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REVIEW
Educational Papers

Clinical management of acute myocarditis in daily practice: an expert practical view

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Acute Myocarditis (AM) encompasses a broad spectrum of clinical presentations and causes. Despite the recent advances in cardiovascular imaging, pathology, virology, and genetics, specific therapies are still lacking. This collaborative review aims to analyse the current evidence to answer practical questions that physicians may face during the early management of patients presenting with an acute form of the disease, complicated or not. This review analyses current evidence to address practical questions posed by acute cardiovascular physicians during the early management of acute, or potentially, myocarditis. Based on the current literature, this review provides a step-by-step approach to treat AM patients from their admission in the cardiac intensive care unit (CICU) to discharge, by answering 10 clinical questions: Might this patient be suffering from an AM? Should I hospitalize this patient and, if so, where? Which cardiac imaging exam should I perform and what can I learn from it? Is this patient requiring an EMB? What should the non-invasive aetiological work-up be? Is her/his episode of AM of viral, toxic, or other origin? Does this patient need specific treatments or mechanical circulatory support? Is there an indication for guideline-directed medical heart failure treatment? When can the patient be discharged and resume physical activity? Notably, this review highlights the need to build a multidisciplinary response team to address the many diagnostic and therapeutic challenges of AM patients. It also points out the lack of evidence to guide the treatment of these patients.

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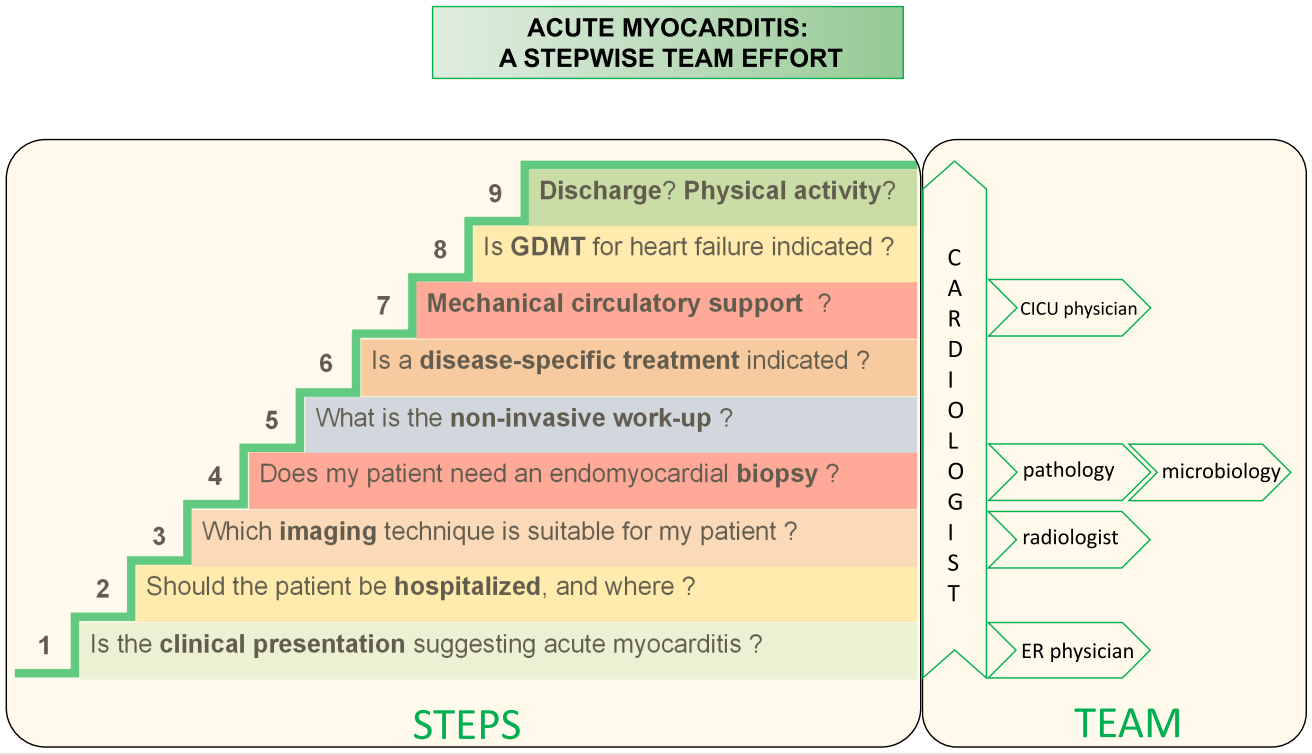
Graphical Abstract



Clinical management of acute myocarditis in daily practice: a stepwise team effort. This central figure illustrates the logical question-and-answer, step-by-step approach used in daily practice.

Keywords Myocarditis • Acute cardiovascular care • Heart failure • Inflammation • Arrhythmias

Introduction

Acute myocarditis (AM) is a growing condition, estimated to affect approximately 1.5 million people worldwide, mostly young men, with a sex ratio of 3/1.[1–3] AM is defined as inflammation of the myocardium and is characterized by a significant heterogeneity of causes and phenotypes, that make the clinical decision process complex in every step of its management.[4–6] While most cases are considered low risk and self-limiting, acute myocarditis still exposes young patients to a 4% risk of all-cause death or heart transplantation at 5 years.[7] Among those patients presenting with impaired left ventricular ejection fraction or ventricular arrhythmias, this rate increases to 16%.[7] Despite significant advancements over the past decade in understanding the disease, its diagnosis, and treatment, acute myocarditis remains a subject of ongoing debate.[6] Early recognition and optimal management might significantly improve patient outcomes, underscoring the need for awareness among the acute cardiovascular care community regarding the available evidence on AM. A recent review provides a comprehensive view of available guidelines.[8] Here, we aim to analyse the current literature to address practical questions that acute cardiovascular care physicians may face during the initial management of patients presenting with acute myocarditis with haemodynamic instability. It provides a step-by-step approach to treat acute myocarditis patients from admission in the cardiac intensive care unit through to discharge, as presented in *Graphical Abstract*.

Step 1—Is my patient suffering an acute myocarditis?

AM encompasses a clinical spectrum, from pauci-symptomatic to fulminant forms. Due to various potential underlying aetiologies, ranging from viral over immunological disorders to drugs, its identification can be particularly challenging, especially in early presenters.[6,9] Given the risk of rapid deterioration and/or severe outcomes, it is imperative for acute cardiovascular care specialists to consider AM in the differential diagnosis, in patients, presenting with STEMI-like symptoms, unexplained acute heart failure, or ventricular arrhythmias (see *Figure 1*). This is especially relevant in children and younger adults[10] due to the higher incidence of AM. Although AM affects men more often than women, it should be noted that women have a higher risk of developing more severe disease forms and have a 2.7-fold increased risk of death or heart transplantation at 10 years.[11,12] In contemporary cohorts of AM, a possible recent infection was found as a trigger (and most often not a cause *per se*) in over 40% of cases.[12] The baseline ECG and altered cardiac biomarkers have variable sensitivity and specificity, further complicating the initial diagnostic process, and should not exclude AM diagnosis when normal.[6,12] Nevertheless, it should be noted that ST modifications are present in more than two-thirds of AM patients, with more than half of AM patients presenting with a STEMI-like presentation.[7] In contrast, patients presenting with severe AM -forms are more likely to have conduction disorders, including left or right bundle

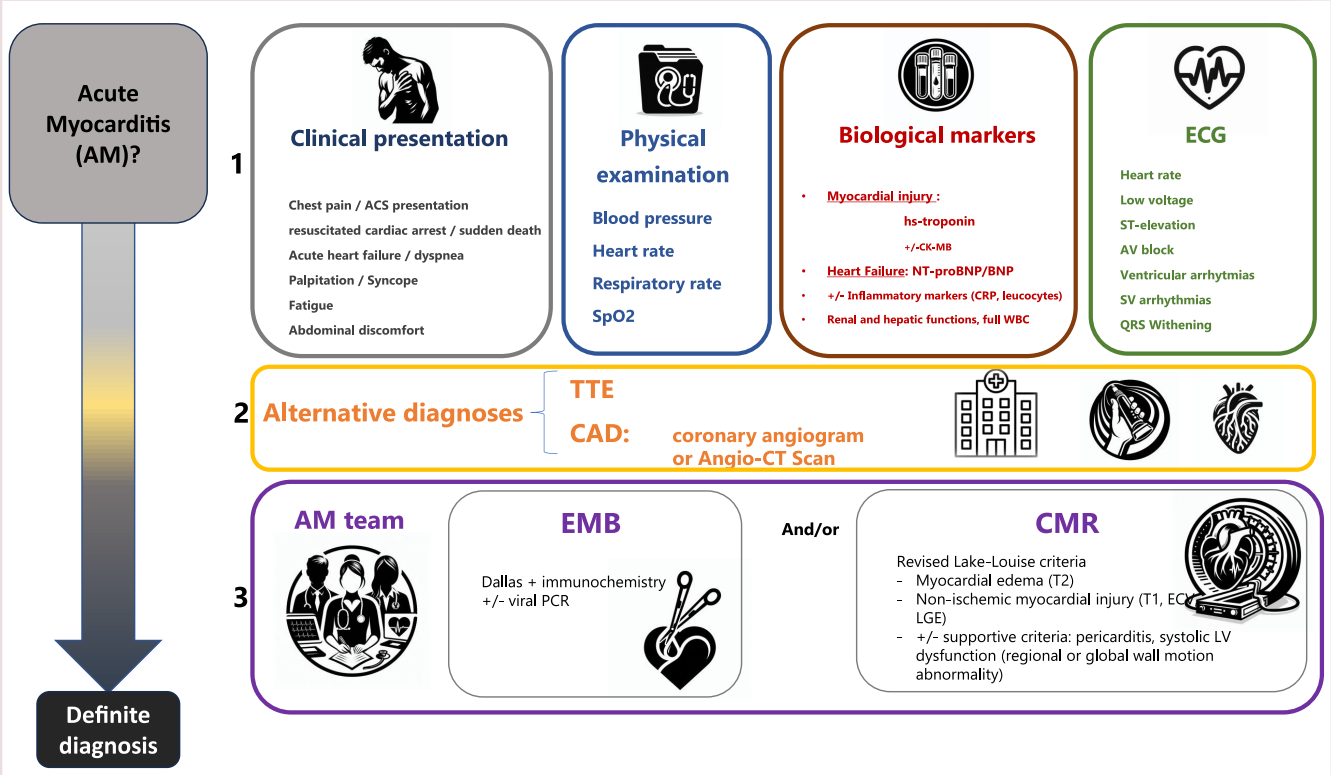


Figure 1 Diagnostic approach. ACS, acute coronary syndrome; AM, acute myocarditis; AV, atrioventricular; CAD, coronary artery disease; CCTA, computed tomography coronary angiography; CICU, cardiac intensive care unit; CMR, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiogram; EMB, endomyocardial biopsy; HF, heart failure; LGE, late gadolinium enhancement; PCR, polymerase chain reaction; TTE, transthoracic echography.

branch or atrioventricular block.[7,13,14] Therefore, high vigilance and a thorough understanding of the diverse presentation forms of AM are essential.

As a result of this heterogeneity, myocarditis has complex definitions and varying terminologies. Historically, it was defined as an inflammatory state of the heart muscle, proven by myocardial histology in accordance with the Dallas Criteria.[15,16] Today, the sensitivity of EMBs increased significantly by performing quantification of the number of immune-stained T cells or macrophages.[4] Most biopsies are performed in patients with fulminant or recurrent forms that represent only 5–10% of the total myocarditis population.[17] For those presenting with a non-fulminant form, cardiac magnetic resonance (CMR) imaging is a valid alternative tool to confirm the diagnosis of myocarditis[18,19] since CMR, using the updated Lake Louise criteria, has the same sensitivity and specificity compared to EMB for the diagnosis of myocarditis. Still, EMBs are strongly advised in those patients with recurrent myocarditis or in the absence of recovery of cardiac dysfunction within the first week of presentation.[4] Hence, patients presenting within the first 3–4 weeks of cardiac symptoms, with either a positive EMB or a CMR in accordance with the updated Lake Louise criteria, are considered as proven acute myocarditis, regardless of the underlying histology or aetiology. In virtue of the limited availability of both EMB and/or CMR in many centres, the diagnosis has several degrees of probability, increasing according to the presence of myocarditis-associated characteristics: case history, patient phenotype, biomarkers, ECG, and finally, the presence of potential causes: viral infection, autoimmune disease, and drugs (*Figure 1*).

Step 2—When should a patient with suspected acute myocarditis be hospitalized and where?

To date, there is no randomized controlled trial evaluating the benefit of hospitalization among patients presenting with uncomplicated forms of myocarditis, nor studies evaluating the benefit of the optimal duration of the hospitalization. Nevertheless, most AM patients in registries are hospitalized. This can be explained by (i) the need to exclude other cardiovascular conditions that may explain the clinical presentation, primarily acute coronary syndrome, (ii) the need to confirm the diagnosis with either an EMB or a CMR and iii) the time to initiate treatment if required, iv) a selection bias, as registries are often being formed with the hospital environment.

Therefore, the '*real life*' question is rather *'What is the severity of the inflammatory response and its related risk for complications which would require monitoring in intensive care?*[9] Indeed, the risk of complications such as AHF/CS, VA, and SCD determines the level of monitoring required

Recently, the Chinese Guidelines on adult fulminant myocarditis recommend the organization of a rapid response team for fulminant myocarditis, considering its rapid progression and high mortality rate, to implement a 'life support-based comprehensive treatment regimen' including mechanical circulatory support and immunomodulatory therapy. In conclusion, patients presenting with acute heart failure, including cardiogenic shock, ventricular arrhythmia, high-degree AV block, or severely impaired left ventricular output, should be hospitalized in a level 3 cardiac CICU (see *Figure 2*).[20] This is explained by the high mortality rate of these patients. This group also includes

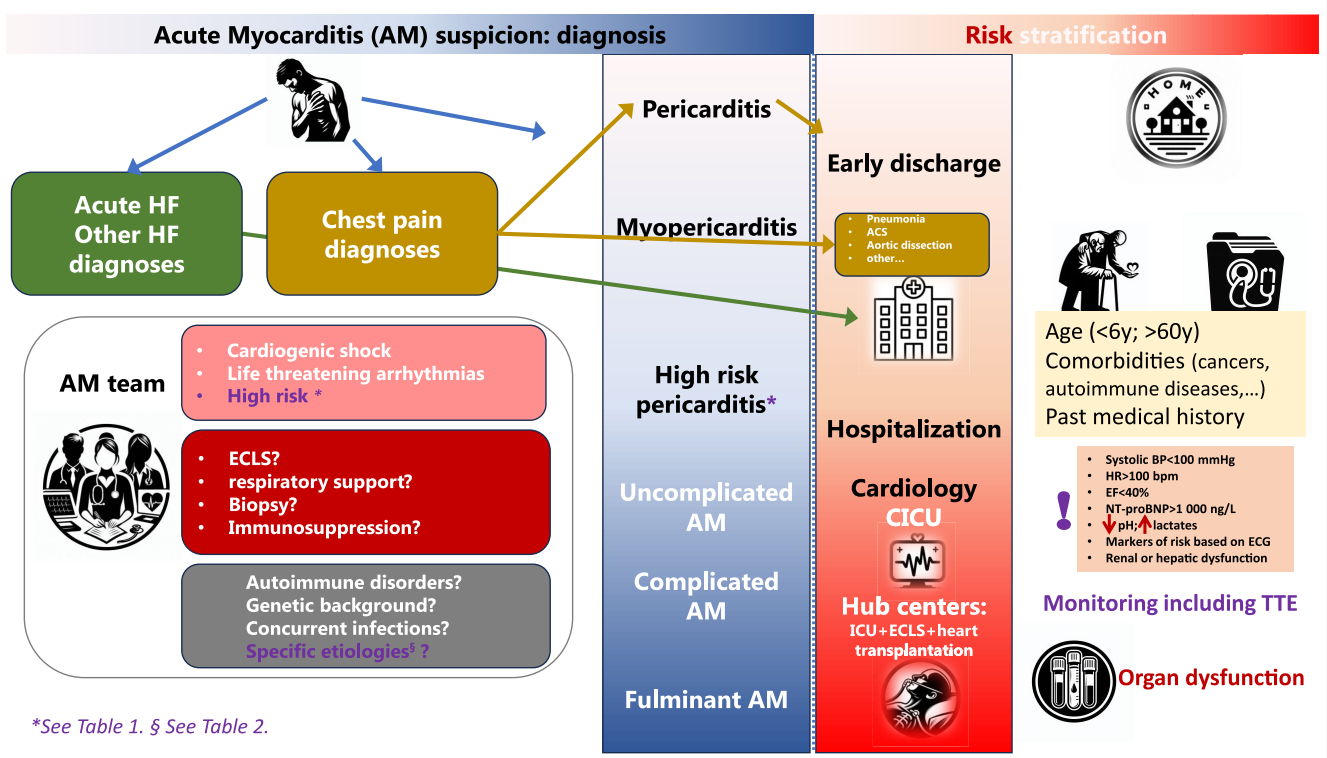


Figure 2 Management of patient admitted for suspected acute myocarditis. ACS, acute coronary syndrome; AM, acute myocarditis; BP, blood pressure; CICU, cardiac intensive care unit; ECG, electrocardiogram; ECLS, Extracorporeal life support; ICU, intensive care unit; HF, heart failure; MCS, mechanical circulatory support; NT-proBNP, N-terminal pro-b-type natriuretic peptide.

patients with fulminant myocarditis, which is defined as acute myocarditis requiring inotropic support or temporary MCS.[21] Whilst there is no data supporting the concept of a multidisciplinary 'response team', providing the best possible care through a 'heart team-like' approach seems essential to optimize care in this potentially unstable patient group. An ideal team would comprise minimally Cardiologists, intensivists, internists/rheumatologists, HF specialists, cardiac surgeons, infectiologists, and other specialists when needed, with the support of nurses qualified as well as other paramedics including psychologists.

Patients presenting with a STEMI-like ECG and/or elevated high-sensitivity cardiac troponin levels (hs-cTn) and/or mildly impaired LV function should be hospitalized in a level-2 cardiac CICU. The fast and unequivocal exclusion of underlying coronary artery disease is indeed the first step in this patient group, warranting a 24/7 coronary angiography service. In a recent adult AM-patient cohort, 40–50% underwent a coronary angiogram in young adults. Importantly, we have to keep in mind that up to one-third of patients with AMI and normal coronary arteries may get a diagnosis of AM based on systematic CMR assessment.[22] These results might depend on the age of patients and local facilities. The 2021 ESC Heart Failure recommendations suggest a minimum duration of hospitalization of 48 h for AM patients with impaired left ventricular function and/or arrhythmias, particularly in patients with elevated hs-cTn. While there is no dedicated data from dedicated studies to support this recommendation, monitoring these patients in a level-2 ICU seems reasonable (see for definitions and organizational considerations[21]). Other guidelines advocate for at least 48-h hospitalization of all AM patients, even in the absence of haemodynamic impairment or HF symptoms. Recently, Japanese guidelines have recommended hospitalization for monitoring for at least 48 h all patients, even for those with stable haemodynamics and no HF symptoms (IIa, level C),

Patients with low levels of inflammatory markers and hs-cTn, preserved cardiac function, and a normal ECG in the absence of arrhythmias could be managed in a regular cardiology ward (level 1) or even discharged after a short observation. This is supported by the Lombardy registry, highlighting the absence of events (5-year cardiac death and heart transplant rate) in patients without cardiac dysfunction (LVEF < 50% on first echocardiogram), ventricular arrhythmias, acute HF, atrial arrhythmia, or unstable haemodynamics.[7]

Hospitalization of suspected AM patients should be considered on a case-by-case base, depending on risk factors and personal history. Finally, psychosocial context, including the patient's social support and mental capacities, should be weighted. Close collaboration between emergency department physicians, cardiologists, intensivists, and acute cardiac care specialists is crucial for optimizing outcomes in patients with suspected myocarditis. *Table 1* overviews these recommendations.

Step 3—What cardiac imaging should be performed and what can one learn from it?

Cardiac imaging plays a crucial role in the diagnosis and management of myocarditis.[23] Echocardiography, CMR, and coronary angiography (invasive or non-invasive) stand as indispensable tools, each offering unique insights into myocardial pathology.[24]

In early clinical management, transthoracic echocardiography (TTE) serves as a frontline diagnostic modality, revealing hallmark indicators such as left ventricular (LV) systolic and diastolic dysfunctions, regional wall motion abnormalities, and pericardial effusion. Moreover, TTE should be offered to all patients with a clinical suspicion of myocarditis at presentation and during hospitalization, especially in the case of haemodynamic deterioration.[25] Common findings on a TTE in a patient

Table 1 Criteria for hospitalization of patients with suspected or proven acute myocarditis

Hospitalization Criteria
Hospitalization in Level 3 ICU/ICCU if one of these criteria is present:
(1) Acute Heart failure symptoms or haemodynamic instability/cardiogenic shock
(2) Ventricular arrhythmias or high-degree AV Block, new LBBB, Q-waves
(3) High-risk features on TTE = left ventricular dysfunction <30%, large or significant new onset pericardial effusion, especially if suspicion of tamponade)
(4) Increased lactate levels
Hospitalization in Level 2 ICU/ICCU if one of these criteria is present:
Symptomatic patients with either:
(1) modification of the ECG or increased biomarkers: hs-cTn or increased BNP and/or NT-proBNP, hs-CRP
(2) Diagnostic uncertainty or complexity, suspected specific aetiology (clinical picture, specific treatments)
(3) Need for specialized monitoring or interventions
Hospitalization in Level 1 ICU/ICCU or cardiology ward if none of these criteria are met

with AM—however aspecific for its diagnosis—include LV systolic dysfunction, diastolic dysfunction, regional wall motion abnormalities, especially with hypokinesia of the inferior and lateral walls, altered tissue Doppler, change in the echogenicity of the myocardium and pericardial effusion.[26,27] Low values of global longitudinal strain and subepicardial strain assessed by speckle tracking analysis have been shown to be associated with scar and predictors of functional outcome and ventricular arrhythmias in patients with acute myocarditis,[28] but are more advanced and often non-applicable in the critically ill. Notably, the presence of a thickened septum in a hypokinetic ventricle aids in differentiating acute from fulminant myocarditis.[26,27,29]

Moreover, computed tomography coronary angiography (CCTA) or conventional coronary angiography could be indicated in the early management to rule out acute coronary syndrome (ACS) in patients at low-pre-test probability or suspected of differential diagnoses such as takotsubo syndrome, pulmonary embolism (PE), or aortic dissection (triple CT-chest for these last cases). CCTA provides detailed imaging of cardiac structures, while conventional coronary angiography remains the gold standard for evaluating coronary artery patency in suspected ACS cases. In recent years, spectral cardiac computed tomography (CT) has emerged as a valuable tool for simultaneously excluding coronary syndrome and confirming AM diagnosis. Integrating these modalities enhances diagnostic precision and ensures a comprehensive assessment of patients with myocarditis-like symptoms, guiding appropriate clinical management strategies. Innovative approaches, such as late iodine enhancement, show promise.[30]

CMR imaging plays a pivotal role in the non-invasive diagnosis of myocarditis, providing detailed insights into myocardial inflammation and injury.[31] CMR remains mandatory as the gold standard but is not always available depending on local facilities. Utilizing the updated 2018 Lake Louise Criteria, CMR has significantly improved the diagnostic accuracy for acute myocarditis. The inclusion of both T1-based and T2-based parameters has, indeed, enhanced the sensitivity and specificity of CMR in detecting myocardial inflammation and injury. Specifically, native T1 mapping and late gadolinium enhancement (LGE) identify myocardial fibrosis and non-ischaemic injury patterns, while increased extracellular volume fraction (ECV) quantifies diffuse myocardial fibrosis and oedema. Additionally, T2 mapping and T2-weighted imaging effectively detect myocardial oedema, a key feature of active inflammation. Prior studies indicate that the sensitivity of CMR using these criteria ranges from 74% to 88%, while specificity ranges from 86% to 92%, providing a robust non-invasive tool for the accurate and early diagnosis of acute myocarditis.[18] The ideal timing for CMR is still a matter of debate but is probably not too early (<3 days) and not too late (>2weeks). In addition, the spatial distribution of late gadolinium enhancement (LGE) identified through CMR serves as an independent prognostic indicator for mortality.[32] Iterative assessments, particularly at 6 and 12 months, provide valuable insights into disease progression and response to treatment.[27,33] Thus, this multiparametric approach not only aids in diagnosis but also guides therapeutic decision-making and prognostic assessment.[34]

Finally, Positron Emission Tomography (PET) scanning is an emerging tool in the diagnosis of acute myocarditis, especially for complex or rare causes. Obviously, this is challenging to obtain in an acute care setting. PET imaging, particularly when combined with 18F-fluorodeoxyglucose (18F-FDG), enables the visualization of inflammation and metabolic activity within the myocardium. PET scans can reveal patterns of myocardial inflammation that are not always evident in conventional imaging methods. Besides 18F-FDG, other tracers such as 68Ga-DOTATATE[35] and 11C-methionine have also shown promise in this indication. 68Ga-DOTATATE targets somatostatin receptors, which are overexpressed in inflammatory cells, providing a complementary approach to detecting myocardial inflammation. Similarly, 11C-methionine is used to highlight protein synthesis in inflammatory and damaged myocardial tissues.[36] These tracers, combined with the high sensitivity and specificity of PET, may enhance the accuracy of diagnosing acute myocarditis.

Step 4—Does my patient require an EMB? Will it change management?

The endomyocardial biopsy (EMB) is still the golden standard for a definitive diagnosis of myocarditis and remains to date the only method exploring the underlying histotype: identifying a lymphocytic, eosinophilic, giant cell myocarditis, or other infiltrates, guides the treatment in specific directions.[37] Quantification of CD3-, CD4-, CD8- or CD45-staining lymphocytes and CD68-macrophages per square millimetre is advised to increase the sensitivity of diagnosis myocarditis. However, EMB is not performed systematically, depending on local resources and habits. General recommendations for its absolute indication include recurrent myocarditis and persistent cardiac dysfunction upon AM. Heterogeneous practices are reported worldwide, despite international consensus and guidelines.[25] In the acute setting, the ESC-HFA- and ACCF/AHA guidelines recommend EMB in the following scenarios: (i) Persistent de-novo heart failure within less than 2 weeks with the abnormal or dilated left ventricle and impaired haemodynamics, or within 2–12 weeks if associated with ventricular arrhythmias, high-grade AV block (II or III degrees), or failure to respond to usual therapy within 1–2 weeks; (ii) Acute myocarditis associated with peripheral eosinophilia; (iii) Acute myocarditis with persistent or relapsing release of myocardial necrosis biomarkers, particularly if related to an autoimmune disorder or ventricular block; (iv) myocarditis

in the setting of immune checkpoint inhibitor therapy, where appropriate diagnosis has implications for further cancer therapy.[25] Hence, in the acute setting, EMB is preferred for patients with a fulminant presentation or in AM with impaired LVEF or specific (infiltrative) aetiologies; (v) recurrent myocarditis.

In a multicentre registry of fulminant myocarditis, Huang *et al.* recently reported that early EMB was associated with a reduction of all-cause death and transplantation when compared with patients undergoing late EMB (70% vs. 49%, $P = 0.004$).[38] After propensity score weighting, the early EMB group still significantly differed from the delayed EMB group in terms of survival free of Heart Tx/LVAD (63% vs. 40%, $P = 0.021$). It should be noted that almost half of the population included in this study did not undergo any EMB. For these patients, there was no reduction of the primary outcomes compared with patients undergoing EMB, raising the presence of potential cofounders and leading to the selection of patients that may benefit from early EMB.

EMB is the only exploration that can provide a virologic status of the myocardium using immunohistochemistry and polymerase chain reaction (PCR) analysis[39] (ref). New techniques including next-generation sequencing (NGS) have emerged as pivotal in the analysis of myocardial biopsies. NGS allows for comprehensive genetic profiling, facilitating the identification of viral genomes, bacterial infections, and other pathogenic factors that conventional methods might miss. This advanced sequencing technology provides high-throughput data with unprecedented accuracy and depth, enabling a better understanding of the molecular mechanisms underlying myocarditis.[40,41] By pinpointing specific pathogens and genetic variations, NGS may significantly enhance diagnostic precision. For optimal accuracy and precise immunohistology and molecular evaluation, at least three–four samples are classically required.[5]

When decided, EMB should be performed by trained teams to limit the risk of complications. Most often, EMBs are performed in RV. There is no strong data supporting the left ventricular EMB over the right ventricular EMB, while biventricular EMB may provide the best diagnostic and prognostic accuracy. Interestingly, the latest ESC guidelines on managing ventricular arrhythmias and preventing sudden cardiac death (SCD) recommend a novel approach using mapping-guided biopsy to diagnose patients with focal myocardial involvement as seen in CMR.[42] Endocardial electroanatomic mapping can be beneficial for targeted EMB, especially in suspected cardiac sarcoidosis or giant cell myocarditis cases.[43]

The complication rate for EMB is generally low, with major complications occurring in less than 1% of cases in high-volume centres.[44] Nevertheless, a recent monocentric registry including patients with fulminant myocarditis supported by V-A ECLS reported a much higher rate of complications, including tamponade requiring emergency pericardiocentesis, in up to 29% of patients after endomyocardial biopsy, highlighting the increased risk in this precarious population on therapeutic anticoagulation. In this small cohort, the rate of biopsy-related treatment modifications was 13%, leading to patients' recovery in only 4%.[39] This advocates better evaluate the role of EMB in AM and improve techniques that can identify the underlying cause.

Step 5—What is the non-invasive aetiological work-up in acute myocarditis?

Anamnestic clues can steer towards specific aetiologies. It is suggested to check for recent respiratory infections, systemic inflammatory conditions, previous myocarditis, allergies, asthma, travels (i.e. dengue viruses), but also illicit drugs, drugs including clozapine and anticancer therapies, vaccine, food (e.g. raw meat consumption), and family history of myocarditis, cardiomyopathy, and sudden cardiac death (e.g. myocarditis with genetic background).

Nasopharyngeal swab polymerase chain reaction can rule out SARS-CoV-2 and other respiratory viruses, such as H1N1 influenza, in patients with recent or ongoing respiratory symptoms or fever, and are recommended to add available specific antiviral treatments. Suggested *laboratory tests* for identification of specific etiologies include differential white blood count (e.g. eosinophil count), C-reactive protein, and CK. First-line *autoimmunity screening* can be performed if an autoimmune cause is suspected (especially in young and middle-aged women). This should include antinuclear antibody and extractable nuclear antigen tests. *Serology* for toxoplasma, cytomegalovirus, borrelia species, dengue viruses, and toxocara can be requested. In selected cases, especially in the paediatric population and patients with immunosuppressed status, viral genome search for viruses like cytomegalovirus and parvovirus B19 is of added value.

When performed, EMB[27,45] can identify specific forms (e.g. giant cell myocarditis, eosinophilic myocarditis, and cardiac sarcoidosis) that might benefit from specific immunosuppressive agents. Viral genome can be searched, in particular in the paediatric population or immunosuppressed individuals to identify virus-induced myocarditis caused by specific cardiotropic cytotoxic viruses such as enteroviruses and adenoviruses since immunosuppression is debated in these cases.[5,46]

Genetic testing might be considered in patients with previous myocarditis, family history of myocarditis, cardiomyopathies, sudden cardiac death, ring-like extension of fibrosis or septal fibrosis on cardiac magnetic resonance imaging, or in those ones with ventricular arrhythmic burden,[47,48] and probably in specific ECG presentation, VA and/or RV abnormalities.[29,49]

More details on common specific aetiologies and investigations to consider are presented in *Table 2*.

Step 6—Does my patient with acute myocarditis need a specific treatment?

Randomized trials evaluating specific therapies, including immunosuppressive, targeted, or antiviral therapies, among patients presenting with myocarditis are lacking in the *acute* setting. Several trials are presently going on, as presented shortly in *Table 3*. In fact, the available evidence is based on RCTs focusing on inflammatory cardiomyopathies and does not support the routine use of immunosuppressive therapy among virus-negative patients; thus, decision-making is based on expert consensus. This advocates the need for a multidisciplinary team to treat these patients, especially those with a complicated presentation.

As reported in two recent registries including all types of AM and fulminant myocarditis, the evaluation of both the severity of the disease (impaired LVEF and/or arrhythmic—haemodynamic instability) and the identification of a suspected mechanism should guide the therapeutic decision to initiate specific treatments in a timely fashion.[50] In daily practice, *early* administration of immunosuppressive or targeted therapies is usually not considered among patients with an uncomplicated form of myocarditis, regardless of the aetiology.[7,27] Since most patients presenting with fulminant myocarditis can recover,[7,27] acute HF therapies, including inotropes and if needed temporary mechanical circulatory support, should be considered to bridge these patients towards recovery and in case of lack of recovery to LVAD or heart transplantation.[51,52]

Observational registries and case reports report the use of corticosteroids among patients with complicated AM and fulminant myocarditis despite unknown myocardial viral replication (i.e. without EMB) and histology (ref). It remains, however, unclear whether such a strategy is beneficial or even potentially harmful. Although the benefit of immunosuppressive therapy has never been demonstrated in the acute setting among patients with virus-negative lymphocytic myocarditis, the TIMIC study revealed that treatment with prednisone and azathioprine led to an improvement in left ventricular ejection fraction and a decrease in left ventricular volumes compared to placebo among selected virus-negative patients with inflammatory cardiomyopathy as

Table 2 Investigations to screen the most common aetiologies of acute myocarditis

	Common specific aetiological agents	consider the following diagnostic tools
Infectious aetiologies		
Virus-triggered myocarditis (likely immune-mediated)	Influenza[a] A, B viruses, coronavirus subtypes (including SARS-cov-2[a]), other respiratory viruses[73]	Search for viral genomes on nasopharyngeal swab (PCR)
Virus mediated-myocarditis	Adenovirus, enteroviruses (including coxsackie)	PCR/RT-PCR for viral genomes on nasopharyngeal swab, blood and/or myocardial biopsy (if available)
Virus-induced myocarditis (likely with immune component)	PVB19, HIV (seroconversion), CMV, HHV-6, and DENV	Serology, search for genome in the blood (for PVB19, CMV in the myocardium if available)
Bacterial associated myocarditis	Borrelia burgdorferi, Campylobacter jejuni, Salmonella spp.	Serology, ECG (advanced AV block), stool culture (Campylobacter, Salmonella), and anamnestic clues
Myocarditis associated with parasitic infections	Toxacara canis, toxoplasma	Serology, whole blood count (eosinophilia—toxacara)
Primary autoimmune/inflammatory aetiologies		
Myocarditis associated with systemic or organ-specific autoimmune disorders	Systemic lupus erythematosus, eosinophilic granulomatosis with polyangiitis, vasculitis, systemic sclerosis, hypereosinophilic Syndrome, inflammatory bowel disease, systemic sarcoidosis	Antinuclear antibody and ANCA, CRP, whole blood count (i.e. eosinophilia) search for other extracardiac signs (i.e. Raynaud sign, asthma), in selected cases: CT chest scan, FDG-PET (sarcoidosis, vasculitis)
Idiopathic myocarditis with autoimmune aetiology	Giant cell myocarditis, idiopathic eosinophilic myocarditis, isolated cardiac sarcoidosis	Endomyocardial biopsy, whole blood count
Other aetiologies		
Myocarditis with genetic background	Pathogenic or likely pathogenic gene variants (i.e. *DSP, PKP2, TTN*),[48,49] Dystrophinopaties	Genetic testings,[47] anamnestic clues (previous myocarditis, family history of myocarditis, cardiomyopathies, sudden cardiac death), CK
Allergic and drug-associated myocarditis	ICI (i.e. nivolumab, pembrolizumab, combination with ipilimumab),[74] vaccines (i.e. Antii-SARS-cov-2, smallpox),[74] clozapine, carbamazepine, minocycline[24]	Anamnestic clues, ECG (advanced AV block, VA for ICI), CK (in ICI-associate forms)
Toxic myocarditis	various drugs (i.e. cocaine)	drug testing

[a]Direct involvement remains debated.

diagnosed by increased cardiac inflammation along cardiomyocyte necrosis.[53] The lack of robust data explains the absence of clear recommendations on the use of corticosteroids or immunosuppression in lymphocytic myocarditis and should be, therefore, considered as a therapeutic approach based on expert opinion. Some recent data support safety and efficacy,[54] whereas other works are not so promising.[55] Anyway, the level of evidence remains low until now, and the MYTHS trial will address specifically this question (NCT05150704, see *Table 3*). Finally, there is also no strong evidence to support the use of antiviral drugs in the treatment of AM. However, specific cases of herpes or Epstein-Barr virus infections may qualify for treatment with acyclovir or ganciclovir.[53] In addition, the use of Intravenous zanamivir or oral oseltamivir among patients with influenza-related myocarditis has been reported and may be associated with improved outcomes.

The fact that the use of immunosuppressive drugs, especially corticosteroids, in an early phase overall shows very heterogeneous results, can in part be explained by the—still actual—lack of understanding of the excessive organ-specific inflammatory response by the immune system, even if the initial trigger has long disappeared. Indeed, it has been shown, e.g. that in the majority of patients with acute viral myocarditis, the organ-specific damage occurs several days after the viremic phase of the initial infection.[56] Furthermore, close attention is warranted in patients with fulminant viral myocarditis, caused by, e.g. Parvovirus B19 or Coxsackieviruses, which normally cause very mild symptoms, e.g. upper respiratory tract infection, fatigue, or gastro-enteritis. Why a specific subset of patients develops potentially life-threatening myocarditis remains elusive but is linked to the huge complexity of the immune response. It seems hence understandable that corticosteroids are not a one-size-fits-all.[45,57] On the other hand, when a patient develops ICI-related myocarditis,[29] it is the interference of the ICI with the immune system itself that causes the organ-specific damage, which is probably a deeply different pathophysiology. Therefore, it makes sense that 'cooling down' the adverse inflammatory response in these patients is mandatory.[58]

Indeed, patients with specific forms of myocarditis that may benefit from early immunosuppressive therapy should be identified during the acute phase. These include mostly eosinophilic, ICI-induced, and giant cell myocarditis (GCM).

An observational registry reports that the vast majority of patients presenting with eosinophilic myocarditis were treated by i.v. corticosteroids, regardless of the aetiology of the myocarditis. In this population, the eosinophils-associated risk of RV or LV thrombus may also require the administration of parenteral anticoagulants.

Patients with known autoimmune disorders and severe presentation may benefit from immunosuppressive therapy, with i.v corticosteroids along with other immune-suppressive/immune-modulatory drugs pending on the underlying immune disorder. In this population at higher risk of GCM, early EMB and careful monitoring of the associated risk of

Table 3 Clinical trials presently ongoing on treatments for acute myocarditis

CT number	ACRONYM	Name	Status	Location	Type	Design	Phase	Population	Inclusion criteria	Exclusion criteria	Experimental arm	Primary enpoint
NCT05150704	MYTHS	Myocarditis Therapy with Steroids	Recruiting	USA	Interventional	Multi-centre, international	3	288	Age 18–69 years, AHF presentation, LVEF < 41% + LVEDD < 56 mm, Troponin > 3URL, Onset of symptoms < 3weeks, Randomization < 120 h after admission, Exclusion of CAD	Knowm AI disease, Already on corticosteroid therapy, CI to corticosteroids, Hypereosinophilia, AM associated with immune checkpoint inhibitor agents, Previous known cardiac disease, Active bacterial/fungal infection, OHCA, pregnant women, Life expectancy < 12-months, t-MCS instituted > 72 h before randomization	Methylprednisone 1 g IV/day for 3 days	Time to first combined endpoint (all-cause death, Htx, long-term LVAD, need t-MCS escalation, VT/VF treated with shock, first rehospitalization for HF or VT or AV block
NCT05974462	MYTHS-MR	Myocarditis Therapy with Steroids in patients with mildly reduced ejection fraction	Recruiting	Italy	Interventional	Multi-centre, international	3	174	Age 18–69 years, LVEF < 50% + LVEDD <56 mm, Troponin > 3URL, Onset of symptoms < 3weeks, Randomization < 120 h after admission, Exclusion of CAD	Known AI disease, Already on corticosteroid therapy, CI to corticosteroids, Hypereosinophilia, AM associated with immune checkpoint inhibitor agents, Previous known cardiac disease, Active bacterial/fungal infection, OHCA, Pregnant women, Life expectancy < 12-months	Methylprednisone 125 mg IV/ day for 3 days	LVEF ≥55% or an absolute increase in LVEF ≥ 10% on echocardiogram after 5 days
NCT05180240	ARCHER	Impact of CardiolRx on Myocardial Recovery in Patients with Acute Myocarditis	Completed. Results are expected in 2025	USA	Interventional	Multi-centre, international	2	100	Age 18–75 years, AM (chest pain + troponin elevation + CMR and/ or EMB)	CAD, severe valvular heart disease, inability to undergo CMR, eGFR < 30 mL/min, ALT and/ or ASAT > 3URL, sepsis, severe LV dysfunction requiring inotropes or t-MCS	CardiolIRx increasing dose up to 10 mg/kg for 12 weeks	Extracellular volume and global longitudinal strain on CMR at 12-week
NCT05855746	ARGO	Colchicine vs. Placebo in Acute Myocarditis Patients	Recruiting	France	Interventional	Multi-centre	3	300	Age 18–65 years, Symptoms onset < 21 days, Troponin > URL, AM (chest pain or AHF or palpitations + CMR findings), exclusion of CAD, pregnant women	Cardiogenic shock, giant cell or eosinophilic AM, toxic cardiomyopathy, active chronic inflammatory disease or infection or cancer, chronic corticosteroids treatment, sarcoidosis, severe liver or renal dysfunction, cytopenia, major digestive disorders, immunosupression, hemopathy, hypereosinophilia	Colchicine 0,5 mg × 2/days for 6-months (beginning < 72 h post-randomization)	LGE on CMR at 6-month and a composite clinical primary outcome (rate of HF or AM recurrence, rate of clinically relevant chest pain reccurence, rate of VT/VF, rate of LVAD and Htx and rate of cardiovascular death)
NCT05335928	ATRIUM	Abatacept in Immune Checkpoint Inhibitor Myocarditis	Recruiting	USA	Interventional	Multi-centre	3	390	Age >18 years, recent use of ICI, diagnosis of AM, ongoing treatment by solumedrol 1 g/ day, serum evidence of ongoing myocardial injury, WBC > 2500 + neutrophil > 1500 ALAT and ASAT < 20URL	Sudden cardiac arrest, VT/VF or cardiogenic shock in the previous 30 days, recent exposure to abatacept/belatacept, recent use of corticosteroids—NSAI—immunosuppressors, pregnant woemen, active and/or chronic infection	Abatacept 10 mg/kg after randomization, at 24 hours and at day 14 (± at day 28)	Rate of major adverse cardiac events at 6 months (CV death, non-fatal sudden cardiac arrest, cardiogenic shock, VT/VF, significant bradyarrhythmias or HF)
NCT03018834	ARAMIS	Anakinra vs. Placebo for the Treatment of Acute Myocarditis	Completed	France	Interventional	Multi-centre	2/3	120	Age 18–65 years, AM diagnosis (chest pain + troponin > 1,5URL + CMR in the first 72 h of admission, Exclusion of CAD	Active CAD, Autoimmune disease proven or suspected, giant cell AM, active and/or chronic infection, eGFR < 30 mL/min, active cancer or comorbidities limiting survival, recent NSAI or anti-TNF drugs, mechanical ventilation, cirrhosis, t-MCS	In-hospital Ananinkira 100 mg/ day subcutaneously (max 14 days)	Number of days alive free of AM complications (VT/VF, HF, chest pain, LVEF < 50%) within 28 days

AM, acute myocarditis; AV, atrioventricular; CAD, coronary artery disease; CMR, cardiac magnetic resonance; ICI, immune checkpoint inhibitor; HF, heart failure; EMB, endomyocardial biopsy; HTx, heart transplantation; LVAD, left ventricular assist device; LVEDD, left ventricle end-diastolic diameter; LVEF, left ventricle ejection fraction; OHCA, out hospital cardiac arrest; t-MCS, temporary mechanical circulatory support; URL, upper reference limit; WBC, white blood cell.

immunosuppression should guide the need for any intensification of the therapeutic regimen.[59,60]

In GCM, treatment-free survival without cardiac transplant remains very low, and therapy with corticosteroids alone appears insufficient. The addition of cyclosporine was found to improve transplant-free survival from 3 to 12 months.[59] In a prospective registry, patients treated with cyclosporine, corticosteroids, with or without an anti-CD3 antibody had a higher survival rate. Additionally, serial endomyocardial biopsies revealed decreased signs of inflammation and necrosis, as well as fewer giant cells.[60] Due to the adverse effects of anti-CD3 antibodies, triple immunosuppressive therapies using corticosteroids, cyclosporine, and azathioprine or mycophenolate mofetil were preferably used in the past.[61]

In patients with ICI-induced myocarditis, intravenous corticosteroids are recommended as a first-line therapy in the ESC Cardio-oncology guidelines. The association of abatacept/ruxolitinib associated with a screening for concomitant respiratory muscle failure has been recently evaluated and appears as a promising therapeutic strategy to improve prognosis in ICI myocarditis.[62]

Step 7—Does this patient need a mechanical circulatory support (MCS)?

In line with the ESC 2021 guidelines on acute HF, the use of (percutaneous) mechanical support is preferable (Class IIa) over the use of inotropes in cases of severe haemodynamic failure.[51] The initial question that must be asked when introducing MCS in cardiogenic shock patients remains above all: 'What's next ?'. In a comprehensive heart team, it should be discussed whether these patients, before proceeding to MCS, are selected solely as a bridge to recovery or as a bridge to long-term ventricular assist devices or heart transplants.[63] This Multidisciplinary Team discussion before MCS initiation is crucial for outcomes.[64]

The impact of the recent ECLS-shock trial results, which demonstrated no advantage of ECLS over conventional therapy in 417 acute myocardial infarction-associated cardiogenic shock patients on 30-day mortality,[65] on these guidelines will need to be elucidated in the future.[66] Patients with fulminant myocarditis appear to constitute the 'ideal' population for support with MCS, given that this subpopulation of cardiogenic shock is typically younger, more frequently exhibits single-organ failure, and the pathology is often reversible in a relatively short term.[67] Nunez et al. illustrated that mortality in VA-ECLS-supported patients with fulminant myocarditis is high (34%) and significantly higher in older and more obese patients with a more fulminant initial presentation, such as those with eCPR, pre-ECLS sepsis, lower mean arterial pressure, and pH/lactate levels.[68] The latter finding supports the notion that patients are best withdrawn from the negative spiral of cardiogenic shock as early as possible after diagnosis to optimize their outcome.[69] Nonetheless, major ECLS complications (bleeding, limb ischaemia, infections, and ischaemic stroke) strongly compromise their survival.

Similar to any type of cardiogenic shock, the type of MCS device is determined by the degree of respiratory failure and/or involvement of the right ventricle. Most often, VA-ECLS supportive therapy is then preferably chosen, with or without an unloading strategy.[70] Alternatively, right-sided support, such as a Protek-Duo cannula (providing support for the right ventricle plus the capability for oxygenation) combined with a percutaneous left ventricle assist device, could be inserted, although this configuration is more complex. In cases of isolated LV failure, a micro-axial flow pump may be chosen, provided the anatomy allows for it (it could be difficult to manage because of a smaller left ventricular cavity due to myocardial oedema in a non-dilated ventricle).[71] Whether LV unloading/venting or MCS, in general, will positively influence the outcome of fulminant myocarditis patients is suggested but requires further investigation.[69]

Step 8—Is there an indication for guideline-directed medical heart failure treatment?

Despite the lack of evidence addressing the specific setting of acute myocarditis, when systolic LV dysfunction is present (LVEF < 50%), guideline-directed medical treatment for HF with reduced ejection fraction, consisting of an ACE-inhibitor (sacubitril-valsartan can be discussed similarly to other causes of HF), betablocker, aldosterone-antagonist, and SGLT2-inhibitor should be initiated as soon as the patient is haemodynamically stable.[51,52] If LVEF recovery is complete at 6 months' follow-up, discontinuing HF treatment is deemed acceptable, but without data to support this.

Lack of beta-blockers has been associated with worse prognosis in patients with acute myocarditis, independently of LVEF.[72] Thus, the administration of beta-blockers to patients with preserved EF may be beneficial in preventing ventricular arrhythmias and SCD. However, there is a lack of robust data supporting this statement.

Step 9—When can the patient be discharged and resume physical activity?

The timing of discharge will depend on the severity of the condition, the presence of complications, cardiac function, and individual patient risk factors. Although there is no universally accepted set of criteria for discharging hospitalized patients, several key factors associated with an increased risk of events in prior studies should be evaluated before discharge (*Table 4*).

According to the latest ESC guidelines dedicated to HF,[12] moderate- to high-intensity training should be avoided for at least 6 months if symptoms are present or in case surrogate symptoms such as increased hs-cTn, or clinically significant ECG or imaging abnormalities are still observed. This recommendation is based on the possible electrical instability of an inflamed or dysfunctional heart. Scientific evidence for avoiding exercise in an asymptomatic patient with absent hs-cTn and normal cardiac function is lacking. Special attention is given to CMR findings, particularly in patients with extensive LGE areas (>20%) and decreased LVEF; patients with these CMR abnormalities should not engage in moderate- to high-intensity training. Specific guidelines on exercise, including competition in athletes, were updated in 2019[46] and specifically recommend that athletes be restricted from exercise programmes for 3–6 months (Class IIb/Level C). The level of evidence for these recommendations is due to the scarcity of data on the topic, but they suggest that myocarditis could be significantly associated with worse outcomes in athletes, even with minimal symptoms.[47]

Similarly, high-intensity physical exercise may exacerbate myocarditis in the context of COVID-19, supporting the restriction of competitive sports or intense physical activities for 3–6 months after diagnosis.[48] However, the level of evidence is particularly weak, especially in non-athlete patients, as reviewed recently.[49]

Consistently, the Japanese guidelines[8] suggest avoiding intense exercise for 6 months after onset in patients whose HF symptoms, cardiac enzymes, ECG, and imaging findings have improved (IIb, level C), even though the authors acknowledge the lack of robust evidence or data.

In athletes, reconditioning will be challenging, and exercise testing is logically recommended beforehand. The value of dedicated imaging and screening for arrhythmias is not yet established. In non-athlete patients, similar programmes would be logical, but their additional value has not been investigated, and the modalities for returning to activity remain debated. Briefly, there is no strong evidence to support limiting activities, including sports, in non-athlete patients. From a practical point of view, this underscores the need to propose dedicated programmes to address this concern, especially since most registries indicate that patients are aged 20–50 years.

Table 4 Considerations for discharge

Proposed Criteria for discharge
1. Haemodynamic stability and clinical improvement:
• haemodynamic stability (no cardiogenic shock, no clinical HF, no orthostatic hypotension, no tachycardia)
• LVEF > 50%[a] (and is available normal LVOT VTI or cardiac output)
• After a minimal monitoring period of 24 to 48 h allowing exclusion of potential harmful alternative diagnosis or potential complicated AM forms
• Favourable clinical evolution (no complication, no persistent symptoms)
2. Resolution of symptoms and normalization of biomarkers
3. Absence of high-risk features or complications (see *Table 1*)
4. No specific aetiology suspicion with specific management (for instance IV treatments for immunosuppressive drugs)
5. Arrangements for close follow-up and monitoring:
• If the patient has correctly understood the treatment
• Planned diagnostic work-up and follow-up[51]
6. Appropriate social support and home care arrangements

[a]Other cut-of values could be considered, depending on the initial presentation and medical course. In stabilized patients admitted for fulminant myocarditis, for instance.

Step 10—What are the main gaps in knowledge?

- What is the minimal observation period at the hospital required for an uncomplicated form of myocarditis? Is ambulatory management possible?
- What is the minimal set of aetiologies to look for?
- What is the ideal frame time for CMR?
- In whom is EMB mandatory? When and how should the biopsy be performed?
- What is the additional value of genetic testing?
- Who are the best candidates for temporary MCS?
- Are 'myocarditis teams' useful and how to elaborate at a regional level?
- Are corticosteroids indicated in complicated or fulminant myocarditis?
- Which anti-inflammatory or immune-modulatory treatments may be efficacious in (un)-complicated AM?
- What is the place for continued heart failure therapy even after recovery of LV function (HFrecEF)?
- Is physical activity harmful after AM? How long should physical activity be restricted in athletes and non-athletes? When is a return to work possible?

Conclusion

The diagnosis and treatment of patients presenting with acute myocarditis remain a clinical challenge for acute cardiovascular care specialists. We conclude that it requires a high level of awareness, an early recognition, and a multidisciplinary approach with a rapid response team to improve patient outcomes. This review highlights the lack of randomized trials and the need for comprehensive, evidence-based approaches to managing acute myocarditis. While there are no dedicated ESC guidelines on acute myocarditis yet, the first ESC guidelines on the management of myocarditis will be released in 2025 and may provide institutional guidance for cardiologists while clinical trials are eagerly awaited.

Author contribution

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Data availability

Data are available on reasonable request.

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