



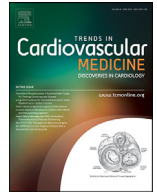
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Update on acute myocarditis

Enrico Ammirati^{a,*}, Giacomo Veronese^{a,b}, Maurizio Bottiroli^a, Dao Wen Wang^c,
Manlio Cipriani^a, Andrea Garascia^a, Patrizia Pedrotti^a, Eric D. Adler^d, Maria Frigerio^a

^a "De Gasperis" Cardio Center, Niguarda Hospital, ASST Grande Ospedale Metropolitano Niguarda, Piazza Ospedale Maggiore, 3, 20162 Milan, Italy

^b School of Medicine and Surgery, University of Milan-Bicocca, Monza, Italy

^c Division of Cardiology, Department of Internal Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

^d Division of Cardiology, Department of Medicine, University of California San Diego, San Diego, United States

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ABSTRACT

Acute myocarditis (AM), a recent-onset inflammation of the heart, has heterogeneous clinical presentations, varying from minor symptoms to high-risk cardiac conditions with severe heart failure, refractory arrhythmias, and cardiogenic shock. AM is moving from being a definitive diagnosis based on histological evidence of inflammatory infiltrates on cardiac tissue to a working diagnosis supported by high sensitivity troponin increase in association with specific cardiac magnetic resonance imaging (CMRI) findings. Though experts still diverge between those advocating for histological definition versus those supporting a mainly clinical definition of myocarditis, in the real-world practice the diagnosis of AM has undoubtedly shifted from being mainly biopsy-based to solely CMRI-based in most of clinical scenarios. It is thus important to clearly define selected settings where EMB is a must, as information derived from histology is essential for an optimal management. As in other medical conditions, a risk-based approach should be promoted in order to identify the most severe AM cases requiring appropriate bundles of care, including early recognition, transfer to tertiary centers, aggressive circulatory supports with inotropes and mechanical devices, histologic confirmation and eventual immunosuppressive therapy. Despite improvements in recognition and treatment of AM, including a broader use of promising mechanical circulatory supports, severe forms of AM are still burdened by dismal outcomes. This review is focused on recent clinical studies and registries that shed new insights on AM. Attention will be paid to contemporary outcomes and predictors of prognosis, the emerging entity of immune checkpoint inhibitors-associated myocarditis, updated CMRI diagnostic criteria, new data on the use of temporary mechanical circulatory supports in fulminant myocarditis. The role of viruses as etiologic agents will be reviewed and a brief update on pediatric AM is also provided. Finally, we summarize a risk-based approach to AM, based on available evidence and clinical experience.

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Introduction

Acute myocarditis (AM) is an inflammation of the heart of recent onset (usually less than 1 month). It may be caused by infections, exposure to drugs or toxic substances, and abnormal immunoreactivity [1]. Its clinical spectrum varies from an asymptomatic or minor illness to high-risk cardiac conditions with severe heart failure (HF), refractory arrhythmias, cardiogenic shock and sudden cardiac death [2]. Not many years ago, with the lack of accurate noninvasive diagnostic tools, clinically suspected AM could be confirmed only by demonstration of inflammatory infil-

trates in myocardial tissue. Percutaneous endomyocardial biopsy (EMB), originally developed to monitor rejection in heart transplant (HTx) recipients [3], gave the opportunity to characterize patterns of cell infiltrates and to identify myocyte loss and replacement fibrosis also in the AM setting [4]. However, with the exception of clinically aggressive forms, labeled as fulminant myocarditis (FM), which were generally associated with diffuse inflammation [5], EMB had a relatively low sensitivity due to the patchy distribution of inflammatory infiltrates [6]. Furthermore, its rate of complications, reported to be low (1–2%) at experienced centers [7], was estimated around 8.9% when including low-volume centers [8]. Considering that spontaneous resolution occurs in many patients, a definite EMB-based diagnosis was reached in a minority of patients with clinically suspected AM, primarily in mid- to high-risk sub-

* Corresponding author.

E-mail address: enrico.ammirati@ospedaleniguarda.it (E. Ammirati).

jects [9–11]. In the last decade, the measurement of high-sensitive (hs) troponin levels for identifying myocardial injury and the use of cardiac magnetic resonance imaging (CMRI) for characterizing myocardial tissue changes, allowed to diagnose AM non-invasively and with reasonable accuracy, in a wider population of patients including low-risk subjects. Therefore, the incidence of AM in the United States gradually increased from 95 to 144 cases per 1 million inhabitants from 2005 to 2014 [12]. Higher left ventricular (LV) ejection fraction (EF) [13–15] and more favorable outcomes have been observed in recent series with a CMRI-based diagnosis than in previously published series with a biopsy-based diagnosis [9–11]. This is not surprising, considering that CMRI is hard to perform in severe acute settings (e.g. severe HF, hemodynamic instability, frequent or sustained arrhythmias). As CMRI cannot identify the subset of inflammatory cells characterizing the histologic type of AM, which has prognostic and therapeutic implications [16], EMB is still thus recommended for optimal medical management in selected clinical scenarios [17]. Of note, United States administrative data from 2005 to 2014 indicate that EMB was performed only in 3% of all suspected AM cases [12]. AM should not be regarded as a uniformly benign condition given the increasing rate of associated cardiogenic shock, from 6.9% in 2005 to approximately 12% in 2014, with ~4% overall in-hospital mortality, substantially stable over time [12]. These data are consistent with those reported by the largest collaborative observational registry on AM (the Lombardy registry, enrolling 443 patients from 2000 to 2017) in which the incidence of cardiogenic shock was 8.6% [13] and the rate of in-hospital mortality or need for HTx was 2.7%. Identification of patients at risk for dismal outcome that may require an EMB-based diagnosis to guide specific treatment and management is of utmost importance.

This review is focused on recent clinical studies and registries that shed new insights on AM. Attention will be paid to contemporary outcomes and predictors of prognosis, the emerging entity of immune checkpoint inhibitors (ICI)-associated myocarditis, updated CMRI diagnostic criteria, new data on the use of temporary mechanical circulatory supports (MCS) in FM. The role of viruses as etiologic agents will be reviewed and a brief update on AM in the pediatric population is also provided. Finally, we summarize a risk-based approach to AM, based on available evidence and clinical experience.

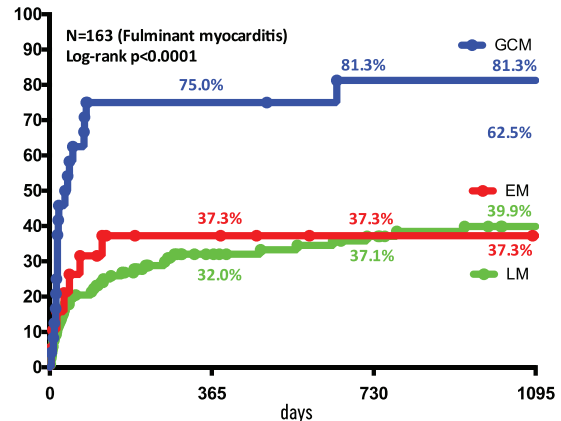
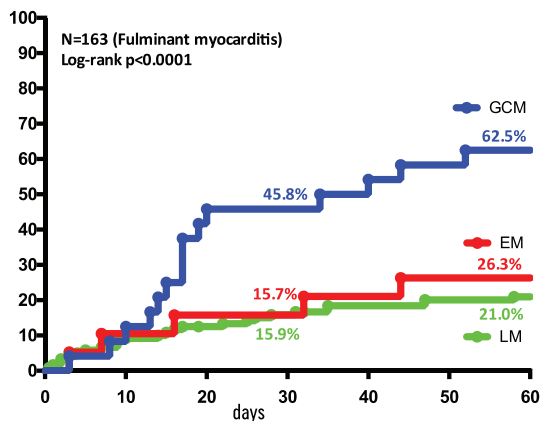
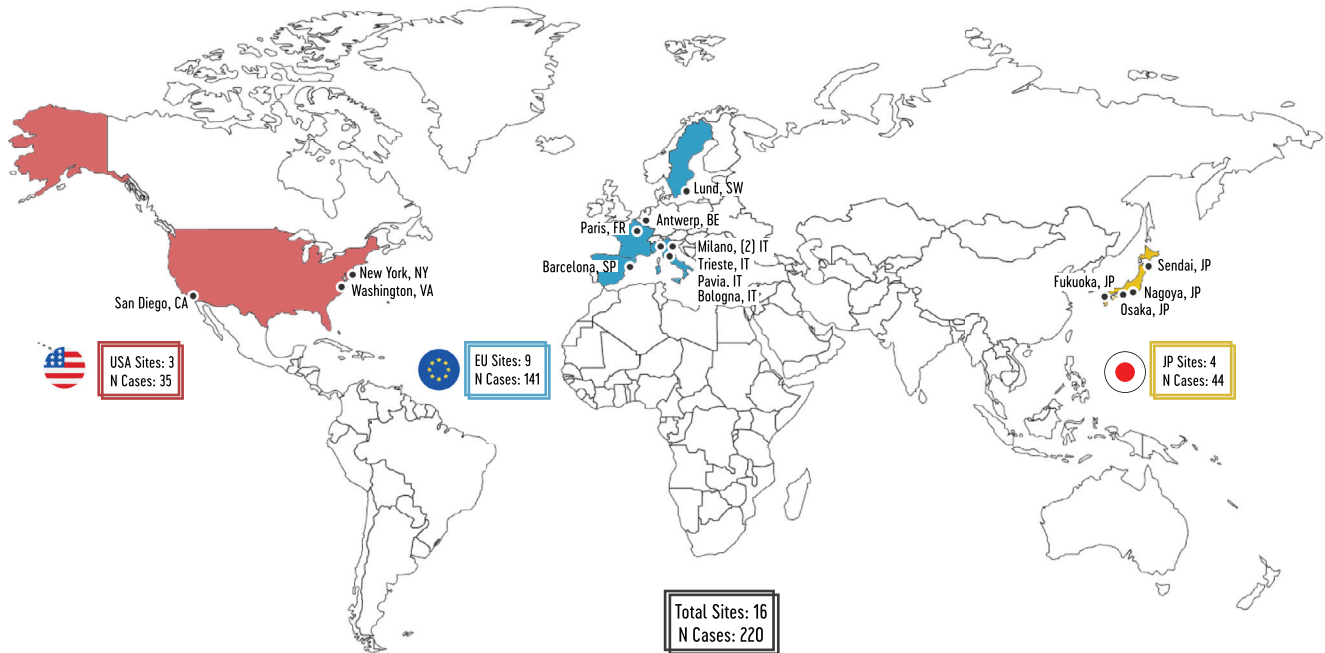
New evidence from recent registries on acute myocarditis

In recent years, retrospective observational registries were launched with the aim to characterize the clinical course and clarify the outcome of patients with AM. By highlighting the differences in mortality and HTx rate among different clinical presentations, they provide rationale for the practical classification of AM that may help clinicians in guiding initial management and treatment. The Lombardy registry, an Italian multicenter registry including 443 patients hospitalized with an established diagnosis of AM based on EMB or a combination of increased troponin plus edema and late gadolinium enhancement (LGE) on CMRI, demonstrated that cardiac mortality and HTx occurred almost exclusively in patients presenting with a *complicated* AM, defined as presenting with LVEF < 50% on the first echocardiogram, and/or sustained ventricular arrhythmias (VA), and/or hemodynamic instability on admission [13]. Specifically, patients with complicated AM had a cardiac mortality or HTx rate of 10.4% at 30 days and 14.7% at 5 year follow up, while *uncomplicated* AM had no cardiac mortality or HTx [13]. Of note, severe hemodynamic compromise on admission was associated with the highest probability of cardiac death and HTx, challenging the historical tenet of the excellent prognosis of FM [5,18–20]. Furthermore, new evidence has emerged from a series of 220 cases with histologically proven AM and systolic

dysfunction (LVEF < 50%) collected from 16 tertiary hospitals, creating one of the largest international registries on biopsy-proven AM [20]. Besides confirming that hemodynamic compromise at presentation is the major determinant of both short and long-term prognosis (cardiac death or HTx at 60 days, 28% in FM vs. 1.8% in non-FM and at 7 years, 47.7% in FM vs. 10.4% in non-FM), this registry provided strong evidence on the role of histological characterization in the setting of FM. Giant cell myocarditis (GCM) was burdened by the highest rate of mortality or need for HTx (81% at 3-year follow-up) (Fig. 1), supporting the recommendations for early implementation of a multimodal, aggressive immunosuppression regimen [21,22]. The risk was also high in eosinophilic myocarditis, which requires specific therapeutic strategies also according to etiology [20,23]. Impressively, lymphocytic FM was also shown to be a high-risk condition, with a death or HTx rate as high as 19.5% at 60 days, and 40% at 3 years, highlighting the need to reconsider the eventual role of immunosuppression in the acute phase also in these patients, in order to raise the probability of functional recovery. This is also supported by the fact that, despite a widespread use of temporary MCS devices, the outcomes did not improve significantly in recent years. Another independent factor associated with an increased risk of cardiac death or HTx was QRS width > 120 ms on ECG (adjusted hazard ratio 2.49) [20]. Thus, simple factors such as clinical presentation, wide QRS, and reduced LVEF on admission can help identifying high-risk patients, in whom EMB is recommended to guide subsequent therapeutic strategies (e.g. search for specific etiologies or associated conditions, immunosuppressive regimen, short-term temporary MCS, and screening for HTx listing).

Viruses and myocarditis

The role of viruses in myocarditis etiology has been historically recognized, with parvovirus (PV)-B19, adenoviruses, Human Herpes virus (HHV)-6 being the most common agents identified in the myocardium of patients with AM [10]. Nevertheless, a growing body of literature indicates that viruses, particularly PVB19 and HHV6, may be found in a large percentage of patients who do not have myocarditis [24], questioning their direct causal role in the pathogenesis of myocarditis. Similarly, despite initial enthusiasm, evidence regarding the role of viral genome persistence in the myocardium in influencing the outcome of patients is still contradictory and was mostly derived from patients affected by chronic inflammatory cardiomyopathy or dilated cardiomyopathy rather than AM. The majority of evidence suggests that *virus-triggered* immune-mediated reactions are the principle cause of cardiomyocyte injury [25] rather than actual direct *virus-mediated* cell injury. Recent studies of influenza associated myocarditis, with influenza viruses only detected on nasopharyngeal swabs [26], seems to support this hypothesis. In a recent series of hospitalized Corona virus disease (COVID-19) patients, the rate of acute cardiac injury demonstrated by elevation of hs-troponin ranged between 7 to 27%, highest in those requiring intensive care unit [27,28], further suggesting the potential role of viruses in triggering abnormal immune-mediated inflammatory injury [29–31]. The controversy matters as it has been stated that the presence of specific viruses in the heart may be a contraindication to the use of immunosuppression, particularly in lymphocytic forms [32,33], where its role is mostly controversial. Indeed, the current European Society of Cardiology (ESC) position statement recommends that immunosuppression should be started only after ruling out active infection on EMB by polymerase chain reaction (PCR), including viruses [32]. Several algorithms based on presence/absence of inflammation and presence/absence of virus identification on EMB to guide management and treatment of AM have been released in recent years [32,33]. However, literature on the role of a myocarditis manage-



	0	10	20	30	40	50	60	0	365	730	1095
GCM	24	22	14	13	12	10	9	24	5	3	3
EM	19	17	16	16	15	14	14	19	9	6	5
LM	120	110	104	99	96	94	93	120	57	48	40

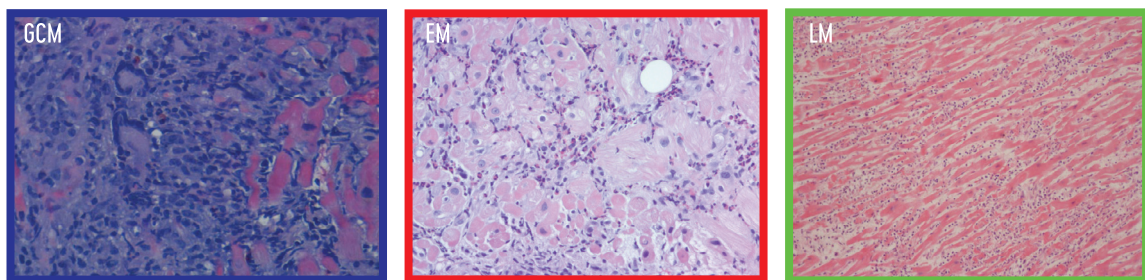


Fig. 1. Incidence of cardiac death and heart transplantation among patients with fulminant myocarditis affected by 3 specific histologic subtypes. Data derived from the largest available dataset collecting 220 cases of histologically proven acute myocarditis from 16 centers, as highlighted in the map on the top of the image. Fulminant myocarditis was defined as requiring circulatory support with inotropes or mechanical devices. The reported analysis excluded patients with acute nonfulminant myocarditis (n, 55) and 2 patients with fulminant presentation due to a sarcoid myocarditis. Log-rank (Mantel-Cox) test confirmed a significantly (p after Bonferroni test) worse prognosis for patients with FM due to GCM versus LM (p < 0.001) and a worse prognosis for patients with FM due to GCM versus EM (p < 0.02) and versus LM (p < 0.001) at long-term follow-up. Patients with FM due to EM or LM did not differ in terms of outcome. On the bottom of the image, representative hematoxylin and eosin sections of GCM, EM, and LM. Reprinted with permission of the Journal of the American College of Cardiology [20].

UPDATED LAKE LOUISE CMRI CRITERIA SUPPORTING THE DIAGNOSIS OF ACUTE MYOCARDITIS

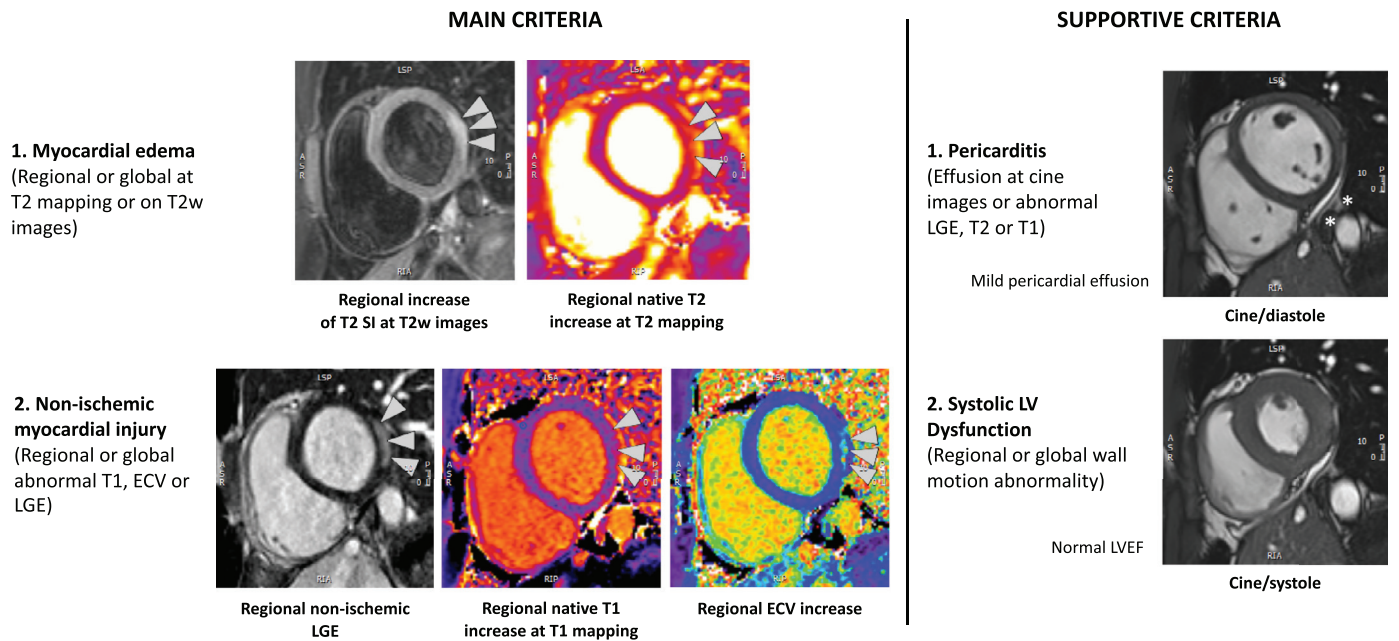


Fig. 2. Representative case of acute myocarditis based on 2018 cardiac magnetic resonance imaging Lake Louise criteria. At least one T2 marker of myocardial edema and one T1 marker of myocardial injury are required. On the left: main criteria are fulfilled, as there are both (1) signs of myocardial edema (regional increase of SI on T2w images and regional increase of native T2 at T2 mapping, underpinned by head arrows in the anterolateral wall) and of (2) non-ischemic myocardial injury (regional LGE, increase native T1 at T1 mapping and ECV expansion in the anterolateral wall, underpinned by head arrows, with non-ischemic pattern). On the right: one supportive criterion is present, in fact a small pericardial effusion is evident at cine images, whereas there are neither global hypokinesia nor regional wall motion abnormalities in this case. Abbreviations: T2w, T2 weighted; SI, signal intensity; LGE, late gadolinium enhancement; ECV, extra-cellular Volume; LVEF, left ventricular ejection fraction.

ment based on viral genome identification has been mostly derived from small studies in patients affected by chronic myocarditis or inflammatory cardiomyopathy with HF symptoms for more than 6 months [34], and the results obtained have been inconsistent [35]. Of note, methods for identifying viral genome and quantifying their replication are not standardized, and the sensitivity of EMB for viral search is low. Results from the international registry on AM further highlight the low prevalence of use of PCR-based viral search on EMB specimens in the real-world practice and the low rate of virus positive cases, with PVB19 being the only detected virus [36]. At present, the role of a routine viral genome search on EMB in guiding patient management and immunosuppression therapy in patients with AM remains largely to be proven. This is especially true in fulminant forms, where early immunosuppression could be crucial to hamper the inflammation process. Results from patients with inflammatory cardiomyopathy and PVB19 persistence showed that immunosuppressant drugs did not aggravate viral replication [37], further questioning the rationale of withholding immunosuppression in the acute phase of suspected *virus-triggered* AM. Thus, the authors feel that the risk-benefit profile of immunosuppression should be reconsidered in patients with severe clinical presentation, in light of their high early and mid-term mortality.

Immune-checkpoint inhibitors associated acute myocarditis

ICI are new anti-cancer drugs that enhance T-cell-mediated immune response against tumor cells. AM, alone or in combination with other manifestations of autoimmunity (e.g. lungs, liver, kidneys, thyroid) is being recognized more frequently than initially appreciated [38]. In a recently published multicenter observational registry, myocarditis was noted in 1.14% of ICI-treated patients, at a median interval of 34 days following the initiation of therapy [39]. This percentage may appear low, but given the

high number of patients that are predicted to receive these drugs in the near future, a growing relevance of this subtype of myocarditis can be expected [40]. ICI-related AM poses quite different, specific challenges. Patients are by far older (median age 64 *versus* 34 years in non-ICI-related forms), and besides being affected by advanced cancer, they commonly have other chronic comorbidities. These factors may contribute to the high mortality rate observed in these patients, and make LVEF at presentation less relevant for prognosis than in non-ICI-related AM [41]. Furthermore, if severe heart dysfunction persists, MCS may be a debatable choice in patients with advanced, often metastatic, cancer. ICI withdrawal and high-dose steroids are first line-therapies. Patients not responsive to steroids should be considered for additional treatment. The proposed regimens include plasmapheresis, immunoglobulins and anti-thymocyte globulin [42]. Promising effects of abatacept (a CTLA-4 agonist) and alemtuzumab (a CD52-binding monoclonal antibody) were recently reported for the treatment of severe, steroid-refractory cases [43,44]. Awareness on this new entity among cardiologists, oncologists and critical care providers would promote early recognition and possibly structured surveillance of this complication [38].

Cardiac magnetic resonance imaging

In the setting of clinically suspected AM, CMRI may characterize alterations of myocardial tissue signal, providing qualitative and quantitative information on their type and distribution, differentiating ischemic from inflammatory cardiomyopathies [45]. In uncomplicated AM, the abnormalities on CMRI are typically in a non-coronary distribution. These include patchy areas of edema with matching areas of LGE, localized to the sub-epicardium with variable intramyocardial extension [19,46]; on the opposite in ischemic heart disease LGE is typically subendocardial up to transmural, and

Table 1
Registries and case reports focused on patients affected by fulminant myocarditis supported by IMPELLA devices published between 2010 and 2020.

Authors	Years	Patients, n.	Mean age, y.	Type of IMPELLA	Mean t on support, h.	Complications	Survival to hospital discharge
Annamalai et al. 2018	01/2009-02/2016	34 EMB in 11 cases	41	2.5 (41%) CP (35%) 5.0 (24%) - Concomitant RP (5%) - Concomitant va-ECMO (6%)	90.5±74.2	- Anemia requiring transfusion (20%) - Hemolysis (12%) - Device malfunction (15%) - Vascular complications (12%)	21 (62%)
Charalambous et al. 2018	01/2013-01/2016	6 Clinical diagnosis in all cases	43	NS	NS	NS	83.3%
Case reports focused on FM cases supported by IMPELLA devices							
Authors	Type of use	Age, y.	Type of IMPELLA	Diagnosis / Histology	Outcome		
Hasegawa-Tamba et al. 2019	Sole assist device	16	2.5	Eosinophilic myocarditis	Survived		
Yamamoto et al. 2019	ECMELLA	26	2.5 followed by 5.0	Lymphocytic myocarditis	Survived		
Ogawa et al. 2019	Sole assist device	39	5.0	Lymphocytic myocarditis	Survived		
Pappalardo et al. 2018	BIPELLA	37	CP and RP	CMRI based diagnosis	Survived		
Garg et al. 2017	Sole assist device	50	NS	GCM	HTx		
Fox et al. 2017	Sole assist device	49	CP	Lymphocytic myocarditis	Survived		
Burns et al. 2015	Sole assist device	48	5.0	Clinical diagnosis of viral myocarditis	Survived		
Narain et al. 2012	ECMELLA	31	2.5	Viral myocarditis	Survived		
Chaparro et al. 2012	ECMELLA	31	2.5	Lymphocytic myocarditis	Survived		
Beurthet et al. 2012	ECMELLA	34	5.0	Eosinophilic myocarditis	Survived		
Suradi et al. 2011	Sole assist device	44	2.5	GCM	Died		
Khouzam et al. 2011	Sole assist device	36	2.5	Clinical diagnosis H1N1 positive	LVAD		
Andrade et al. 2010	Sole assist device	13	5.0	Biopsy-proven viral myocarditis	Died		
					Survived		

follows coronary artery distribution. CMRI is not the initial diagnostic technique in patients in critical conditions, for whom EMB is crucial. In recent years, mapping techniques measuring myocardial T1 and T2 signal (T1 and T2 mapping) in milliseconds and calculating the percentage of extracellular volume (ECV) have been introduced, thus providing a quantitative approach to tissue characterization [16]. T1 and T2 mapping can be performed on native myocardium, while the quantification of ECV requires the administration of contrast medium. In light of scientific evidence on mapping technique in the assessment of myocarditis, the Lake Louise Criteria (LLC) for the diagnosis of myocarditis have been updated in 2018 [16]. According to this formulation, CMRI provides evidence of myocardial inflammation when at least one criterion for each of the following categories is positive: (1) T2 marker of myocardial edema (T2-weighted images or mapping) and (2) T1 marker of associated myocardial injury (LGE, T1 mapping or ECV; Fig. 2) [16]. Pooled data on original 2009 LLC show a sensitivity of 80% and a specificity of 87% to detect acute inflammation [47]. Preliminary data have shown that the diagnostic performance of CMRI has improved with revised 2018 LLC, with a sensitivity of 87.5% and a specificity of 96.2% [48]. False negative scans can occur and could be related to the timing of acquisition, as the presence of edema is time dependent [49], or to the entity of myocardial injury; nonetheless the presence of a negative scan (normal ventricular volumes and functions, no edema and no LGE) in a patient with suspect myocarditis is relevant information, as it portends a good prognosis at follow-up [50]. On the contrary, in 2017, two multicenter studies involving >1000 patients showed that septal localization of LGE can identify patients at risk of death or major cardiovascular events after discharge [15,51]. CMRI cannot identify the specific cause of myocardial inflammation and has limited sensitivity in chronic inflammatory cardiomyopathy and in patients with arrhythmic presentation, in whom also inflammatory infiltrates at EMB are less florid [52]. Frequent arrhythmias, difficulties in breath holding and intolerance to examination (e.g. claustrophobia) negatively affect image acquisition and quality. CMRI can be repeated during follow-up, generally after 6 to 12 months, to identify post-inflammatory scars [46], which are associated with a higher risk of death or major cardiovascular events [53]. In athletes, it is suggested to perform a follow up scan before re-starting competitive training [54]. However, currently available data are insufficient to derive evidence-based recommendations for physical activity reintroduction. Therefore, the decision is often based on expert consensus and shared decision making with the patient. In our clinical practice, we evaluate at 6 months: (1) absence of symptoms, (2) demonstration of normal levels of hs-troponin, (3) no residual signs of edema on CMRI and (4) no evidence of repetitive premature ventricular contractions, non-sustained or sustained VA triggered by exercise test or on prolonged ECG monitoring.

Mechanical circulatory supports in fulminant myocarditis

In patients with FM presenting with cardiogenic shock, the first step is to ensure adequate perfusion pressure and oxygenation, thus inotropes, vasopressors, and mechanical ventilation may be required [5]. However, high doses of vasoactive agents in patients with poor systolic function may increase myocardial oxygen consumption, reducing the probability of myocardial recovery [55]. In the last decades the results obtained with temporary MCS in FM refractory to medical therapy have been described [56]. The main goals for temporary MCS in FM are: (1) biventricular unloading, (2) optimal systemic and coronary perfusion, (3) venous decongestion. The achievement of these goals is fundamental to prevent multiple organ dysfunction and death and allow a safe bridge to recovery, HTx or a durable assist device implant [57]. The most commonly implanted temporary MCS devices reported in several

ACUTE MYOCARDITIS SCENARIOS

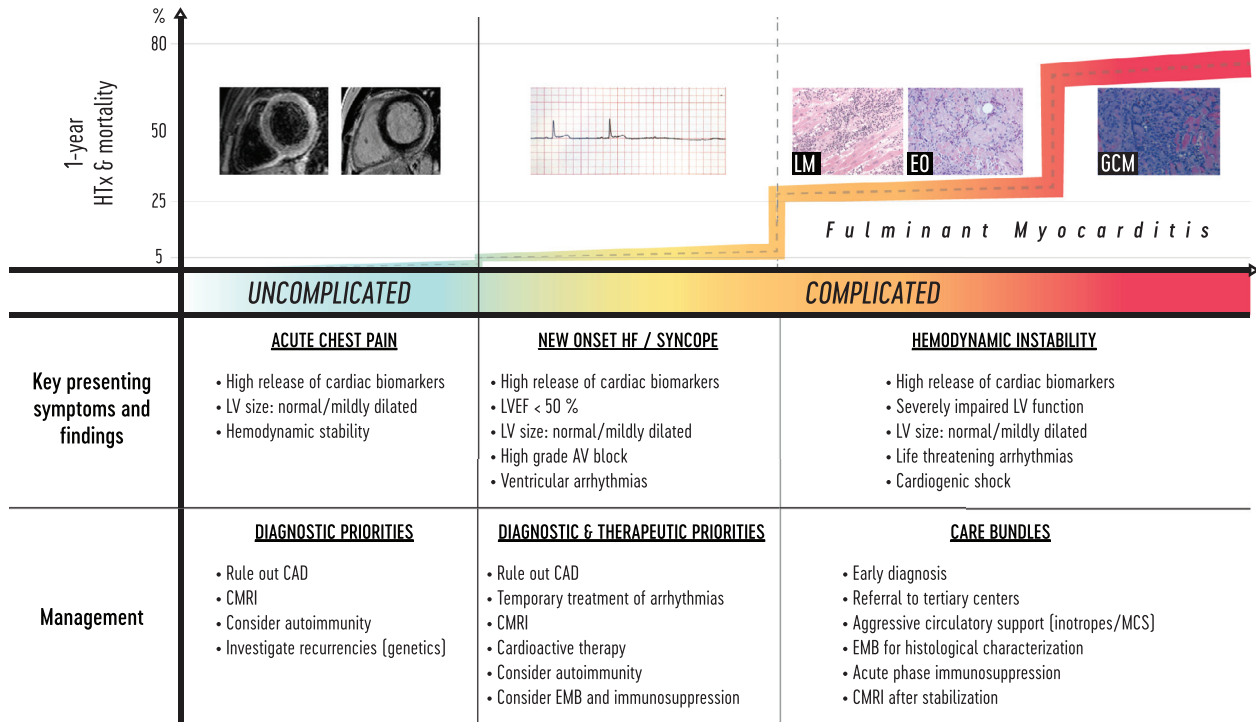


Fig. 3. Acute myocarditis scenarios. The figure stratifies acute myocarditis according to the clinical presentation at admission and its corresponding outcome. Uncomplicated acute myocarditis is characterized by a benign course, with a low 1-year mortality or heart transplant rate. Therefore, a CMRI-based diagnosis is recommended in the absence of complicated features. CMRI images within the box of uncomplicated myocarditis are representative, with short tau inversion recovery (STIR) sequences revealing increased signal intensity suggestive of edema and transmural late gadolinium enhancement (LGE) involving LV basal-lateral and -inferior walls. Complicated acute myocarditis, defined by the presence of either impaired left ventricular function or arrhythmias or hemodynamic instability requiring circulatory support (i.e. fulminant myocarditis), is associated with an increased risk of death and heart transplant at 1 year, which is highest in case of fulminant giant cell myocarditis. Complicated acute myocarditis requires active treatment, including an EMB-based diagnosis for optimal management, aggressive circulatory support when deemed necessary and, eventually, immunosuppression. The EKG shows the presence of a high grade atrioventricular block; on the upper right of the image, representative histological specimens show the subtypes of inflammatory cells that can be found in acute myocarditis: (LM) lymphocytic inflammatory infiltrates, (EO) eosinophilic infiltrates, and (GCM) lymphocytic infiltrates with giant cells. Abbreviations: HTx, heart transplant; LM, lymphocytic myocarditis; EO, eosinophilic myocarditis; GCM, giant cell myocarditis; LV, left ventricular; HF, heart failure; LVEF, left ventricular ejection fraction; AV, atrio ventricular; CAD, coronary artery disease; CMRI, cardiac magnetic resonance imaging; EMB, endomyocardial biopsy; MCS, mechanical circulatory support.

registries are intra-aortic balloon pump (IABP) and venous-arterial extra corporeal membrane oxygenator (VA-ECMO) with peripheral cannulation [20,58]. IABP alone provides only a small increase in cardiac output and may be insufficient to support circulation when profound cardiogenic shock is established. On the other hand, VA-ECMO guarantees a rapid and full cardio-respiratory assistance, with reported survival rates in the setting of FM ranging from 56% to 87% [58–61]. Nevertheless, VA-ECMO alone might increase LV afterload, thus additional LV venting-strategies to prevent LV distension and pulmonary edema may be required [62]. Low-dose inotropes and vasodilators and/or IABP implantation are the most common strategies for reducing afterload. Percutaneous LV assist devices, such as the microaxial pump Impella system (2.5, 5.0 or CP), have been increasingly used in the setting of FM in recent years (Table 1). These devices directly unload the LV, reducing myocardial oxygen consumption, meanwhile lowering LV wall stress and improving subendocardial coronary blood flow. The strategy of combining Impella and VA-ECMO provides adequate circulatory support and could also facilitate myocardial recovery [63]. Indeed, some authors suggested a possible link between LV-overload and inflammatory reaction and demonstrated anti-inflammatory disease-modifying effects mediated by prompt and prolonged Impella support [64]. The use of LV-Impella alone as a bridge to recovery in FM was firstly described in 2003 [65]. The prerequisites of its efficacy are: (1) preserved right ventricle (RV) function, (2) absence of left intraventricular thrombi, that would represent

a risk for systemic embolism, and (3) adequate LV-cavity size, to avoid suction phenomenon [66]. The last prerequisite is of particular concern in FM patients, as they often present with a relatively small LV cavity and thickened walls due to myocardial edema and the recent onset of myocardial damage. In patients with biventricular dysfunction without hypoxia the use of Impella for both LV and RV support has been described [67]. This strategy may be particularly useful in those that may not be able to tolerate the degree of anticoagulation required for ECMO. It must be remembered that in the much more frequent setting of cardiogenic shock associated with acute coronary syndrome, there are no data showing the superiority of a single MCS device over another or over medical therapy alone [68]. Furthermore, large observational studies, small randomized studies, and meta-analyses have confirmed no benefit in terms of survival from pulmonary artery catheters (PACs) in critically ill patients. Though, we consider PAC useful in almost all severe patients presenting with cardiogenic shock, especially those with rapidly progressive low cardiac output syndrome, where identification of the exact timing for escalating treatment towards MCS is crucial. PAC may also provide key information during MCS treatment, i.e. LV filling pressure monitoring to guide eventual LV unloading strategies. In the absence of recommended protocols regarding temporary MCS use and escalation, their utilization should be tailored to the single case according to the experience of the center.

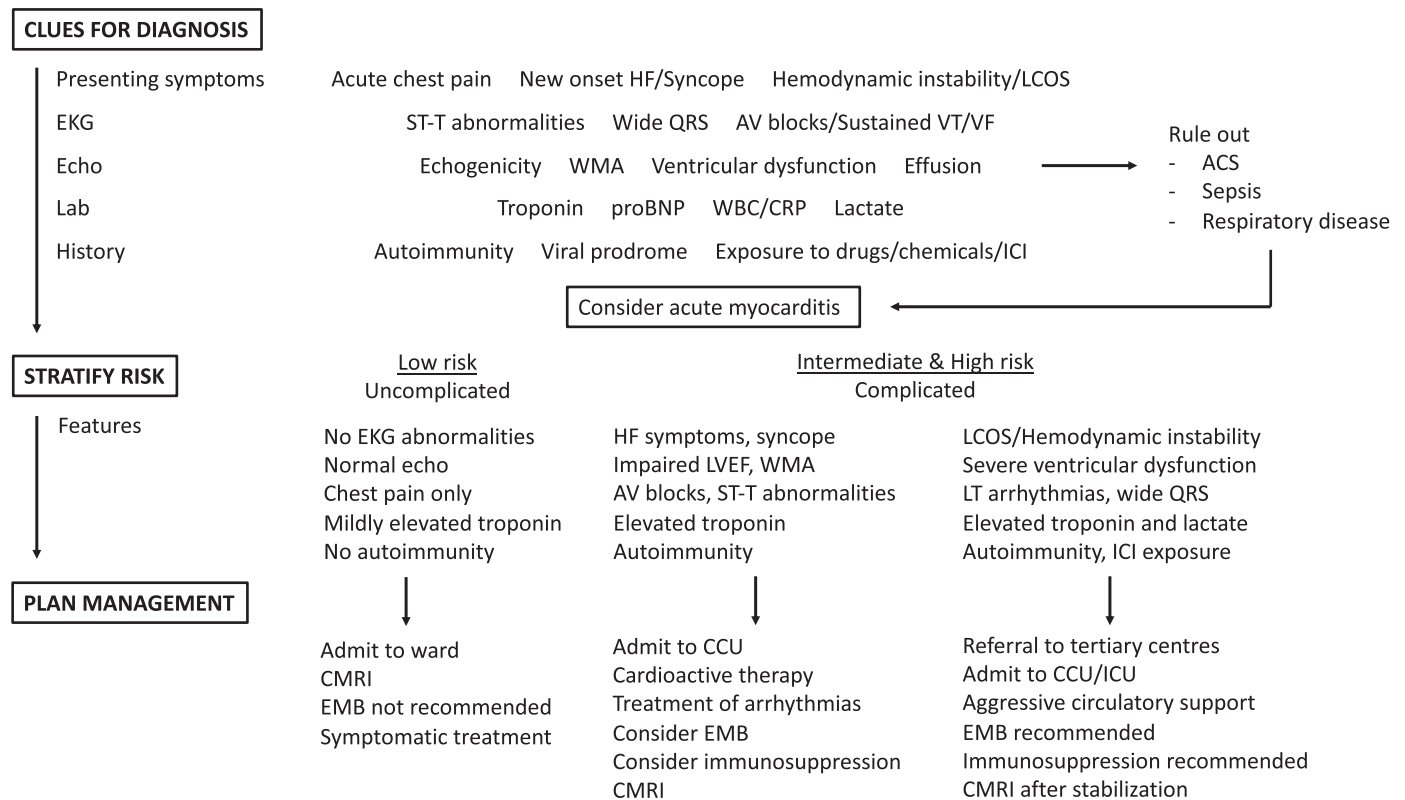


Fig. 4. A risk-based approach for clinically suspected acute myocarditis currently in use in our institution. As explained in the text, several clues may lead clinicians to suspect a diagnosis of acute myocarditis. Once clinicians have ruled out differentials, a risk-based approach must be followed to properly manage acute myocarditis. Low risk uncomplicated acute myocarditis deserves admission to ward, CMRI-based diagnosis and symptomatic treatment. Complicated acute myocarditis with features of high risk (e.g. impaired left ventricular function, wide QRS, arrhythmias, hemodynamic instability) requires admission to CCU/ICU and bundles of care, including an EMB-based diagnosis, aggressive circulatory support and immunosuppression in selected cases. Abbreviations: HF heart failure; LCOS, low output cardiac syndrome; AV, atrioventricular; VT, ventricular tachycardia; VF, ventricular fibrillation; WMA, wall motion abnormalities; ACS, acute coronary syndrome; proBNP, pro b-type natriuretic peptide; WBC, white blood cells; CRP, C-reactive protein; ICI, immune checkpoint inhibitors; LVEF, left ventricular ejection fraction; LT, life threatening; CMRI, cardiac magnetic resonance imaging; EMB, endomyocardial biopsy; CCU, coronary care unit; ICU, intensive care unit.

New evidence from pediatric registries on acute myocarditis

The diagnosis of AM in the pediatric population is often clinically based, since EMB is perceived as an high risk procedure, and CMRI usually requires adequate deep sedation, especially in young children [69]. A recent registry of all Finnish children (<16 years) hospitalized for clinically diagnosed AM from 2004 to 2014 (n=213) estimated an incidence of AM of 1.95/100,000 patients/year [70]. The median age was 14 years, 77% were boys and it was observed that the incidence of AM increased significantly after 7 years of age. A viral etiology (that means isolation of a virus during hospitalization) was identified only in 11% of patients; these were mainly upper respiratory infections with the most frequent virus identified being influenza (in 1.9% of patients). The in-hospital rate of death or HTx was 1.9%, in line with the estimates derived from the adult population. Furthermore, the rate of temporary MCS use was 1.4%, and 6.1% of the patients were treated in intensive care unit [70]. In a German registry including 195 children diagnosed with AM from 2013 to 2016, all presenting with HF, the median age was 13 years and 66.2% were male. The need for MCS was as high as 14%, in-hospital death or HTx rate was 7.7%, and the overall mortality rate was 4.6% with a median follow up of 8 months [61]. The need for MCS was more common in infants (0-2 years) compared with other ages, with the median age of patients receiving MCS being 1.5 years. Of note, in infants, enteroviruses, such as coxsackie virus, are more common than in adults [71]. These viruses are qualified as cardiotropic, i.e. able to cause direct myocardial injury [72], thus the search for viruses in

infants may guide specific antiviral therapy [73], even if its efficacy in adults with AM remains unproven. Recent reports have also suggested that arrhythmogenic cardiomyopathies in children may present clinically as an AM and are sometimes triggered by viral infections [74–76], highlighting the importance of an accurate diagnosis. Based on these observations, genetic tests for mutations of genes related to arrhythmogenic cardiomyopathy may be considered in patients with recurrent AM or in patients with AM and personal history of VA or family history of sudden cardiac death [74,76].

Risk-based approach to patients with suspected acute myocarditis

Traditionally, the histopathologic demonstration of myocarditis has been considered necessary for the diagnosis of AM, since the accuracy of noninvasive tools was poor [4,32]. However, pathological diagnosis was rarely pursued in clinical practice, due to the invasiveness, low sensitivity and the perceived limited incremental value of EMB in what was considered in most cases a self-limiting and benign condition. The combination of measurement of hs-troponin levels and CMRI has made AM diagnosis possible with sufficient accuracy for non-complicated forms [13]. Contrarily, in patients with complicated AM, and especially in those presenting with FM, highly coordinated care is required to minimize morbidity and mortality, as illustrated in Fig. 3. Critical elements of care for these patients include early recognition, temporary MCS when necessary, rapid referral to tertiary centers (hub centers), histologi-

cal characterization by EMB and, when indicated, immunosuppression [2,5,59]. Of note, electroanatomic mapping-guided EMB is an emerging and promising technique [77]. By identifying regions corresponding to areas of diseased or replaced myocardium, it may guide a site for biopsy, finally improving the differential diagnosis with other cardiomyopathies or the sensitivity of EMB [78-80]. Due to the significant increase in cost and duration of electroanatomic mapping-guided EMB compared with traditional fluoroscopic guided EMB, it is mainly performed before ventricular ablation to differentiate the etiology of VA [78,80].

A stepwise, risk-based approach to the diagnosis of suspected myocarditis is represented in Fig. 4. In summary, CMRI should be performed in all adult patients, except in those in critical conditions, or with usual contraindications. As stated in the joint statement from the American Heart Association (AHA), American College of Cardiology and ESC in 2007, further confirmed and expanded in 2016, EMB is highly recommended in specific scenarios where it may be fundamental in clarifying the cause of disease and in guiding therapy [5,17,20,81], i.e. high-risk forms like FM, AM with rapidly progressing overt HF due to worsening LV dysfunction and/or sustained arrhythmias [5,17]. Moreover, EMB should be considered when history or available data suggest specific etiologies (e.g. use of ICI, suspected autoimmune disorder, peripheral eosinophilia) that may be associated with severe forms of myocarditis that require specific treatment. Hs-troponin levels contribute to clinical suspicion and diagnosis. Absolute troponin values and their trend are only roughly related with AM severity and prognosis. While high or very high values should be looked as a marker of high risk, the opposite is not true with moderately or only mildly increased values [82]. An early rise and steep decline of hs-troponin is generally associated with the resolution or at least attenuation of the inflammatory process and with a good prognosis; while recurrently or persistently abnormal hs-troponin values, even if mildly increased, may suggest relapsing or ongoing myocardial damage, as may happen in patients with AM associated with systemic inflammatory disorders or cardiac sarcoidosis. The latter scenario could lead to further investigations, including thoracic computed tomography or ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography [83] for detection of systemic sarcoidosis, or EMB to identify uncommon forms like eosinophilic myocarditis. Finally, it must be remembered that in the setting of cardiogenic shock with elevated troponin levels and decreased LVEF, other differential diagnoses beyond the acute coronary syndromes should be considered, such as septic shock, thiamine deficit [84], systemic capillary leak syndrome [85], antiphospholipid syndrome [86], and pheochromocytoma [87]. EMB may be essential in clarifying the diagnosis and distinguishing myocarditis from alternative diagnoses.

Beyond supportive measures, even though not standardized, early administration of immunosuppressive agents is the cornerstone of treatment for eosinophilic and GCM [22,23], cardiac sarcoidosis [88], and, regardless of the underlying histology, for myocarditis related to systemic autoimmune diseases and ICI [43]. As reported series have described spontaneous recovery with supportive therapy alone, immunosuppression is largely debated in the setting of virus-triggered lymphocytic myocarditis. We consider initiation of immunosuppressive treatment (e.g. pulse steroid therapy) in all cases presenting with complicated AM (Figs. 3 and 4), especially those presenting with FM [19,89], where early immunosuppression may be crucial and where the risk of death or HTx has been demonstrated to be high regardless of the underlying histology [20]. We can consider cessation or implementation of a tailored immunosuppression after final histopathological characterization, eventual virus detection and in the evidence of systemic autoimmunity. In line with this management, the AHA recently stated that if a high suspicion for immune-mediated FM exists, 1 g

methylprednisolone may be administered urgently, before biopsy-confirmed diagnosis or further diagnostic testing [5]. Intravenous immunoglobulin is also frequently used in pediatric lymphocytic myocarditis, but the experience in adults is limited. Large prospective studies are warranted to address the role of immunosuppression in acute and FM in order to provide evidence for standardized treatment regimens.

Future directions

Significant improvements in the diagnosis and supportive care for patients with AM have occurred over the last 20-30 years. Nonetheless, the prognosis of the worst forms of AM, namely FM, remains dismal despite the broadened use of temporary MCS. Given the potential increased prevalence of AM due to expanding indications for ICIs, new studies are mandated to help understand the pathobiology of disease. In particular, a better understanding of how genetics influence the development and prognosis of AM would be beneficial. Furthermore, the relationship between AM, viral infection and autoimmunity requires further investigation if tailored therapies are to be developed.

Disclosures

EDA is a consultant for Abbott, Abiomed, AstraZenica, Endotronix, Ionis, Medtronic, Novartis, and is on the board of directors of Genstem Therapeutics and shareholder of Rocket Pharmaceuticals. Other Authors have no disclosures.

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