ infiltration+ myocardial damage or fibrosis+HLA class II+).	All, within 5 d from admission.	Viral PCR for PVB19, HHV6, and EBV detected in 81%; PVB19, 56%; HHV6, 24%; EBV, 1%.	LVEF: 45% on CMRI; LV dimension: LVEDV, 165 mL.	Median follow-up of 4.7 years: survival, 80%. Best independent predictor: LGE presence.
Anzini et al[20]	1981–2009	Not specified whether prospective, monocentric; Italy	82	38 y; 70%	Median duration of symptoms, 8 d	All based on EMB (positive Dallas criteria for active myocarditis), including all histologies (lymphocytic, 91%; eosinophilic, 6%; GCM, 1%).	None	Viral PCR in the myocardium for all cardiotropic viruses (results not reported).	LVEF: 32%, LV dimension: LVEDDi, 35 mm/m.	At 9 y: estimated survival free of HTx, 64%. Independent predictors: LVEF <50%, enlargement of the left atrium.

(*Continued*)

Table 2. Continued

First Author	Years	Type of Study and Country	n	Age, y; Male Sex, %	Time Since the Onset of Symptoms	Histology	CMRI	Viral Search in the Heart	LVEF, %, and LV Dimension at Admission	Outcome
Sanguineti et al[18]	2008–2011	Prospective, monocentric; France	203	43 y; 76%	Mean duration of symptoms, 8 d	None	All (all with the presence of LGE)	None	LVEF: 57% on CMRI; LV dimension: LVEDVi, 73 mL/m^2.	Median follow-up of 19 mo: survival, 100%.
Inaba et al[34]	2007–2009	Retrospective, multicenter; Japan; Tokyo CCU Network: they compared fulminant (in-hospital death or need for MCS, n=42) versus nonfulminat myocarditis (survivors without MCS, n=96). Cases <15 y were excluded.	138	42 y; 57%	Not reported	In 21% (n=29) of cases, EMB was performed. 21% lymphocytic histology, 3% GCM, and 76% nonspecific findings.	In 20% (n=28) of cases. LGE detected in 64% of them.	None	In FM, LVEF: 31% at echo; LV dimension: LVEDD, 46 mm. In NFM, LVEF: 49% at echo; LV dimension: LVEDD, 49 mm.	In-hospital mortality, 14%. At multivariate analysis, low systolic blood pressure and QRS >120 ms were associated with death or need for MCS.
Ammirati et al[35]	2001–2016	Retrospective, multicenter (n=2); Italy (only FM)	55	33 y; 49%	Symptom duration, <30 d	In 71% of cases. Based on EMB, autopsy or explanted heart (positive active and borderline Dallas criteria). All histologies.	In 45% of cases	None	LVEF: 22% at echo; LV dimension: LVEDD, 48 mm.	At 9 y: estimated survival free of HTx, 65%.
Ammirati et al[35]	2001–2016	Retrospective, multicenter (n=2); Italy (only acute non-FM)	132	33 y; 88%	Symptom duration, <30 d	In 8% of cases. Based on EMB (positive active and borderline Dallas criteria). All histologies.	In 94% of cases	None	LVEF: 55% at echo; LV dimension: LVEDD, 49 mm.	At 9 y: estimated survival free of HTx, 100%.
Grani et al[17]	2002–2015	Not specified whether prospective, monocentric; US (not all admitted as inpatients; only 38% cases were admitted)	670	48 y; 59%	52% with symptom onset <2 wk; 48% with symptom onset above 2 wk (the median duration not specified)	None	All	None	LVEF: 50% on CMRI, of whom 30% with LVEF <40%; LV dimension: LVEDVi, 98 mL/m^2; LVEDV, 189 mL.	Median follow-up of 4.7 y: survival, 95.7%. 0.3% lost at follow-up. Main predictors: age, presence of LGE, LVEF <40%, reduced RVEF.
Aquaro et al[14]	2006–2013	Not specified whether prospective, multicenter (n=10); Italy	374	35 y; 77%	Symptom duration not specified	18 EMB (5%). Results not reported.	All (the presence of 2 Lake Louise criteria was used).	None	LVEF: 61% on CMRI; LV dimension: LVEDVi, 83 mL/m^2.	Median follow-up of 4.3 y: survival, 1.1%. Independent predictor: presence of anteroseptal LGE.
Ammirati et al[13]	2001–2017	Retrospective, multicenter (n=19); Italy. Per protocol, all patients were hospitalized.	443	34 y; 81%	Symptom duration, <30 d	In 14% cases. Based on EMB, autopsy or explanted heart (positive active and borderline Dallas criteria). All histologies.	In 94% of cases (all with the presence of 2 Lake Louise criteria).	Occasionally. Not reported.	LVEF: 55% at echo; LV dimension: LVEDD, 49 mm.	At 5 y: estimated survival free of HTx, 96%. Markers of unfavorable prognosis: presence of LVEF <50%, SVT or low cardiac output syndrome at presentation. Lost at follow-up, 1%.
Imazio et al[36]	2010–2016	Retrospective, monocentric; Italy	71	47 y; 75%	Symptom duration, <30 d (median time from symptoms to CMRI, 11 d)	None	All (Lake Louise criteria was used).	None	Mean LVEF: 52% on CMRI; not reported mean LV dimension.	At a mean follow-up of 5 y: estimated survival free of HTx, 100%.
Berg et al[37]	2010–2017	Retrospective, monocentric; Switzerland	45	34 y; 87%	Symptom duration, <11 d	None	All (Lake Louise criteria was used).	None	Mean LVEF: 56% on CMRI.	At 1 y: survival free of HTx, 100%.

(*Continued*)

Table 2. Continued

First Author	Years	Type of Study and Country	n	Age, y; Male Sex, %	Time Since the Onset of Symptoms	Histology	CMRI	Viral Search in the Heart	LVEF, %, and LV Dimension at Admission	Outcome
Ammirati et al[38]	2001–2018	Retrospective, multicenter (n=16); US, Europe, Japan. Per protocol, all patients hospitalized with LVEF <50%.	220	42 y; 54%	Symptom duration, <30 d	All based on EMB, autopsy, or explanted heart (positive active and borderline Dallas criteria). All histologies (lymphocytic, 73%; GCM, 14%; eosinophilic, 11%; sarcoidosis, 2%).	Not reported	Viral PCR search in the myocardium in 29% (n=63) of cases (FM, 20%; NFM, 55%). Positive in 19% (n=12) of cases. PVB19 (n=8; 67%) was the most frequently reported. Other viruses: 2 EBV, 1 HHV6, 1 unspecified.	In FM, LVEF: 22% at echo; LV dimension: LVEDD, 49 mm. In NFM, LVEF: 33% at echo; LV dimension: LVEDD, 56 mm.	At 60 d: estimated survival free of HTx in FM, 72%; in NFM, 98%. At 7 y: estimated survival free of HTx in FM, 52%; in NFM, 90%. Markers of unfavorable prognosis at muntivariate analysis: fulminant presentation, GCM on histology, QRS >120 ms on ECG. Lost at follow-up: 1.8%.
Ammirati et al[38]	2001–2018	Subanalysis of the retrospective, multicenter (n=16); US, Europe, Japan. Per protocol, all lymphocytic myocarditis, LVEF <50%, age >15 y.	146	40 y; 52%	Symptom duration, <30 d	All based on EMB, autopsy, or explanted heart (positive active and borderline Dallas criteria). All lymphocytic histologies.	Not reported	Viral PCR search in the myocardium in 36% (n=52). Positive in 15% (n=8) of cases. PVB19 (n=6; 75%) was the most frequently reported. Other viruses: 1 HHV6 and 1 EBV.	In FM, LVEF: 21% at echo; LV dimension: LVEDD, 49 mm. In NFM, LVEF: 30% at echo; LV dimension: LVEDD, 56 mm.	At 60 d: estimated survival free of HTx in FM, 80%; in NFM, 100%. At 7 y: estimated survival free of HTx in FM, 59%; in NFM, 97%. Markers of unfavorable prognosis at muntivariate analysis: fulminant presentation.
White et al[16]	2009–2014	Retrospective, monocentric; Canada	100	40 y; 82%	Symptom duration, <10 d	None	All. LGE detected in 72% of patients.	None	Mean LVEF: 57% on CMRI; LV dimension: LVEDVi, 84 mL/m^2.	At 1 y: survival free of HTx, 100%.
Younis et al[15]	2005–2017	Retrospective, monocentric; Israel	322	37 y; 84%	Symptom duration, <30 d	In 3% cases (lymphocytic histology, 25%; GCM, 13%; eosinophilic, 6%; borderline/negative, 56%).	In 73% of cases (83% with LGE, the presence of edema not specified).	None	Mean LVEF: 58% on CMRI; LV dimension: LVEDD, 50 mm.	In-hospital mortality: 0.

CMRI indicates cardiac magnetic resonance imaging; EBV, Ebstein virus; echo, echocardiogram; echo, echocardiogram; EDD, end-diastolic diameter; EMB, endomyocardial biopsy; FM, fulminant myocarditis; GCM, giant cell myocarditis; HHV6, human herpes virus-6; HLA, human leukocyte antigen; HTx, heart transplant; LGE, late gadolinium enhancement; LV, left ventricle; LVEDDi, indexed left ventricular end-diastolic diameter; LVEDVi, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; NFM, nonfulminant myocarditis; NYHA, New York Heart Association; PCR, polymerase chain reaction; PCWP, pulmonary capillary wedge pressure; PVB19, parvovirus-B19; RV, right ventricle; RVEF, right ventricular ejection fraction; SVT, sustained ventricular tachycardia; and US, United States.

an associated autoimmune disorder. Furthermore, differential white blood count can show eosinophilia, suggesting the presence of eosinophilic myocarditis (EM).[39] Finally, peripheral blood serological and virological tests are rarely informative,[2] with some exceptions (eg, HIV and Borrelia burgdorferi antibodies). A search for viral genomes with polymerase chain reaction in aerial tract fluids and pharyngeal swabs can identify viruses of the respiratory tract, such as influenza, and severe acute respiratory syndrome coronavirus-2, which can trigger an AM.[42,43] Autoantibodies (eg, antinuclear antibody test) and other tests may be indicated in patients with known or possible history of autoimmune disorders.[2]

AM: Echocardiography

Echocardiography is part of the standard evaluation of patients with a suspected acute cardiac condition and may show a broad spectrum of findings. Even when LVEF is normal, the presence of increased wall thickness, mild segmental hypokinesia, in particular, in the inferior and inferolateral walls, diastolic dysfunction, abnormal tissue Doppler imaging, mild right ventricular dysfunction, pericardial effusion, and abnormal myocardial echogenicity may suggest AM. In the early phase, LV dimensions are generally normal even when LVEF is low or very low[38]—a condition that may result in severe stroke volume reduction and tachycardia. LVEF on admission is a powerful prognostic marker.[13,15,38] Furthermore, cardiac function may evolve rapidly during AM, either spontaneously or after treatment.[13,15]

Suggested Indications for Cardiac Magnetic Resonance Imaging in AM and Chronic infl-CMP

Cardiac magnetic resonance imaging (CMRI) has emerged as a powerful noninvasive diagnostic tool for tissue characterization, including recognition and quantification of

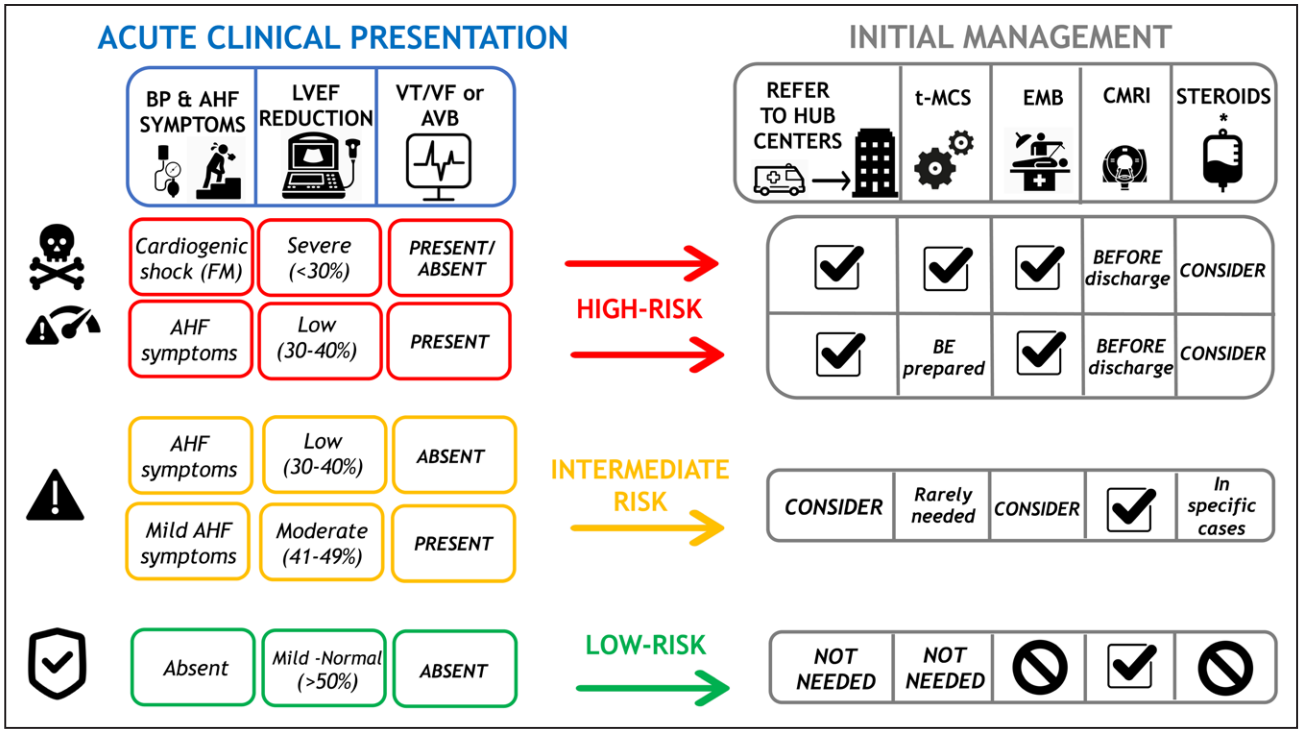

Figure 3. Proposed risk-based approach to acute myocarditis.
Left, Clinical features that characterize high (red boxes), intermediate (orange boxes), or low (green boxes) risk are summarized, according to the presence of low blood pressure (BP) and severity of acute heart failure (AHF), initial left ventricular ejection fraction (LVEF) on first echocardiogram, and ECG (presence of ventricular tachycardia [VT] or ventricular fibrillation [VF] or advanced atrioventricular block [AVB]). **Right**, How these risk features may influence patient management in terms of referral to expert centers, temporary mechanical circulatory support (t-MCS), need for endomyocardial biopsy (EMB) or cardiac magnetic resonance imaging (CMRI), and consideration for steroid treatment. Tag sign indicates recommended actions. No symbol indicates not recommended. *Immunosuppression with intravenous steroids may be considered and often used in patients with fulminant myocarditis; however, clinical studies that demonstrate their efficacy are lacking.

inflammation and replacement fibrosis in the setting of AM, and infl-CMP.[44,45] Furthermore, CMRI is the gold standard for the quantification of biventricular volumes, ejection fraction, and cardiac mass (Table II in the Data Supplement).[44] CMRI is recommended in patients with clinically suspected AM or in patients with chest pain, normal coronaries, and raised troponin, for the differential diagnosis of ischemic versus nonischemic origin,[46] with the exception of those in critical condition or with usual contraindication for this diagnostic tool.[2,44] CMRI should be performed in patients who initially presented with fulminant forms to assess the presence, extent, and localization of residual inflammation and replacement fibrosis when they are hemodynamically stable (Table 3). Unless recurrent flares occur, edema tends to decline 4 weeks after disease onset.[47] Therefore, to rule in or rule out myocardial inflammation reliably, CMRI should be performed within 2 to 3 weeks from the onset of symptoms, although accuracy may be lower during the first days. The availability of high-sensitivity troponins and CMRI have improved the accuracy of noninvasive diagnosis of AM,[44] which resulted in the identification of more low-risk patients than before, when diagnosis was mainly based on endomyocardial biopsy (EMB), which was performed more often in sicker patients. Thus, observational studies reported a more favorable prognosis of AM over the last decades (Table 2).[13–20,28–38] In fact, in 5 of 6 studies with EMB-based diagnosis, the mean echocardiographic LVEF was <40%.[20,28,29,31–33] In 2009, a consensus group published the original Lake Louise Criteria, which identified 3 hallmarks of myocardial inflammation with corresponding CMRI markers[45]: (1) hyperemia, that is, intense signal in early gadolinium enhancement images; (2) tissue edema, that is, increased myocardial T2 relaxation time or an increased signal intensity in T2-weighted images; and (3) necrosis/fibrosis based on late gadolinium enhancement (LGE) images. If 2 of these 3 criteria are positive, AM can be diagnosed with 74% sensitivity and 86% specificity.[48] With mounting evidence that CMRI mapping increases the overall diagnostic accuracy, the Lake Louise Criteria have been recently updated (Figure II in the Data Supplement).[44] The updated criteria include T2 mapping for edema and native T1, as well as extracellular volume for inflammatory injury.[44] A study has confirmed an increased sensitivity of the updated criteria (87.5%) while keeping a high specificity in AM (96.2%).[49] A single positive criterion can support diagnosis of myocardial inflammation if clinical suspicion is strong.[44] CMRI cannot identify specific cause of myocardial inflammation, and the histological subtypes, although regional distribution of inflammatory changes in the tissue provide diagnostic clues (eg, basal septal involvement in

Table 3. Comparison of Suggested Indications for Endomyocardial Biopsy, Viral Search, and Cardiac Magnetic Resonance Imaging Among Previous US and European Scientific Statements and Current Document

Document	AHA/ACC/ESC Scientific Statement (Cooper et al[54])	ESC Position Statement (Caforio et al[2])	AHA Scientific Statement (Bozkurt et al[9])	AHA Scientific Statement (Kociol et al[55])	Expert Consensus Document (Ammirati et al)
Year	2007	2013	2016	2020	2020
Specific disease	Role of EMB in the management of cardiovascular disease	Myocarditis	Specific dilated cardiomyopahy	FM	AM and chronic inf-CMP
Standard diagnostic tools		ECG, echocardiogram, measurements of blood markers of myocardial necrosis and inflammation (eg, CRP and WBC), and invasive or CT coronary angiography.			
Suggested indication for EMB	Specific indications in case of: new-onset HF of 2-wk duration associated with a normal sized or dilated LV and hemodynamic compromise (recommendation I, level of evidence B). New-onset HF of 2-wk to 3-mo duration associated with a dilated LV and new ventricular arrhythmias, second- or third-degree AVB, or failure to respond to usual care within 1–2 wk (recommendation I, level of evidence B). HF of >3-mo duration associated with a dilated LV and new ventricular arrhythmias, second- or third-degree AVB, or failure to respond to usual care within 1–2 wk (recommendation IIa, level of evidence C). HF associated with a DCM of any duration associated with suspected allergic reaction or eosinophilia (recommendation IIa, level of evidence C). New-onset HF of 2-wk to 3-mo duration associated with a dilated LV, without new ventricular arrhythmias or II- or III-degree AVB, which responds to usual care within 1–2 wk (recommendation IIb, level of evidence B–the writing group did not recommend performing EMB for the routine evaluation of this clinical scenario). HF of >3-mo duration associated with a dilated LV, without new ventricular arrhythmias or II- or III-degree AVB, which responds to usual care within 1–2 wk (recommendation IIb, level of evidence C–the writing group recognized that divergent evidence existed with regard to the utility of EMB in this clinical scenario).	All patients with clinically suspected myocarditis should be considered for EMB and coronary angiography. EMB may be repeated if necessary to monitor response to etiology-directed therapy or if a sampling error is suspected in a patient with unexplained progression of HF. Follow-up EMB may be required to guide the intensity and the length of immunosuppression.	Myocarditis: unexplained acute cardiomyopathy requiring inotropic agents or MCS. Unexplained acute cardiomyopathy with Mobitz type 2 second-degree or higher AVB. Unexplained acute cardiomyopathy with sustained or symptomatic ventricular tachycardia. Unexplained acute cardiomyopathy with failure to respond to guideline-based medical management within 1–2 wk (for all recommendation I, level of evidence B). HES (presence of eosinophils >1500/uL for a 6-mo duration): if suspected eosinophilic myocarditis is suspected, EMB is reasonable (level of evidence C). Autoimmune cardiomyopathy: EMB can be useful to confirm hydroxychloroquine-mediated HF (level of evidence C). Routine use of EMB is not recommended in patients with cardiomyopathy caused by suspected autoimmune, rheumatologic, or collagen vascular disease (level of evidence C). CS: EMB can be useful to confirm CS when pathology yields evidence of noncaseating granulomas, but absence does not rule out the possibility of CS (level of evidence C).	Unexplained acute cardiomyopathy: same indications as reported in the 2016 AHA Scientific Statement by Bozkurt et al[9].	Specific indications: in case of the following: AM presenting with cardiogenic shock (ie, FM)/acute HF, ventricular arrhythmias, or high-degree AVB, especially in case of non/mildly dilated LV and recent onset of symptoms; myocarditis in the setting of ICI where appropriate diagnosis has implications for patient receiving additional cancer therapy and accuracy of CMRI for diagnosis is not known; AM or chronic infl-CMP associated with peripheral eosinophilia; AM or DCM suspected for chronic infl-CMP with persistent/relapsing release of myocardial necrosis markers, especially if associated to suspected/known autoimmune disorders or ventricular arrhythmias or II/III-degree AVB for therapeutic implications.

(*Continued*)

Table 3. Continued

Document	AHA/ACC/ESC Scientific Statement (Cooper et al[54])	ESC Position Statement (Caforio et al[2])	AHA Scientific Statement (Bozkurt et al[9])	AHA Scientific Statement (Kociol et al[55])	Expert Consensus Document (Ammirati et al)
Year	2007	2013	2016	2020	2020
Relevant points for EMB	Timing of onset (in most of cases <3 mo from symptom onset). LV dimension: nondilation together with hemodynamic compromise and recent symptom onset are recognized strong indications for EMB. Presence of ventricular arrhythmias or II/III-degree AVB are modifiers of the indication for EMB, leading to include also patients with subacute presentation and LV dilation. Eosinophilia as marker of specific form of myocarditis that can be specifically treated.	Extensive indication for EMB independently of points that AHA Scientific Statements recognized as clues that increase the likelihood of a diagnostic EMB or when EMB can change management.	Needs of inotropes or MCS in the setting of acute unexplained setting: acute setting of unexplained cardiomyopathy presenting with ventricular arrhythmias or II/III-degree AVB. Confirmation of the indication in case of eosinophilia compared with the 2007 AHA Scientific Statement.	Confirmation of the indications reported in the 2016 AHA Scientific Statement.	Differentation of indications in AM (generally with normal/mildly increased LV and symptom duration <1 mo) from new-onset unexplained DCM suspected for chronic infl-CMP (dilated LV with symptom duration >1 mo) even in the acute setting of presentation. In the setting of AM indications in case of complicated presentation by acute HF (or FM) or in the presence of ventricular arrhythmias or II/III-degree AVB, while uncomplicated cases have no indication due to observed good prognosis. Relevance of persistent troponin release especially in case of chronic infl-CMP. Recognition of new AM/chronic infl-CMP related to ICI: relevance to perform an accurate diagnosis due to clinical implication of withdrawing life-saving treatments. Recognition of reaching accurate diagnosis in autoimmune-related AM/DCM suspected for chronic infl-CMP: as the inflammatory involvement of the heart has a prognostic impact on several autoimmune disorders (including inflammatory disorders like sarcoidosis) that can lead to changes in the treatments. Confirmation of the AHA Scientific Statements regarding indications in case of ventricular arrhythmias–II/III-degree AVB and eosinophilia.
Suggested indication for viral search in the myocardium	Because of uncertainties in the methods (for instance sampling errors and false negative results), and interpretation at centers not experienced in these techniques, the consensus is that routine testing for viral genomes in EMB specimen is not recommended at this time outside of centers with extensive experience.	Suggested in all cases to differentiate virus-positive (infective) from virus-negative myocarditis (on heart tissue and blood sample).	Myocarditis: the role of viral genome analysis of EMB tissue to guide management remains uncertain.	Further precision may be achieved by the use of viral genome analysis when diagnostic uncertainty exists despite histology.	We report different opinions among the experts of this document. Specifically, German authors recommend viral search in all cases. For other Italian and US authors, there is not enough evidence to routinely perform viral search as no clear therapeutic or prognostic benefit is demonstrated especially in the setting of AM. The presence of enteroviruses has a prognostic implication in particular in newborns and infants. They generally have poor prognosis, and it is believed that immunosuppression can be harmful based on animal studies. The presence of enteroviruses is currently considered rare in particular in adults. The presence of PVB19, which is the most common virus found in the myocardium, has no clear utility to further guide treatment; thus some experts do not suggest systematic search for viruses. In immunosuppressed (ie, patients with HIV) subjects, search for CMV could be relevant, in particular, if suggestive signs of cytolysis are found on H&E.
Suggested indication for CMRI	Not reported.	CMRI may be considered in clinically stable patients before EMB. CMRI does not replace EMB in diagnosis of myocarditis and should not delay EMB in life-threatening presentations.	Myocarditis: CMRI is reasonable for the diagnosis of myocarditis in clinically stable patients with clinically suspected myocarditis (recommendation II, level of evidence C). Autoimmune cardiomyopathy: CMRI or FDG-PET imaging can be useful to identify patients at risk for HF and to identify the degree of fibrosis (level of evidence B). CS: CMRI or FDG-PET imaging can be useful to diagnose CS or follow response to therapy (level of evidence B).	Myocarditis: CMRI is reasonable for the diagnosis of myocarditis in clinically stable patients with clinically suspected myocarditis; thus it is rarely indicated in the early diagnosis of FM (recommendation II, level of evidence C).	CMRI is the preferred diagnostic tool for AM without complications on presentation (preserved/mildly reduce LVEF and no ventricular arrhythmias). CMRI should be avoided in hemodinamically unstable patients (ie, FM), and EMB must be performed in particular to rule out GCM or other specific histology. CMRI should be performed even in FM when they are hemodynamically stable to assess the presence/extent and localization of LGE. It is recognized that CMRI's diagnostic accuracy for detecting chronic infl-CMP is reduced in case of ventricular arrhythmias or frequent PVCs. CMRI is suggested at 3–6 mo of follow-up to demonstrate resolution of edema (to modulate immunosuppression if any or to resume intense physical activities) and define the final LGE extent.

(*Continued*)

Table 3. Continued

Document	AHA/ACC/ESC Scientific Statement (Cooper et al[54])	ESC Position Statement (Caforio et al[2])	AHA Scientific Statement (Bozkurt et al[9])	AHA Scientific Statement (Kociol et al[55])	Expert Consensus Document (Ammirati et al)
Year	2007	2013	2016	2020	2020
Suggested indication for immune suppression	Not reported	Immunosuppression should be started only after ruling out active infection on EMB by PCR. The rationale for routine use of immunosuppression in virus-negative myocarditis is that the ESC task group considers infection-negative myocarditis (negative viral search in the myocardium) as an autoimmune form of myocarditis. Steroid therapy is indicated in CS in the presence of ventricular dysfunction or arrhythmia. Steroid therapy is indicated in some forms of infection-negative eosinophilic or toxic myocarditis with HF or arrhythmia.	Myocarditis: do not generally recommend empirical, upfront, immunomodulatory agents before diagnosis for myocarditis. Autoimmune cardiomyopathy: IV steroids, systemic immunosuppressants, or immunomodulatory agents can be useful for biopsy-proven myocarditis believed to be caused by SLE, RA, and PAN. CS: corticosteroids are recommended to treat patients with CS (level of evidence B). Other immunosuppressive therapies (eg, MTX, AZA, MMF, cyclophosphamide, pentoxifylline, and thalidomide) are reasonable in patients who cannot tolerate corticosteroids and in patients who continue to worsen clinically despite treatment with corticosteroids (level of evidence C). In collaboration with a pulmonologist or rheumatologist, immune-modulating therapy can be useful to treat sarcoidosis (level of evidence C).	Myocarditis: Compared with the 2016 AHA Scientific Statement, this document introduces this new concept: "If a high suspicion for immune-mediated FM exists (eg, GCM), 1 g solumedrol is often administered urgently, before biopsy-confirmed diagnosis or further diagnostic testing. Steroids will not obscure the results of the biopsy if given before this diagnostic test. If the diagnosis is GCM, other immunosuppressing agents will need to be added to obtain effective treatment."	AM: in case of FM or complicated AM by acute HF or ventricular arrhythmias or high-degree AVB, use of empirical IV corticosteroids can be considered. Maintenance of immunosuppression is based on the results of EMB. Specifically, maintenance of immunosuppression is useful in case of eosinophilic myocarditis, GCM, or sarcoidotic myocarditis or in case of demonstrated new diagnosis of a systemic autoimmune disorder. Viral search in the myocardium can identify patients in whom to withdraw immunosuppression in case of positive results, especially for enterovirus, CMV, and adenovirus. Maintenance of immunosuppression in case of positive PVB19 and HHV6 can depend on (1) observed initial response to immunosuppression (significant reduction of troponin or recovery of LVEF) or (2) low viral load. In all cases of ICI-associated AM, immunosuppression is suggested, with IV corticosteroids as the first line of therapy. Chronic infl-CMP: Immunosuppression can be started in case of eosinophilic myocarditis, GCM, or CS or in case of associated systemic autoimmune disorder. In isolated lymphocytic forms, search for viral genomes is suggested to exclude the presence of enterovirus, CMV, or adenovirus that can contraindicate immunosuppression. Immunosuppression can be considered in lymphocytic forms without evidence of viral genomes or in patients with PVB19. Clear demonstration of a survival benefit is lacking, while some studies suggest LVEF improvement. Rational to wait for viral genomes in chronic infl-CMP is that delays in the initiation of therapy are not expected to affect the prognosis as it could happen in FM.

ACC indicates American College of Cardiology; AHA, American Heart Association; AM, acute myocarditis; AVB, atrioventricular block; AZA, azathioprine; CD, cluster of differentiation; CMRI, cardiac magnetic resonance imaging; CMV, cytomegalovirus; CRP, C-reactive protein; CS, cardiac sarcoidosis; CT, computed tomography; DCM, dilated cardiomyopathy; EMB, endomyocardial biopsy; ESC, European Society of Cardiology; FDG-PET, fluorodeoxyglucose positron emission tomography; FM, fulminant myocarditis; GCM, giant cell myocarditis; H&E, hematoxylin and eosin; HES, hypereosinophilic syndrome; HF, heart failure; HHV6, human herpes virus-6; ICI, immune checkpoint inhibitors; infl-CMP, inflammatory cardiomyopathy; IV, intravenous; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MMF, mycophenolate mofetil; mo, month(s); MTX, methotrexate; PAN, polyarteritis nodosa; PCR, polymerase chain reaction; PVB19, parvovirus-B19; PVC, premature ventricular contractions; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; US, United States; WBC, whole blood count; and wk, week(s).

CS). In patients with de novo DCM or unexplained ventricular arrhythmias, CMRI can suggest previous myocardial inflammation based on the regional distribution of LGE; however, its sensitivity is not high in chronic forms.[50] The presence and location in the mid layer of the septum (mid-wall strip) of LGE and low LVEF at baseline appear to be the strongest negative predictors of outcome.[17,51] CMRI is useful also in the follow-up of AM and is generally performed 6 to 12 months after the index event (Table 3). Disappearance of edema is frequent at follow-up (up to 84% of cases), whereas LGE generally persists (in up to 89%), although its extent is reduced from 6.2% to 4.1% of LV mass after 6 months in the Italian Multicenter Study on Acute Myocarditis registry including 187 cases.[52] This finding is in keeping with other studies that analyzed the changes in LGE and edema at follow-up.[16,53] The extent of LGE is a dynamic process in AM, mainly related to tissue edema in the acute phase that progressively vanishes over time, whereas in the late phase, LGE mainly reflects postinflammatory replacement fibrosis.[53] Persistence of LGE and disappearance of edema are markers of unfavorable prognosis compared with complete resolution or persistence of both LGE and edema.[52] A potential explanation is that persistent edema can suggest a still active process with some residual chance of recovery,[52] further stressing the role of CMRI also in monitoring patients with AM and infl-CMP over time.

Suggested Indications for Positron Emission Tomography in AM and Chronic infl-CMP

Although positron emission tomography (PET) is not usually used in the setting of AM or chronic infl-CMP, it can

be considered as an alternative noninvasive diagnostic tool in stable patients with contraindication to CMRI or in patients with suspected systemic autoimmune disease where other organs could be involved by the inflammatory process.[56] PET is especially useful for the diagnosis and monitoring of CS.[57,58] T cells, macrophages, or granulocytes that infiltrate the myocardium, either as a nonspecific response to cell injury or as primary lesion in CS, are characterized by an enhanced glucose metabolism that can be detected by the focal uptake of the glucose analogue 18F-fluorodeoxyglucose. PET can reveal hypermetabolic mediastinal and hilar lymph nodes differentiating CS from other autoimmune disease with cardiac involvement (eg, vasculitis). This technique provides a tool to monitor the progression of damage and its regression in response to immunosuppressive therapy.[57] Recent development of additional immuno-PET tracers in oncology has dramatically expanded the usefulness of PET imaging to detect endogenous immune cells and may provide novel diagnostic and prognostication strategies in the myocarditis patients.

Suggested Indication for EMB in AM and Chronic infl-CMP

EMB is considered the reference standard for the diagnosis of myocarditis[2,7]; however, it is an invasive procedure that portends some risks. Cardiac complications have been reported in 1% to 2% of the patients at expert centers but in up to 8.9% at low-volume centers.[59,60] The sensitivity of EMB is relatively low when evaluated with standard hematoxylin-eosin staining,[61] since sampling sites do not always correspond to the distribution of inflammation. Sensitivity may be increased by increasing the number of collected specimens over the minimum recommended number (from 4 to 6 specimens).[2] Immunohistochemistry-specific antibodies for leukocytes (CD45), macrophages (CD68), T cells (CD3) and their main subtypes, helper (CD4) and cytotoxic (CD8) cells, and B cells (CD19/CD20) can also increase the sensitivity of EMB.[2] Quantitative criteria to improve the diagnostic yield of EMB in myocarditis include the Marburg criteria, based on the presence of >14 mononuclear leukocytes/mm^2 on bioptic samples,[62] with the presence of >7 T lymphocytes per mm^2.[63] These criteria were adopted in a position statement by the European Society of Cardiology experts.[2] Despite relatively low sensitivity, the information derived from EMB is fundamental for identifying the mechanisms and deciding therapy in specific clinical scenarios both in AM and chronic infl-CMP (Table 3):

1. AM presenting with severe heart failure (HF) or cardiogenic shock (ie, FM)[55];
2. AM complicated by severe myocardial dysfunction, acute HF, ventricular arrhythmias, or high-degree atrioventricular block;
3. AM or suspected chronic infl-CMP associated with peripheral eosinophilia;
4. AM or chronic infl-CMP with persistent or relapsing release of biomarkers of myocardial necrosis, particularly if associated to a suspected/known autoimmune disorder or ventricular arrhythmias or high-degree atrioventricular block; and
5. Myocarditis in the setting of ICI, where appropriate diagnosis has implications for patients receiving additional cancer therapy.[64]

Most of these recommendations were first released in the 2007 American Heart Association/American College of Cardiology (ACC)/European Society of Cardiology Scientific Statement on the role of EMB in the management of cardiovascular disease,[54] which were validated by a retrospective analysis on 851 patients with unexplained HF who underwent EMB.[59] The diagnostic yield of EMB in the setting of AM is considered to be higher if performed within 2 weeks since symptom onset and in case of normal sized or mildly dilated LV or in presence of markers (ventricular arrhythmias or high-degree atrioventricular blocks) of specific subsets such as giant cell myocarditis (GCM) or CS. AM is often a self-limiting disease and can be managed noninvasively in low-risk patients.[60] However, at present, EMB is largely underutilized also in the recommended settings, as shown by some reports on the use of temporary mechanical circulatory supports (MCS) in FM.[65] Thus far, a relationship between the extent of inflammatory infiltrates with prognosis and its therapeutic implications have not been consistently found across different settings of inflammatory cardiac disorders. In a retrospective study, patients with acute lymphocytic myocarditis who received an MCS or died during hospitalization had more inflammatory infiltrates compared with patients who survived without MCS.[35]

Differential Diagnosis

Invasive coronary arteriography or computed tomography angiography are often necessary to rule out an acute coronary syndrome.[2] Furthermore, patients with AM and acute pericarditis can complain of similar symptoms. Elevation of high-sensitivity troponin can steer the diagnosis toward AM. AM can be also associated with signs of pericarditis (ie, pericardial effusion on echocardiogram or CMRI; evidence of inflammation of pericardial layers on CMRI). FM should be differentiated from other conditions that may cause hypotension,[55] acute myocardial dysfunction, and cardiac shock (such as septic shock, Shoshin beriberi syndrome, systemic capillary leak syndrome, and pheochromocytoma).

Chronic infl-CMP

Chronic infl-CMP can be found in patients at their first evaluation for new-onset HF symptoms or in patients with subacute/chronic HF and DCM or hypokinetic nondilated phenotype. Chronic infl-CMP may represent the evolution of ≥1 AM episodes that, either diagnosed or missed in the acute phase, caused myocardial damage and systolic dysfunction. A mild elevation of troponin out of proportion compared with LVEF impairment, associated with a dilated LV with normal or mildly increased wall thickness, can suggest a chronic infl-CMP over AM.[8] Accordingly, CMRI and EMB may show less florid inflammation, and replacement fibrosis may prevail. Furthermore, cardiomyocytes with morphological abnormalities may be found at histology (Figure 1; Figure I in the Data Supplement). Due to progressive LV remodeling, patients presenting with a chronic infl-CMP have chronic HF symptoms (generally >1 month) but may be hemodynamically stable and are treated as patients with DCM.[9] Anamnestic clues, subtle electrocardiographic alterations (such as low voltage or fragmentation of QRS in peripheral leads, minor conduction disturbances, and nonspecific ST-T abnormalities), low-grade, persistent elevation of troponin, and failure to respond to standard HF treatment should promote the search for an inflammatory cause.[9] In chronic infl-CMP, the presence of high number of T lymphocytes or macrophages on EMB has a unique value in predicting an increased risk of mortality or transplantation over the next decade.[66] The extent of myocardial fibrosis should be reported as it could be related to the likelihood of recovery. Finally, the additional analysis to search for cardiotropic viruses (eg, RNA enteroviruses and DNA adenoviruses), bacteria, and parasites in biopsy specimens using quantitative real-time polymerase chain reaction is recommended by the European Society of Cardiology experts to guide immunosuppressive therapy in the setting of chronic infl-CMP.[2,67] Conversely, American Heart Association experts do not recommend routine viral genome analysis outside of centers with experience,[9] even if they consider it as an additional option when diagnostic uncertainty exists.[55]

VIRUS-INDUCED AND IMMUNE-MEDIATED LYMPHOCYTIC AM AND INFL-CMP

Lymphocytic AM and chronic infl-CMP have been attributed to a variety of pathogens, mainly viruses (by direct virus-mediated or indirect immune-mediated myocardial injury), toxic effect of drugs or radiation, and autoimmune injury in the setting of systemic inflammatory disorders.

Virus-induced AM can refer to both virus-mediated myocarditis and virus-triggered myocarditis. Enteroviral (coxsackievirus) myocarditis are examples of virus-mediated AM, as viral replication can cause direct cardiomyocyte injury.[68] The cases of enterovirus-mediated AM have been mainly reported in newborns and infants in recent years.[69] Respiratory viruses, such as influenza and coronaviruses, are examples of common viruses that can trigger an immune-mediated lymphocytic myocarditis in the absence of viral genome in the myocardium.[42,70] In virus-triggered AM, molecular mimicry between viral and cardiac antigens, which can result in autoreactive T-cell infiltration in the myocardium in predisposed individuals, is suspected to be the underlying mechanism of myocardial injury.[22] The resolution of the viral syndrome with the extinction of viral antigens could explain the frequent self-resolving natural history of most AMs. Of note, PVB19 appears to cause both virus-mediated and virus-triggered myocarditis. In children in particular, PVB19 may cause a systemic infection associated with AM where PVB19 can be detected both in plasma and myocardium. In adults, PVB19 has been associated with both AM and chronic infl-CMP,[71] and the viral genome has been detected with different titers in the myocardium of these subjects, while it is not generally detected in the bloodstream. PVB19 has been the only virus found in patients with lymphocytic FM in an international registry.[25,38] A preliminary report showing a benefit from immunosuppression in chronic infl-CMP with PVB19 presence in the myocardium seems to support the hypothesis that the immune response plays a role in the development of myocardial inflammation after viral infection.[72] Alternatively, low copy number of PVB19 DNA may reflect latent infection and should be interpreted as a bystander, since they can be found also in normal myocardium.[73] These findings may suggest that immunosuppression is not contraindicated in all virus-positive myocarditis, but the involved virus (eg, it may be considered with PVB19 but not with coxsackievirus), the host (eg, infants versus adults or immunodeficient versus immunocompetent individuals), and the setting (noncomplicated versus FM) should be considered in the decision to start immunosuppressive drugs. According to several researchers, high viral loads and replicating (versus nonreplicating) viruses could stand against the use of immunosuppression and possibly in favor of treatment with antiviral drugs or with agents that reinforce native immune response, for example, interferon-β,[74] even if clinical data from trials are substantially lacking in the setting of AM. Similarly to PVB19, human herpes virus-6 has been occasionally found in the myocardium of patients with AM and chronic infl-CMP, but its pathogenetic role is unclear.[19]

Immune-Mediated AM and Chronic infl-CMP

AM or chronic infl-CMP can be associated with systemic autoimmune disorders (eg, systemic lupus erythematosus or dermatomyositis) or organ/system-specific autoimmune/inflammatory diseases (eg, inflammatory bowel disorders). The immune system activation stimulated by an intercurrent infection could favor a flare of

the underlying immune disorder involving the heart. The identification of the myocarditis-associated condition is relevant for the specific treatments, given that not infrequently AM is the first manifestation of a systemic inflammatory/autoimmune disease.[39] The Lombardy registry of AM reported that 7.2% of patients had associated autoimmune or systemic disorders, and this condition was more frequent in patients with complicated presentation (15.4%).[13]

ICI-ASSOCIATED MYOCARDITIS

ICIs have transformed cancer treatment, with regulatory approval in ≈20 different cancer types. The percentage of patients with cancer who were eligible for ICI increased from 1.5% in 2011 to ≈50% in 2020.[75] These agents include monoclonal antibodies, which block immune brakes or regulators, termed CTLA-4 (cytotoxic T-lymphocyte antigen-4), PD-1 (programmed death receptor-1), and its ligand (PD-L1 [programmed death-ligand 1]) that, when stimulated, can dampen the immune response to an immunologic stimulus. By blocking these checkpoints from binding with their partner proteins, ICIs inhibit the off signal, activating T cells and promoting killing of cancer cells. By activating the immune system, ICI can also lead to immune-mediated adverse events (such as colitis, dermatitis, and pneumonitis).[76]

Etiology and Pathogenesis

In 2016, Johnson et al[77] described 2 cases of fatal FM after treatment with ICI. These patients presented with refractory electrophysiological disturbances and concomitant myositis, with pathology indicating T-cell and macrophage-dependent myocardial infiltration. Other case series of ICI-associated AM reported an incidence between 1% and 2% when ICIs are used in combination.[21,78] Preclinical data suggest a critical role for CTLA-4 and PD-1 in the cross talk between the cardiovascular and immune systems. Inhibition of CTLA-4 and PD-1, either genetically or pharmacologically, was found to contrast ICI-associated myocarditis and other cardiovascular toxicities in mice.[79]

Diagnosis

The largest case series of 122 patients with ICI-associated myocarditis had an early onset of symptoms (median of 30 days after initial exposure to ICI), and up to 50% died.[40] The increasing number of reports in the past few years is consistent with the growing awareness of this new clinical syndrome, as well as with the more widespread use of ICI. Patients on combination ICI treatment (eg, ipilimumab and nivolumab) should have an ECG and troponin assay at baseline. Once started on therapy, troponin should be checked weekly during the first 6 weeks. In addition, given concomitant myositis in a substantial number of cases of ICI-associated myocarditis, a defined workup for myositis (including checking for creatine kinase [CK] and possibly skeletal muscle biopsy) is recommended in suspected cases.

Treatment

High-dose intravenous corticosteroids associated with withdrawal of ICI are considered the first-line therapy, although mortality remains high. Alemtuzumab (anti-CD52 antibody), antithymocyte globulin (anti-CD3 antibody), and abatacept (a CTLA-4 agonist) have been proposed as second-line therapy (Table 3).[100–102] A better mechanistic understanding of ICI-associated cardiovascular toxicity by using preclinical models could help for defining preventive and treatment strategies in patients.

EOSINOPHILIC MYOCARDITIS

EM is relatively uncommon, but it is often unrecognized; thus its incidence may be underestimated. The rate of death or HTx in patients with EM and a fulminant presentation was over 26% at 60 days after admission.[38]

Etiology and Pathogenesis

EM is generally associated with hypersensitivity reactions to chemicals (in particular, clozapine, carbamazepine, minocycline, and β-lactam antibiotics and occasionally vaccination) or with systemic conditions such as eosinophilic granulomatosis with polyangiitis (EGPA; former Churg-Strauss syndrome) or hypereosinophilic syndrome (HES; idiopathic or clonal) or with a parasitic infection, mainly due to Toxocara canis transmitted by raw meat.[39] In rare circumstances, EM can be associated with solid-organ malignancy as a paraneoplastic event (ie, lung cancer). A 3-phase process of the eosinophilic injury has been proposed: an initial inflammatory/necrotic phase (observed during AM), followed by thrombotic and fibrotic remodeling of the endomyocardium (typical of Loeffler cardiomyopathy; Figure 4).

Diagnosis

EM may affect middle-aged individuals, with similar prevalence in both sexes, presenting mainly with chest pain and dyspnea, with evidence of LV systolic dysfunction. The diversity of possible underlying causes may be responsible of the variety of clinical scenarios; specifically, fever and skin rash are more common in hypersensitivity-related EM and asthma in EGPA-related EM.[39] Eosinophilia can be evident in the course of the disease,[80] but it is absent in about 25% of the patients at admission.[39] Echocardiography and CMRI provide information on cardiac function and may detect intracardiac thrombosis

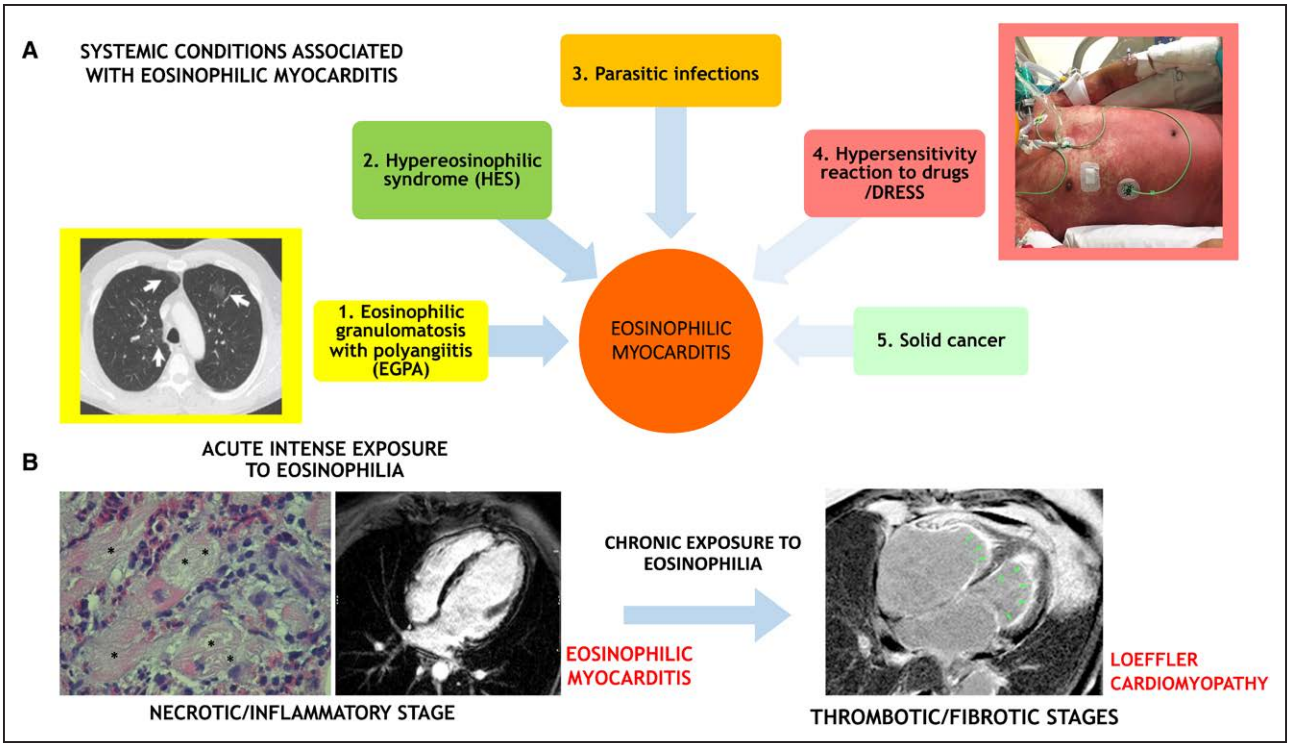

Figure 4. Eosinophilic myocardial injury: associated conditions and transition from acute myocarditis to inflammatory cardiomyopathy.
A, Eosinophilic myocarditis can be idiopathic or associated with a systemic disorder. The associated conditions can be (1) eosinophilic granulomatosis with polyangiitis (EGPA), which is often associated with asthma, pulmonary nonfixed infiltrates (arrows on a chest computed tomographic scan image in the yellow inset), and paranasal sinus abnormalities; (2) hypereosinophilic syndromes (HES) characterized by persistent peripheral eosinophilia (≥1.5×109/L for over 6 mo), which can be a complex idiopathic form or a myeloproliferative variant like the clonal form associated with FIP1L1/PDGFRA fusion gene; (3) parasitic infections; (4) hypersensitivity reactions to drugs and drug reaction with eosinophilia and systemic symptoms (DRESS) that are generally characterized by fever and diffuse skin rush (like in the patient with DRESS showed in the rose inlet), with frequent delay onset after drug initiation (up to 2–6 wk); and rarely, (5) solid tumors. While in the acute phase, the eosinophilic myocarditis is the main determinant of prognosis, the associated conditions can be the major determinants of prognosis in the mid and long term. **B**, An acute intense exposure to eosinophilia can cause an acute eosinophilic myocarditis (**left**), which in some case can be described as necrotizing due to extensive areas of the cardiomyocyte necrosis (*) caused by diffuse eosinophilic infiltrates on endomyocardial biopsy histology. The acute inflammatory phase can cause subendocardial and transmural injuries, identified by late gadolinium enhancement on cardiac magnetic resonance imaging (CMRI). If the eosinophilic exposure persists, eosinophilic injury evolves to a thrombotic and fibrotic stage, with diffuse subendocardial fibrosis with apical thrombi (green arrows), as identified by CMRI; the latter are characteristic features of Loeffler cardiomyopathy (**right**).

(particularly at the LV apex), mostly described in HES-related EM (up to 29% of cases) and EGPA-related EM (up to 19% of cases).[39] In contrast with the typical subepicardial LGE pattern observed in other forms of myocarditis, EM is generally associated with subendocardial LGE.[39]

Treatment

A meta-analysis of 179 cases has shown a lower incidence of in-hospital mortality with the use of corticosteroids, although randomized trials are lacking.[39] Identification and treatment of the underlying causes should be promptly considered. In particular, immediate withdrawal of the offending substance in combination with corticosteroid administration is recommended in hypersensitivity-related EM. Albendazole and corticosteroids should be given in EM associated with Toxocara canis infection,[39] and imatinib is utilized in myeloproliferative variants of HES. Combined immunosuppressive therapy, including corticosteroids and cyclophosphamide, azathioprine, or methotrexate, may be considered in EM associated with EGPA and HES.[39] The rate of recurrence is not known, but fatal recurrences have been reported.[39] Patients with HES and EGPA are at increased risk of late recurrence, in particular if immunosuppressive agents are withdrawn.

GIANT CELL MYOCARDITIS

GCM is a form of rapidly progressing necrotizing myocarditis with a poor prognosis including an ≈85% rate of death or HTx at 3 years.[38,81] GCM is responsible for ≈1 in 200 cases of myocarditis and ≈10% of all FM.

Etiology and Pathogenesis

GCM is characterized by myocardial destruction mediated by a large number of cytotoxic T cells, macrophages, giant cells, and eosinophils. This leads to LV dysfunction and ventricular arrhythmias. Associated autoimmune disorders, in particular, inflammatory bowel diseases and thyroid disorders, have been reported in ≈20% of cases.[81]

Diagnosis

GCM affects equally men and women. Median age at onset is between 43 and 53 years, higher than observed in lymphocytic myocarditis.[38,81] GCM frequently presents as acute HF or cardiogenic shock and with ventricular tachycardia or complete atrioventricular block.[82] EMB is generally the first diagnostic tool. GCM shares some histological features with CS; therefore, the differential diagnosis can be challenging.[82]

Treatment

Immunosuppressive therapy should be initiated promptly. Treatment with anti–T-lymphocyte–based (ie, antithymocyte globulin) and calcineurin inhibitor therapy can lead to clinical remission in up to two-thirds of patients, in particular, in those not requiring MCS.[83] The initial approach may vary based on the clinical presentation. In case of FM, antithymocyte globulin associated with pulse high dose of corticosteroids is preferred, and cyclosporine is titrated to trough levels of 150 to 250 ng/L a few days after the administration of antithymocyte globulin (Table 4).[84,94–96] There is a variable rate of LVEF recovery without transplant, among published series.[38,81,83,85] Dosage of oral corticosteroids after the acute phase is 1 mg/kg in the first months with subsequent slow tapering over 1 year, while cyclosporine is generally maintained >2 years, with a target plasma through level of 80 to 100 ng/L. Azathioprine at 1 to 2 mg/kg per die divided into 2 daily doses or mycophenolate mofetil (500–1000 mg BID) can be added. There are anecdotal but consistent data suggesting that discontinuation of immunosuppression after 1 year of treatment may be followed by relapse and death.[84] GCM patients have a high risk of ventricular tachycardia, and placement of an implantable cardiac defibrillator (ICD) is generally recommended in all patients including those with full recovery of LVEF.[86] Compared with historical results, current combined immunosuppressive treatment suggests an improvement in transplant-free survival from 11% to 55% at 1 year.[83,85] HTx is an effective therapy, with similar post-transplant survival in patients with GCM as in those with other causes. Nevertheless, recurrence of GCM on the transplanted hearts and a higher rate of early cellular rejection have been reported.[87]

SARCOIDOTIC MYOCARDITIS

Sarcoidosis is a worldwide disease with a prevalence of about 4.7 to 64 in 100 000; the highest rates are reported in Northern European and African American individuals, particularly in women.[57]

Etiology and Pathogenesis

Sarcoidosis is a multisystem, granulomatous disease of unknown etiology. Accumulating evidence suggests an immunologic response to an unidentified antigenic trigger in genetically susceptible individuals. Organ involvement is variable, but most patients have pulmonary and lymph node involvement.[57] Clinically manifest cardiac involvement occurs in about 5% of patients with pulmonary/systemic sarcoidosis.[57] Sarcoidotic myocarditis is characterized by infiltration by activated macrophages, which in some cases can lead to chronic inflammation and fibrotic replacement with non-necrotizing granulomas. Eosinophils and necrosis are rare or absent.[82] The macrophages within sarcoid granulomas tend to become epithelioid and form multinucleated giant cells.

Diagnosis

Most cases occur in patients 25 to 60 years of age. The 3 principal manifestations of CS are conduction abnormalities, ventricular arrhythmias, and HF.[57] There is a growing awareness that CS can be the first manifestation of sarcoidosis in any organ.[108] For example, between 16% and 35% of patients presenting with complete atrioventricular block (<60 years of age) or ventricular tachycardia of unknown etiology had previously undiagnosed CS as the underlying etiology.[108] The ventricular septum and LV basal free wall are most commonly affected. EMB has only 20% to 30% sensitivity, [57] if not imaging guided.[109] Experts' position statements propose criteria to reach diagnosis of CS that are mainly based on positive histology in the heart or extracardiac histological evidence of sarcoidosis plus demonstration of cardiac involvement based on imaging (Table III in the Data Supplement).[57]

Treatment

Corticosteroids therapy is advocated for the treatment of CS by most experts. It is unknown whether all patients with CS should be treated or only those with clinical manifestations of the disease.[57] Optimal doses of corticosteroids and how best to assess response to therapy is unknown. Methotrexate is often used as a second-line agent in refractory cases or if there are significant steroid side effects. Other therapies that have been used in CS include azathioprine, cyclophosphamide, infliximab,[57] and rarely rituximab (Table 4).[104–107]

Table 4. Immunosuppressive Treatment Used for Fulminant myocarditis or Acute Myocarditis Complicated by Severe Heart Failure Not Supported by Evidences From Clinical Trials

	Lymphocytic FM	ICI-Associated Myocarditis	Eosinophilic Myocarditis	Giant Cell Myocarditis	CS
First line	i.v. methylprednisolone, 7–14 mg/kg, pulsed doses for 3 d, then 1 mg·kg^{-1}·day^{-1} and subsequent tapering.[35,70,88]				
Alternative/ additional	Alternative: IVIG (2 g/kg),[89,90] single continuous infusion in 24–48 h or divided in 4 d or plasmapheresis, 3–5 sessions in 5–10 d.	Withdraw ICI therapy.	If EGPA: i.v. cyclophosphamide, 600 mg/m^2 (BSA) at days 1, 15, and 30.[39,91] If HES, myeloproliferative variant: imatinib 100–400 mg daily for 4–28 d (up to normalization of eosinophilic count).[92] If helmintic infection: albendazolo 200 mg OD to 400 mg BID for 2–7 wk.[93] If hypersensitivity reaction: withdraw medication suspected for the allergic reaction.	±ATG, 1 mg/kg, usually single-dose[55,84,94–96] or (alternative) i.v. alemtuzumab (anti-CD52 antibody) single dose of 30 mg[97] plus oral CyA, BID, target through levels 150–250 ng/mL[84]. If hemodynamically stable patients: only oral CyA, BID, target through levels 150–250 ng/mL.[83]	
Second-line treatment	If associated systemic autoimmune disorders (eg, SLE and APS): add aggressive treatment of associated conditions.[98,99]	ATG, 1 mg/kg, usually single dose[100] or i.v. alemtuzumab (anti-CD52 antibody), 30 mg, single dose[101] or i.v. abatacept (a CTLA-4 agonist), 500 mg every 2 wk, for a total of 5 doses.[102]	If HES, myeloproliferative variant: i.v. alemtuzumab (anti-CD52 antibody), 3, 10, and 30 mg on consecutive days, then 30 mg 3× a week for a total of 12 doses.[103]	See above, alternative or i.v. rituximab 375 mg×m^2 (BSA) mg (once a week for 4 wk and then every 4 mo as maintenance therapy).	+s.c. methotrexate 15–20 mg/wk[104–106] or i.v. infliximab 5 mg/kg (up to 500 mg) at time 0 and after 2 and 4 wk.[104,107]

Immunosuppression is not routinely recommended for all forms of acute lymphocytic myocarditis. Recommendations for this and other forms of acute, complicated myocarditis are not supported by evidences from randomized clinical trials but are derived from case series and pathophysiological considerations. Drugs and dosages are based on published clinical cases and revised by the authors, which are reported in the references or in the text. APS indicates antiphospholipid syndrome; ATG, antithymocyte globulin; BSA, body surface area; CD, cluster of differentiation; CS, cardiac sarcoidosis; CTLA-4, cytotoxic T-lymphocyte antigen-4; CyA, cyclosporine; EGPA, eosinophilic granulomatosis with polyangiitis; FM, fulminant myocarditis; HES, hypereosinophilic syndrome; ICI, immune checkpoint inhibitors; i.v., intravenous; IVIG, intravenous immunoglobulin; s.c., subcutaneous; and SLE, systemic lupus erythematosus.

Patients with CS are at risk of SCD, and there are limited data to help with risk stratification (Table III in the Data Supplement). In a recent Finnish nationwide study, 10-year survival was 92.5% in 102 patients.[110] Notably, CS can recur in transplanted hearts.[105] Key unresolved questions related to treatment are whether we should treat clinically silent CS and which drugs should be first- and second-line therapies for CS.

SPECIFIC TREATMENTS

Patients with AM or chronic infl-CMP associated with autoimmune disorders are treated according to indications regarding the systemic condition. Corticosteroids are generally the cornerstone of therapy, frequently in combination with another agent. During the acute phase, drugs with a rapid onset of action such as intravenous immunoglobulin, cyclophosphamide, and rituximab may be preferred, while for maintenance therapy, mycophenolate mofetil, methotrexate, and azathioprine may be used to allow tapering of corticosteroids over time. Plasmapheresis is occasionally used in the acute setting, for instance in AM associated with antiphospholipid syndromes. Excluding AM associated with systemic inflammatory conditions, no specific evidence-based treatments are available for lymphocytic AM. Only one trial is currently recruiting patients with AM (https://www.clinicaltrials.gov; unique identifier: NCT03018834), testing the efficacy of anakinra. AM is often a self-limiting disease, and spontaneous recovery of myocardial dysfunction may occur. There is a rationale for using immunosuppressive treatments in high-risk AM, but no trial has tested this hypothesis in the acute phase. Thus, there are no specific recommendations for therapy in the acute phase beyond standard therapy for LV dysfunction and acute HF. The only study that assessed the efficacy of immunosuppression in AM, the MTT (Myocarditis Treatment Trial), reported no benefit from immunosuppression.[29] However, the initiation of treatment was delayed, since patients were enrolled between 2 weeks and 1 year from symptom onset. Almost all studies with corticosteroids focused on chronic infl-CMP with 6-month history of HF symptoms. An improvement of cardiac function has been observed, but most studies were inadequately powered,[67] and there was no improvement in survival.[111] The single-center Tailored IMmunosuppression in Inflammatory Cardiomyopathy trial that randomized 85 patients with virus-negative chronic infl-CMP at a 6-month course of prednisone plus azathioprine or standard HF medications only showed a significant improvement of symptoms and echocardiographic parameters (median LVEF from 27% to 46% after 6 months) in the prednisone and azathioprine group. Given these findings, a large randomized trial is needed to assess the benefit and risk of long-term immunosuppression. Furthermore, few data exist supporting treatments for patients with virus-positive chronic infl-CMP. Usual HF treatments are recommended in those patients with chronic inf-CMP or AM with reduced LVEF and stable hemodynamics. β-Blockers are often used after an AM also in patients with uncomplicated presentation (53.8% based on the Lombardy registry of AM),[13]

probably due to the perceived protection against arrhythmic events. Finally concerning the prevention of SCD at discharge, patients with infl-CMP follow the general indication for ICD, with the abovementioned exceptions concerning GCM and CS. In patients with AM, a multiparametric stratification of risk is reasonable for decision on ICD implantation. It may include family history of SCD or arrhythmogenic cardiomyopathy, ventricular tachycardia on presentation,[112] presence and septal localization of LGE on CMRI,[14,17] and histology compatible with CS or GCM. Currently, ICD is rarely implanted after an AM with preserved LVEF (2% in the Lombardy registry[13] and 1.6% in the ITAMY registry). The cumulative percentage of SCD, resuscitated cardiac arrest, and appropriate ICD shock was 2.1% at 4.3 years of follow-up in the ITAMY registry.[14]

MCS AND HTx

Patients with AM complicated by refractory HF or cardiogenic shock require inotropic agents or MCS.[55] Myocarditis is often a reversible condition; thus temporary devices such as intra-aortic balloon pumps, venoarterial extracorporeal membrane oxygenator, rotary pumps, or intra-aortic axial pumps should be considered first. Observational studies and multicenter registries report a short-term transplant-free survival of 55% to 80% in patients with FM who received temporary MCS.[113,114] An analysis of trends in myocarditis incidence and management in the United States between 2005 and 2014[115] has reported a growing rate of use of any temporary MCS, from 4.5% to 8.6%, with a significant trend for all devices except intra-aortic balloon pump, which anyway was the most frequently used support (3.8% overall). In theory, the use of devices that reduce LV afterload, such as centrifugal pumps or intra-aortic axial pumps, alone or in combination with venoarterial extracorporeal membrane, could favor myocardial recovery more than venoarterial extracorporeal membrane alone, through both hemodynamic and anti-inflammatory mechanisms.[116] Nonetheless, a multicenter registry on intra-aortic axial pump use for FM (34 patients from 2009 to 2016) showed a survival to discharge of 62%,[117] not different from the 61% discharge rate reported among 185 patients supported with venoarterial extracorporeal membrane in Taiwan from 2001 to 2011.[118] If there is no weaning from MCS after 2 to 3 weeks, long-term LV assist device or urgent HTx may be considered.

KNOWLEDGE GAPS AND PERSPECTIVE

Critical knowledge gaps exist regarding diagnosis, prognostication, and treatment of AM and chronic infl-CMP, which need to be addressed. Though EMB is the gold reference for diagnosis, it is not available or is underperformed in most hospitals[60] and has a relatively low sensitivity using conventional histology. Hence, novel sensitive and specific biomarkers and imaging modalities are needed. The advent of novel technologies developed in the immuno-oncology space (eg, single-cell RNA sequencing, mass cytometry, high-frequency and deeper T-cell receptor sequencing, multiplex immunofluorescence, and other technologies) should become novel research strategies and further advance the usefulness of tissue analysis. Prospective large interventional trials or registries in the field of AM and chronic infl-CMP could help standardize the diagnostic and therapeutic approaches, which currently vary widely. Prospective registries aimed at identifying low- versus high-risk patients at the time of hospitalization and to refine and characterize the risk for specific events beyond death or HTx (eg, recurrence, evolution to DCM, and arrhythmias) at discharge and during follow-up are needed. Finally, a common terminology to describe cases of AM and infl-CMP, and shared clinical pathways for patient management, could increase our knowledge on this condition, potentially improving patient outcome.

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Supplemental Materials

Figures I and II
Movies I and II
Tables I–III

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