Definition and Diagnosis of Acute Myocarditis: A Position Statement of the Israel Heart Society

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For the position statement on the management of acute myocarditis and post-hospitalization follow-up, see page **525**.

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OBJECTIVES

Myocarditis represents a diagnostic and therapeutic challenge due to the heterogeneity of its clinical presentation and the wide range of etiologies. There is a lack of uniformity among position papers and guidelines from various professional societies regarding the definition and diagnostic workout, including recommendations for performing endomyocardial biopsy (EMB) and medical management, especially the use of immunosuppressive regimens [1-3]. Moreover, there is significant variability among medical centers in Israel in the diagnostic and therapeutic approaches to acute myocarditis. The purpose of this position paper is to present ways to standardize the management of acute myocarditis in Israel [4] by providing up-to-date definitions of the clinical categories of myocarditis, diagnostic criteria, and therapeutic approaches that correspond to the realities of our healthcare system.

DEFINITION

Myocarditis is defined as an inflammation of the heart muscle resulting from infection or exposure to toxic substances or due to an immune response. The most common etiology is viral. It can present as an acute, subacute, or chronic process. The acute period of the disease was previously defined as 3 months [1,2], but was recently limited to only 1 month from the onset of symptoms [3]. Subacute myocarditis refers to a cardiac inflammatory process that lasts between 1 and 3 months after clinical presentation [3]. Inflammatory cardiomyopathy (formerly known as chronic myocarditis) is defined as the continuation of the inflammatory process beyond the acute period [Figure 1]. According to this approach, an inflammatory process in the heart lasting more than 3 months and accompanied by a decrease in heart muscle contraction with or without ventricular dilation is called inflammatory cardiomyopathy [3,5].

In myocarditis, the etiological factors may cause different grades of direct damage to the heart muscle. In other cases, myocarditis is a result of immunological reactions, whether isolated or as part of a multisystem inflammatory disease, and characterized by autoreactive or autoimmune processes [3,5].

CRITERIA FOR CLINICAL AND LABORATORY DIAGNOSIS

The diagnosis of acute myocarditis may be complex and challenging. Definite diagnosis relies on EMB. However, due to potential risks of such an invasive procedure and the skills required to interpret its findings, it is not performed in most patients with clinically suspected myocarditis.

Clinically suspected myocarditis

The diagnosis of clinically suspected myocarditis is based on a combination of clinical findings and auxiliary tests in the absence of an alternative explanation for the findings, such as acute coronary syndrome. According to the European Society of Cardiology (ESC) position paper from 2013, the diagnosis of clinically suspected acute myocarditis is based on a combination of clinical presentations of the disease (chest pain, shortness of breath, palpitations, syncope, sudden cardiac death, and unexplained cardiogenic shock), evidence of an inflammatory process, and/or myocardial damage according to auxiliary tests such as electrocardiogram, laboratory results (especially troponin), and imaging [Table 1]. To suspect myocarditis the suggested diagnostic algorithm is based on the combination of at least one clinical

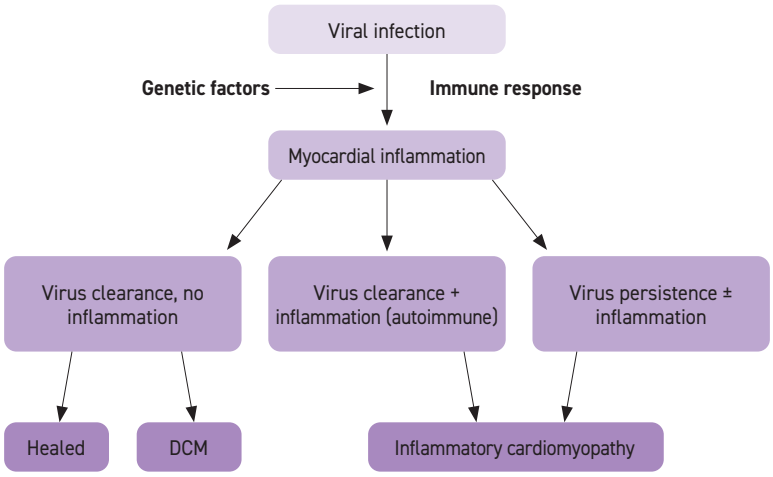
Table 1. Diagnostic criteria for clinically suspected myocarditis (reproduced with permission and modified [1])

Clinical presentation	
Acute chest pain	
New onset (≤ 1 months) of dyspnea and/or fatigue with/without heart failure signs	
Palpitations and/or unexplained arrhythmia and/or syncope or aborted sudden death	
Unexplained cardiogenic shock	
Diagnostic findings	
12 lead ECG/Holter/stress test	New abnormality including AVB, bundle blanch block, intraventricular conduction delay, Q waves, ST or T wave changes, decrease in ECG voltage, unexplained tachycardia, multiple premature beats, ventricular tachycardia, atrial fibrillation and any type of atrial or ventricular tachy- or bradyarrhythmia
Biochemical evidence of myocardial injury	Elevated troponin I or T
Functional or structural abnormality on cardiac imaging	Regional or global systolic wall motion abnormality and/or diastolic dysfunction with or without ventricular dilatation, wall thickening, pericardial effusion or endocavitary thrombi on echocardiogram, angiogram, or CMR

AVB = atrio-ventricular block, CMR = cardiac magnetic resonance, ECG = electrocardiogram

Figure 1. Pathophysiology of viral myocarditis and the transition to inflammatory cardiomyopathy and/or dilated cardiomyopathy

DCM = dilated cardiomyopathy



feature and at least one diagnostic finding or more than two diagnostic findings in an asymptomatic individual [Table 1]. Prodromal symptoms of a viral infection strengthen the suspicion [1].

Since the publication of the ESC position paper in 2013 [1] there have been advances in the routine use of high-sensitivity troponin testing and cardiac magnetic resonance imaging (MRI). As a result, the reliability of clinical diagnosis of acute myocarditis improved.

Clinically confirmed myocarditis

Recently, a new diagnostic category of clinically confirmed myocarditis has been introduced based on a combination of clinical signs, elevation of troponin levels, and fulfilment of diagnostic criteria for acute myocarditis by cardiac MRI [6,7] [Figure 2].

Pathologically confirmed or proven myocarditis

The diagnosis of proven myocarditis is still based on pathology findings (EMB or autopsy).

We recommend using the terminologies of *clinically suspected myocarditis*, *clinically confirmed myocarditis*, and *pathologically confirmed* or *proven myocarditis* [Figure 2]. A similar approach is currently used for diagnosis of myocarditis following vaccination for coronavirus disease 2019 (COVID-19) [7] and for diagnosis of myocarditis in children according to the American Heart Association guidelines [6].

CLINICAL PRESENTATION

Fever is the most common prodrome, occurring in about 65% of patients, in association with flu-like symptoms, gastrointestinal symptoms, and sore throat. These symptoms strengthen the suspicion of a viral infection, but they are not included among the clinical criteria for diagnosis of acute myocarditis due to low specificity [1].

Most patients diagnosed with acute myocarditis present with chest pain (up to 95% of cases) and half of those patients present with shortness of breath and/or fatigue [1-3]. Other symptoms include palpitations, syncope, and even sudden cardiac death. These complaints may last from hours to several weeks before individuals seek medical care.

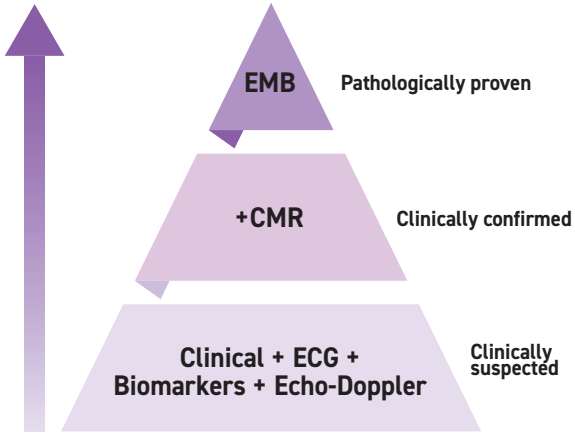
AUXILIARY TESTS

Laboratory tests

Blood tests that should be routinely performed in all patients with suspected myocarditis include a blood count plus differential, high-sensitivity troponin, creatine kinase, natriuretic peptides (brain-type natriuretic peptide [BNP] or NT-proBNP), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Additional tests may be performed depending on the clinical circumstances: PCR for viruses in a

Figure 2. Proposed diagnostic categories of acute myocarditis (reproduced with permission and modified [6])

ECG = electrocardiogram, Echo-Doppler = echocardiogram and Doppler echocardiography, EMB = endomyocardial biopsy, +CMR = positive cardiac magnetic resonance findings supporting the diagnosis of myocarditis



throat swab and in blood (such as influenza, cytomegalovirus, COVID-19, and Parvo B19), tests for collagen vascular diseases (ANA, anti-DNA, C3-4, anti-RNP, anti-RO, anti-LA, C-ANCA, P-ANCA, and rheumatoid factor). The absence of eosinophilia does not rule out eosinophilic myocarditis. In fact, in 25% of pathologically proven eosinophilic myocarditis, there was no eosinophilia on admission to the hospital [8]. Serologic tests for viruses have low sensitivity. A negative result does not rule out a viral disease as the cause of myocarditis. No correlation was found between serologic findings and viruses identified in EMB specimens [1]. However, serological tests for hepatitis C (HVC), human immunodeficiency virus (HIV), *Borelia burgdorferi*, *Coxiella burnetii*, and *Trypanosoma cruzi* may contribute in specific cases to establishing the diagnosis [9].

Electrocardiogram

The findings in myocarditis can include concave and diffuse elevations in the ST-T segment, usually without reciprocal changes, and unrelated to the area perfused by a specific coronary artery. Q waves may also occur in myocarditis; therefore, their presence does not rule out this diagnosis. Atrioventricular conduction disorder and complex ventricular arrhythmias may occur more frequently in myocarditis secondary to giant cell, eosinophilic myocarditis, sarcoidosis, Lyme disease, and myocarditis following treatment with immune checkpoint inhibitors (ICIs).

Echocardiogram

All patients with suspected myocarditis should undergo an echocardiogram soon after their admission. The test should be repeated during hospitalization depending on the clinical situation. Patients with impaired cardiac function on admission or with clinical worsening during hospitalization should also undergo an echocardiogram. Myocarditis may also present as cardiac wall thickening/hypertrophy, normal systolic function, or global or regional decrease in ventricular contraction. The echocardiographic findings may resemble restrictive, hypertrophic, dilated, or even arrhythmogenic right ventricular cardiomyopathy (ARVC).

Coronary angiography

Invasive or computed tomography coronary angiography should be performed shortly after admission, to rule out acute coronary syndrome unless the likelihood of this etiology is extremely low [Figure 3].

Cardiac magnetic resonance imaging

Cardiac magnetic resonance allows the detection of inflammation, perfusion, and edema with the help of T1 and T2 mapping and assessment of extracellular volume. It provides information on the location and extent of the pathological changes. In addition, late gadolinium enhancement (LGE) demonstrates the presence of myocardial damage and scarring (fibrosis). The established criteria for diagnosis of acute myocarditis by MRI (2018 Lake Louise criteria) have a sensitivity of 87.5% and a specificity of 96% [10]. The diagnostic accuracy of MRI varies according to the clinical background. The highest sensitivity is obtained if the test is performed within 2 to 3 weeks from the clinical presentation [9]. These values are typical for the most common form of acute myocarditis that manifests as chest pain. The diagnostic accuracy is lower in myocarditis that manifests as arrhythmia or heart failure [11].

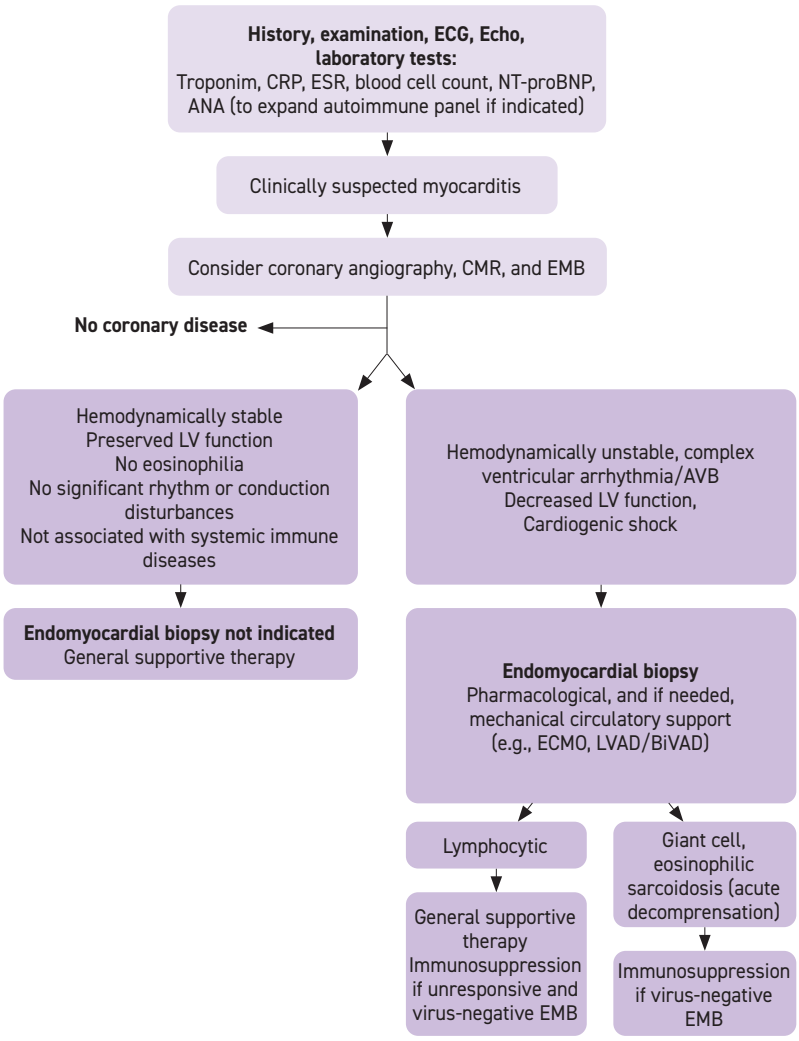
MRI also has value in differential diagnosis [12] and prognosis [13]. A negative cardiac MRI result in a patient with clinically suspected myocarditis does not rule out myocardial inflammation but is associated with a good prognosis. In contrast, a finding of LGE in the mid-layer of the interventricular septum and a low left ventricular ejection fraction (LVEF) on admission have been identified as the strongest predictors of cardiovascular complications, especially when the findings persist on repeat examinations [13].

Cardiac MRI is recommended for all patients with clinically suspected myocarditis [3,14] within 2–3 weeks from the onset of symptoms, in mild cases, and in severe, complex patients during hospitalization after their clinical condition stabilized [3,9]. MRI should not be performed in hemodynamically unstable patients.

The details of the imaging techniques are beyond the scope of this position paper. It is important that

Figure 3. The diagnostic and therapeutic approach to myocarditis according to clinical severity and etiology (reproduced with permission and modified [22])

ANA = antinuclear antibodies, AVB = atrio-ventricular block, CMR = cardiac magnetic resonance, CRP = C-reactive protein, ECG = electrocardiogram, Echo-Doppler = echocardiogram and Doppler echocardiography, EMB = endomyocardial biopsy, ESR = erythrocyte sedimentation rate, NT-proBNP = N-terminal pro-brain natriuretic peptide, LV = left ventricle, LVAD/BiVAD = left ventricular, bi-ventricular assist device



the test be performed using appropriate protocol and up-to-date technology to provide diagnostic and prognostic information as specified in consensus recommendations and current guidelines [10-12].

Nuclear imaging

The routine use of nuclear imaging such as ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (PET/CT) is not recommended. This test can help in cases in which MRI is contraindicated and specifically in cases of suspected cardiac sarcoidosis. PET-CT should be performed using a cardiac protocol, which includes prolonged fasting and a special diet prior to the test to suppress physiological glucose uptake in the normal cardiac muscle.

Endomyocardial biopsy

EMB is considered the gold standard for diagnosis of myocarditis and can identify the underling etiology and the type of inflammation, thereby guiding specific treatments [Figure 3]. The biopsy involves risks of 1–2% in experienced hands and up to 9% in low-volume centers [3]. Therefore, it is recommended to limit its use to cases where the results of the EMB may impact therapy [15,16]. With advanced imaging methods, especially cardiac MRI, EMB is not required in cases of uncomplicated myocarditis; that is, hemodynamically stable patients, without a decrease in cardiac function (LVEF > 50%) and/or life-threatening arrhythmias or conduction disturbances. When EMB is indicated, the patient should be transferred to a medical center that specializes in advanced heart failure care and has experience in performing EMBs, thus minimizing complication rates associated with this procedure.

INDICATIONS FOR PERFORMING EMBs

Performance of EMB is recommended in the following cases [1-3,14-19] [Figure 3]:

- Acute myocarditis presenting as severe heart failure or cardiogenic shock (fulminant myocarditis)
- Acute myocarditis presenting as heart failure with significant decrease in systolic function (LVEF below 40%) that does not improve with treatment
- Complex ventricular arrhythmias, sustained ventricular arrhythmia, or recurrent non-sustained ventricular tachycardia, as well as high-grade atrioventricular conduction block unrelated to the severity of myocardial dysfunction
- Suspicion of acute myocarditis during ICI therapy when the diagnosis is uncertain; definitive diagnosis of the disease has major implications on the continued treatment of the cancer
- Dilated cardiomyopathy with newly diagnosed heart failure, with or without a history of myocarditis, in the presence of moderate or severe decrease in heart function that does not respond to standard treatments for

3–6 months. A biopsy in such cases may reveal inflammatory cardiomyopathy, which may respond to immunosuppressive therapies [18,19]

- Suspected inflammatory cardiomyopathy with sustained damage to the heart muscle manifesting as persistent troponin release, especially in patients with heart failure or in the presence of progressive atrioventricular conduction disorder or ventricular arrhythmias
- EMB should also be considered in suspected myocarditis with an autoimmune disease or unexplained eosinophilia.
- Recurrent acute myocarditis: biopsy should be considered in such cases [16]

METHODS FOR PERFORMING EMBs AND SAMPLES

EMB is usually performed from the right ventricle but can be performed from the left ventricle in some cases, depending on clinical and imaging information (such as MRI and/or PET/CT). Intracardiac electrocardiogram can indicate the location and extent of the disease in the heart. EMB should be performed at an early stage of the disease. It is important to obtain several samples (preferably 5–7) to reduce sampling error. The samples for pathology should be kept in 10% formalin at room temperature or in the refrigerator (4°C) and the samples for virology should be frozen in liquid nitrogen or kept in an appropriate medium immediately after collection. Fresh frozen samples at -70°C and in glutaraldehyde for electron microscopy may be obtained depending on the clinical scenario. First, the tissue should be stained with hematoxylin-eosin. To increase the sensitivity, immunohistochemical staining is indicated with specific antibodies against inflammatory cell markers, in particular T cells (CD3) and macrophages (CD68). Other possible markers include HLA DR, subtypes of T cells (CD4 and CD8), and B cells (CD20). After an initial examination, performance of additional tests, such as Masson`s trichrome for fibrosis and Congo red for amyloid staining, should also be considered.

The PCR test for viruses from the tissue is an important tool to identify the viral etiology. The sensitivity of this test is much higher than PCR from blood and throat swabs, especially in cases of a viral infection limited to the heart (i.e., cardiotropic viruses). In addition, tests for the following viruses should be conducted: enteroviruses (e.g., coxsackievirus, echovirus), Parvo B19 (PVB19), and HHV6. In specific cases, testing for cytomegalovirus, Epstein-Barr virus, HVC, influenza, HIV, and coronaviruses should be considered. PVB19 is the most common virus found in cardiac biopsies, but it may also be found in healthy individuals, like HHV6. Therefore, the number of PVB19 and HHV6 copies in the biopsy has clinical significance. It is accepted that ≥ 500 copies per µg of nucleic acids of these viruses extracted from a biopsy sample express an active inflammatory process in the myocardium [9,20,21].

CONCLUSIONS

The diagnosis of acute myocarditis can be challenging due to the heterogeneity of its presentation. Acute coronary syndrome should be excluded on admission and the diagnosis must be based on a combination of clinical features, laboratory findings (primarily high sensitivity troponin), and imaging (echocardiography and cardiac MRI). EMB is not required in uncomplicated cases but should be performed in complicated cases to confirm the diagnosis, to define the etiology, and to guide management. For the position statement on in-hospital and post-discharge management of acute myocarditis, see our position paper on management of acute myocarditis [4].

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Capsule

Fighting fibrosis

Treatment for non-small cell lung cancer (NSCLC) has improved considerably since the development of immune checkpoint blockade therapies, but many tumors still fail to respond. **Herzog** and colleagues found that tumor-associated fibrosis, which is common in patients but is not found in murine models, impaired antitumor immune responses. The authors modeled fibrosis in murine models of NSCLC and found that targeting fibrosis by inhibition of transforming growth factor β signaling could sensitize tumors to immune checkpoint blockade when used in combination with chemotherapy. These results highlight a potential path forward to increasing the sensitivity of NSCLC tumors to immunotherapy.

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Eitan Israeli

Capsule

SARS-CoV-2-specific immune responses and clinical outcomes after COVID-19 vaccination in patients with immune-suppressive disease

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immune responses and infection outcomes were evaluated by **Barnes** and colleagues in 2686 patients with varying immune-suppressive disease states after administration of two coronavirus disease 2019 (COVID-19) vaccines. Overall, 255 of 2204 (12%) patients failed to develop anti-spike antibodies, with an additional 600 of 2204 (27%) patients generating low levels (< 380 AU ml^{-1}). Vaccine failure rates were highest in antineutrophilic cytoplasmic antibody-associated vasculitis on rituximab (21/29, 72%), hemodialysis on immunosuppressive therapy (6/30, 20%), and solid organ transplant recipients (20/81, 25% and 141/458, 31%). SARS-CoV-2-specific T cell responses were detected in 513 of 580 (88%) patients, with lower T cell magnitude or proportion in hemodialysis, allogeneic hematopoietic stem cell transplantation, and liver transplant recipients (vs. healthy controls). Humoral responses against Omicron (BA.1) were reduced, although cross-reactive T cell responses were sustained in all participants for whom these data were available. The BNT162b2 vaccine was associated with higher antibody but lower cellular responses compared to ChAdOx1 nCoV-19 vaccination. The authors reported 474 SARS-CoV-2 infection episodes, including 48 individuals with hospitalization or death from COVID-19. The decreased magnitude of both the serological and the T cell response was associated with severe COVID-19. Overall, they identified clinical phenotypes that may benefit from targeted COVID-19 therapeutic strategies.

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Management of Acute Myocarditis and Post-hospitalization Follow-up: A Position Statement from the Israel Heart Society

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For a position paper on the definition and diagnosis of acute myocarditis, see page **519**

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In the position statement on the definition and diagnosis of acute myocarditis on page 519 of this issue of the *Israel Medical Association Journal* (*IMAJ*), we discussed contemporary criteria for definition of acute myocarditis and inflammatory cardiomyopathy [1-7]. We also addressed current diagnostic methods including indications for endomyocardial biopsy (EMB) [8-22]. In this position statement, we discuss the management approaches during hospitalization and following hospital discharge, including specific forms of myocarditis and recommendations for returning to physical activity after myocarditis [22-37].

DEFINITION OF MYOCARDITIS SEVERITY

The risk level of a patient with myocarditis can be assessed according to clinical criteria based on the clinical presentation (e.g., symptoms of heart failure, cardiogenic shock), left ventricular function on admission echocardiogram, and the presence of sustained ventricular arrhythmias or advanced atrioventricular block (second-degree Mobitz type II or third-degree atrioventricular block) [Table 1].

TREATMENT OF MYOCARDITIS ACCORDING TO CLINICAL SEVERITY AND ETIOLOGY

The treatment of myocarditis is based on disease severity, level of risk, and etiology. The principles of therapy according to clinical severity are presented in Table 2, and treatment modalities according to the myocarditis type are summarized in Table 3.

In most cases, myocarditis is a mild and time-limited disease that requires supportive treatment, rest, and observation during hospitalization. Due to the concern for arrhythmias, heart rhythm monitoring is recommended for all patients, at least for the first 24 hours.

In severe cases, pharmacological and mechanical circulatory support may be necessary. In these cases, the patient should be transferred to a tertiary center with expertise in EMB and with capability of providing advanced mechanical circulatory support. In addition, intravenous steroids may be considered even before performing EMB or receiving the biopsy results, especially in cases with fulminant myocarditis or where an immune-mediated process is highly suspected [4,17]. After receiving the biopsy results, the treatment should be continued according to diagnosis [Table 3].

In patients with myocarditis from enterovirus, cytomegalovirus, or adenovirus, immunosuppressive treatment should be stopped. In patients with myocarditis from parvovirus B19 or human herpesvirus 6, continuation of immunosuppressive treatment should be carefully considered based on the initial response to steroids, of significant improvement in troponin and in left ventricular ejection fraction, and low viral load [4,9,20,21].

In cases of moderate severity, besides supportive care and supervision, treatment for heart failure and arrhythmias should be administered according to the existing guidelines. In such cases, transfer of the patient to a tertiary center should be considered to perform EMB and provide mechanical circulatory support. This decision should be taken in accordance with the condition of the pa-

Table 1. Definition of myocarditis severity (reproduced with permission and modified [4])

Risk level	Clinical presentation	Left ventricular ejection fraction	Ventricular arrhythmias (VT/VF) or atrioventricular block
High	Cardiogenic shock	< 30%	+/–
	Symptoms of acute heart failure	30–40%	+
Medium	Symptoms of acute heart failure	30–40%	–
	Mild symptoms of acute heart failure	41–49%	+
Low	Without heart failure symptoms, with normal blood pressures	≥ 50%	–

VF = ventricular fibrillation; VT = ventricular tachycardia

Table 2. Treatment of acute myocarditis: general principles

Treatment and follow-up of acute myocarditis	
	Hospitalize and rest with heart monitoring for at least 24 hours
	Perform laboratory tests, electrocardiogram, and an echocardiogram on admission to the hospital
	Rule out coronary disease using coronary computed tomography or coronary catheterization unless the likelihood of this etiology is extremely low
	Perform cardiac magnetic resonance imaging (see text for timing of the test)
	Consider genetic or immunological etiology. Family history of myocarditis, cardiomyopathy, sudden death, or systemic inflammatory disease should be documented. In cases of a suspected genetic background, performance of an echocardiogram and an electrocardiogram in first-degree family members and genetic-molecular testing for hereditary cardiomyopathy are recommended
Treatment of fulminant myocarditis (i.e., a patient with hemodynamic deterioration or with life-threatening ventricular arrhythmias or high degree conduction disorders)	
	Initiate intensive pharmacological and mechanical circulatory support according to available means
	Transfer to a tertiary center where advanced mechanical circulatory support can be provided and an EMB can be performed
	Perform, if possible, the EMB before connecting the patient to ECMO
	Consider starting steroid therapy before performing EMB or receiving the biopsy results, especially when immunological etiology is highly suspected
	Consider continuation or cessation of immunosuppressive treatment based on the results of EMB

ECMO = extracorporeal membrane oxygenation, EMB = endomyocardial biopsy

tient and the clinical course during hospitalization.

The results of the biopsy help define the etiology of myocarditis and determine the type of treatment and prognosis. Lymphocytic myocarditis is associated with a good prognosis in most cases. However, the prognosis is worse in cases of giant cell myocarditis (GCM), eosinophilic myocarditis, cardiac sarcoidosis, and myocarditis related to immune checkpoint inhibitors (ICIs) treatment or an autoimmune disease. All these conditions may require treatment with steroids alone or in combination with other immunosuppressive agents [Table 3].

In acute myocarditis that does not respond to conventional treatment or in cases of chronic inflammatory cardiomyopathy, with lymphocytic inflammation on histology, immunosuppressive treatment can be considered with careful monitoring as shown in Figure 3 in the position statement on page 519 of this issue of *IMAJ* and in Table 3 of this article [2,4,9,18,19]. Generally, the presence of a virus in the heart tissue is a contraindication to immunosuppressive treatment. In myocarditis associated with a systemic inflammatory disease, the treatment is often directed to the underlying disease and is usually based on immunosuppression.

DISCHARGE AND POST-DISCHARGE FOLLOW-UP

Candidates for discharge must be hemodynamically stable with a decreasing trend in troponin levels and the absence of symptomatic or life-threatening arrhythmias.

A repeat echocardiogram should be considered when there is a decrease in systolic function at presentation, if there is a worsening in the clinical condition, and in the presence of signs of heart failure during hospitalization. Whenever possible, cardiac magnetic resonance imaging (MRI) should be performed during hospitalization, especially for moderate and severe cases. MRI can be performed within 2–3 weeks after presentation in mild cases.

The use of a wearable defibrillator vest (VEST) after discharge from the hospital should be considered in patients with a severe decrease in left ventricular systolic function on echocardiogram prior to discharge and/or in patients who present with life-threatening ventricular arrhythmias during hospitalization. In patients with sustained ventricular arrhythmias associated with hemodynamic instability, an implantable cardioverter defibrillator (ICD) should be considered prior to hospital discharge [26].

In patients with decreased systolic function, cardioselective beta blockers, angiotensin-converting enzymes (ACE) inhibitors, angiotensin receptor blockers (ARB), and other anti-remodeling therapies should be initiated in the hospital according to the European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines [14,27]. In patients in whom a complete recovery of function and left ventricular dimensions are documented by the end of the acute phase of myocarditis, these therapies,

Table 3. Treatment of myocarditis according to type and biopsy results (reproduced with permission and modified [4])

	Lymphocytic [4,9]	Giant cell [23]	Eosinophilic [8]	Cardiac sarcoidosis [24]	Related to ICI therapy [25]	Inflammatory cardiomyopathy [18, 19]
Basic treatment	Supportive care	Steroids + cyclosporine or tacrolimus + Imuran or mycophenolate	IV methylprednisolone followed by oral prednisone	Steroids	Discontinue the offending drug+ IV methylprednisolone dose of 500–1000 mg for at least 3 days	Imuran + prednisone in patients with recently diagnosed myocarditis or DCM and heart failure without significant improvement of cardiac function despite optimal heart failure therapy concomitant with chronic increase in troponin level and on EMB with signs of inflammation in the absence of a virus
Second-line treatment	Prednisone +/- Imuran or mycophenolate in patients who deteriorate despite optimal treatment for heart failure with signs of inflammation and the absence of virus in the EMB	ATG or Alemtuzumab (antiCD52)	Depending on the severity and type of disease, cyclosporine IV or anti-CD52 can be considered	Steroid sparing: methotrexate or mycophenolate	In an unstable patient with no response to initial treatment, switch to second line treatment, e.g., mycophenolate, ATG, IVIG	
Additional treatment	IVIG?	Rituximab (antiCD20)		Anti-TNF	Investigational drugs	
Duration of treatment	As necessary	For at least a year, continuation of treatment followed by gradual reduction of doses and types of medications	As necessary	At least 1 year	Gradually decrease steroid dosage until resolution of troponin release and disappearance of arrhythmias/ conduction disturbances	6 months

ATG = anti-thymocyte globulin, anti-TNF = anti-tumor necrosis factor, DCM = dilated cardiomyopathy, EMB = endomyocardial biopsy, ICI = immune check point inhibitors, IVIG = intravenous immunoglobulin

particularly beta blockers and ACE inhibitors/ARBs, should be continued for at least 6–12 months.

Patients with heart failure symptoms and/or persistent decrease in left ventricular systolic function, recurrent myocarditis, or ventricular arrhythmia, or those with a family history of myocarditis or cardiomyopathy, should be referred for further evaluation and follow-up at a heart failure/cardiomyopathy center.

All patients recovering from myocarditis should have an electrocardiogram, repeat echocardiogram, and cardiological evaluation at 3 months and again at 6–12 months after discharge. Subsequently, the length of follow-up should be determined individually according to the clinical presentation and clinical course during hospitalization and follow-up. According to the most recent ESC guidelines, follow-up for at least 4 years post-discharge from the acute phase of myocarditis is recommended [14].

A summary of the diagnosis, treatment and follow-up process after acute myocarditis is presented in Table 4.

If possible, a decision on CRT/ICD/CRTD implantation should be postponed for 3–6 months to allow potential recovery of the left ventricular systolic dysfunction.

A repeat MRI 6–12 months after discharge may be considered in cases with increased risk features on the first MRI, such as extensive LGE or LGE located in the mid-wall of the interventricular septum (mid-septum) and/or extensive inflammation. Repeat MRI may also be considered in cases of persistent cardiac dysfunction on follow-up echocardiograms, complex arrhythmias, or clinical suspicion of a continued inflammatory process in the myocardium [9,13,14].

Patients who do not improve or who deteriorate despite guideline-recommended therapy [14,27] must be re-evaluated by tests that include high-sensitivity troponin, natriuretic peptides (if available), and EMB. Immunosuppressive therapy may be considered, as shown in Figure 3 in the position statement on page 519 of this issue of *IMAJ* and in Table 3 of this article, according to the EMB results.

SPECIFIC FORMS OF MYOCARDITIS

Recurrent and familial myocarditis

Recurrent myocarditis is an uncommon condition characterized by repeat episodes of myocarditis with periods of

Table 4. Summary of clinical presentation, diagnosis, and treatment of acute myocarditis

Clinical presentation	LVEF (%)	VT/ VF or AVB	Risk	Transfer to a tertiary center*	Temporary hemodynamic support	CMR	EMB	Treatment	Hospitalization place and duration	Echocardiogram before discharge	Follow-up
Cardiogenic shock/ fulminant myocarditis*	Usually < 30%	+/-	Critical	+	+	Before discharge	+	Inotropes, mechanical support, high-dose steroids** (until biopsy results are received), consider IVIG*** Consider VEST	ICU/ICCU, duration of hospitalization as required	Yes	Heart failure and arrhythmia clinic for at least 4 years
Severe heart failure*	30-40%	+	High	+	As needed	Before discharge	+	Supportive care, consider high-dose steroids until biopsy results are received, consider VEST	ICU/ICCU, duration of hospitalization as required	Yes	Heart failure and arrhythmia clinic for at least 4 years
Arrhythmia with or without heart failure*	Across the entire range	+	High	+	As needed	Before discharge	+	Supportive care, consider high-dose steroids (until biopsy results are received), consider VEST	ICU/ICCU duration of hospitalization as required	Yes	Arrhythmia and heart failure clinic for at least 4 years
Mild-to-moderate heart failure	Less than 50%	–	Moderate	Consider	–	During hospitalization or within 2–3 weeks	Consider	Supportive care. Consider steroids in accordance with biopsy results	Cardiology unit, at least 5 days	Yes	1, 3, 12 months and once a year for at least 4 years
Without symptoms of heart failure or arrhythmias	≥ 50%	–	Low	–	–	During hospitalization or within 2–3 weeks	–	Supportive care	Electrocardiogram monitoring for at least 24 hours, hospitalization for 3–5 days	Consider	1, 3, 12 months and once a year as appropriate

*Transfer to a tertiary center with the ability to perform and interpret endomyocardial biopsies and provide advanced mechanical circulatory support is recommended

**Intravenous methylprednisolone 7–14 mg/kg for 3 days. According to clinical response and/or biopsy result, administration can be stopped or the dose can be reduced to 1 mg/kg a day with withdrawal as customary.

***First line in children and second line in adults

AVB = atrioventricular block, CMR = cardiac magnetic resonance imaging, EMB = endomyocardial biopsy, ICCU = intensive cardiac care unit, ICU = intensive care unit, IVIG = intravenous immunoglobulins, LVEF = left ventricular ejection fraction, VT = ventricular tachycardia, VF = ventricular fibrillation, VEST = wearable defibrillator vest

clinical and laboratory remission, particularly return of troponin to a normal range between episodes. This condition must be distinguished from chronic inflammatory cardiomyopathy (formerly known as chronic myocarditis), which is characterized by a constant release of troponin with periods of exacerbation and improvement in clinical symptoms. In both cases, there is a concern of deterioration in cardiac function and development of heart failure. These patients require evaluation and follow-up in a heart failure/cardiomyopathy clinic.

Recurrent myocarditis can be part of a systemic inflammatory, autoimmune (e.g., systemic lupus erythematosus, dermatomyositis), or autoreactive syndrome [19]. In the latter cases, there is occasionally an accompanying disease, such as inflammatory bowel disease, inflammation of the thyroid gland, or psoriasis. In case of suspicion of a systemic inflammatory disease, besides MRI, an immunological workup and a ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography scan should be considered.

Recurrent myocarditis or chronic myocarditis can be a hereditary familial phenomenon due to mutations causing arrhythmogenic cardiomyopathies [28]. Therefore, patients should be asked about a family history of nonischemic dilated

cardiomyopathy, familial myocarditis, or sudden cardiac death at a young age. In arrhythmogenic cardiomyopathy with predominant left ventricular involvement, the echocardiogram may be normal or near-normal, but the MRI may show typical characteristics of myocarditis-like presentation of cardiomyopathy or an extensive mid-wall ring-like pattern of LGE [28]. Patients with suspected hereditary cardiomyopathy should be referred to a cardiomyopathy/heart failure clinic for diagnosis and treatment, including assessment of the need for genetic counseling and testing, and for EMB. When recurrent myocarditis is accompanied by pericarditis, it is appropriate to administer colchicine or/and IL-1 inhibitors, such as anakinra.

Acute myocarditis related to treatment with immune checkpoint inhibitors

Immunotherapy with ICIs is revolutionary in cancer management, and nearly 50% of cancer patients are eligible for this treatment [29]. ICIs stimulate anti-tumor immune responses by regulating the activity of T cells. Because of this mechanism, there is a risk of collateral immune-mediated damage to other organs, including the myocardium. While uncommon, occurring in only 1% of cases, it is life-threatening and can manifest as severe to fulminant myocarditis, with a mortality rate reaching 50%. Typically, myocarditis appears between the first and third round of treatment and is often associated with other immunological complications such as colitis, myositis, myasthenia-like syndrome, and pneumonitis. Therefore, early detection and treatment is of the utmost importance [29]. When myocarditis is suspected, ICI treatment should be immediately discontinued and a clear diagnosis should be established using electrocardiogram, biomarkers (troponin and natriuretic peptides), echocardiogram, and cardiac MRI. If the diagnosis is uncertain, an EMB should be considered. In symptomatic patients with a diagnosis of myocarditis, the patient should be continuously monitored, and high dose steroid treatment should be promptly initiated [Table 3]. Patients who respond to treatments are weaned from steroids under close follow-up of their clinical condition and blood troponin levels. Second-line drugs (immunosuppressants or steroid-sparing) are given when the initial response to steroids is insufficient or when it is not possible to taper off steroids [25]. When ICIs are indispensable for cancer treatment, the decision on their renewal requires a joint discussion between cardiologists and oncologists [25].

Acute myocarditis caused by COVID-19 infection or vaccination

Acute myocarditis often develops after a viral infection, including infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19. Myocarditis may also develop after vaccines against COVID-19, especially those based on mRNA technology (e.g., BNT162b2 by Pfizer-BioNTech and mRNA-1273 by Moderna), although this is a rare phenomenon.

According to pathology studies, myocarditis is relatively uncommon among COVID-19 patients [30]. During COVID-19 infection, myocardial damage can occur due to an increase in troponin secondary to the systemic infection and the inflammatory response that accompanies it. Elevated troponin in COVID-19 patients is associated with increased mortality. In most cases, the increase in troponin during COVID-19 is not a manifestation of myocarditis in the classical sense but of myocardial injury secondary to a systemic inflammatory response or other mechanism. Yet, direct myocardial damage by the virus and the resulting immune response is possible.

The diagnosis of myocarditis from COVID-19 and in the context of vaccination against the disease is similar in principle to myocarditis from other causes. The incidence of vaccine-related myocarditis is even lower and is estimated at 0.3–0.5 cases per 100,000 vaccinated persons. In most cases the myocarditis occurs after the second vaccination and mainly among young males [7,31-33]. The disease is mild in most cases and resolves in more than 90% of patients after a short hospitalization. This incidence is much lower, and the severity of the disease is milder, compared to myocarditis or myocardial injury associated with COVID-19 infection.

For the diagnosis of myocarditis secondary to COVID-19 vaccination, clinical and imaging methods, including MRI, are typically used since most patients do not require an EMB [7,31-34]. Evaluation is recommended, including EMB, only in cases with severe disease. Treatment is usually supportive. In cases of severe myocarditis with cardiogenic shock or markedly reduced cardiac function, as well as if there are signs and symptoms of heart failure, steroid treatment (with or without IVIG) can be considered, especially in cases related to the COVID-19 vaccine or in cases of severe myocarditis that are part of a multisystem inflammatory syndrome that may develop as a result of a severe immune response several days to weeks after COVID-19 infection.

The risks of hospitalization and death associated with COVID-19 are much greater than the risks associated with mRNA vaccination for COVID-19. Importantly, COVID-19 vaccines dramatically reduce the risk of severe infection and complications, including the relative risk of acute myocarditis and myocardial damage. Because myocarditis that develops after vaccination is a rare and relatively mild phenomenon, it is recommended to vaccinate the entire population, both adults and young people, against COVID-19 [33,35].

RETURN TO PHYSICAL ACTIVITY AFTER ACUTE MYOCARDITIS

Moderate or higher intensity physical activity should be avoided during the acute phase of the disease and for 3–6 months thereafter [2,3,36]. The period of abstinence from physical activity should be determined according to the severity of myocarditis; that is, 3 months after mild myocarditis and up to 6 months in more severe cases [Table 1]. Before returning to

full physical activity, it is recommended to perform CRP/ESR, an echocardiogram, exercise test, and a 24-hour Holter electrocardiogram with emphasis on return to normal left ventricular function and the absence of arrhythmias. Patients who are asymptomatic and have preserved cardiac function on echocardiogram and normal inflammation indices without arrhythmias on Holter monitoring and maximal stress test can gradually return to full physical activity after the recovery periods [2,3,36]. According to the ESC guidelines, competitive athletes or recovering patients who plan to perform high-intensity physical activity should also perform a troponin test [36]. Considering the difficulty in performing this test in the ambulatory setting in Israel, we recommend limiting it to situations when there is a suspicion of persistent inflammatory process or to specific cases [Figure 1].

In recovering patients who continue to be symptomatic or in cases where one of the tests is abnormal, a troponin test and repeated cardiac MRI is recommended. A repeat MRI is recommended for athletes whose first MRI showed features of increased risk of cardiovascular complications, such as extensive LGE or LGE located in the middle of the interventricular septum or evidence of extensive inflammation [13,36].

When a repeat MRI shows persistent LGE that is non-extensive and is without other markers of increased cardiovascular risk, a return to moderate to high intensity physical activity can be considered after a detailed discussion with an asymptomatic patient whose left ventricular function is preserved on echocardiogram and has no arrhythmias [36]. However, in patients with extensive scarring on repeat MRI, especially when there is significant involvement of the middle septum and/or persistent inflammation, persistent decrease in left ventricular function, or complex arrhythmias, it is recommended to avoid moderate- or high-intensity physical exertion [Figure 1].

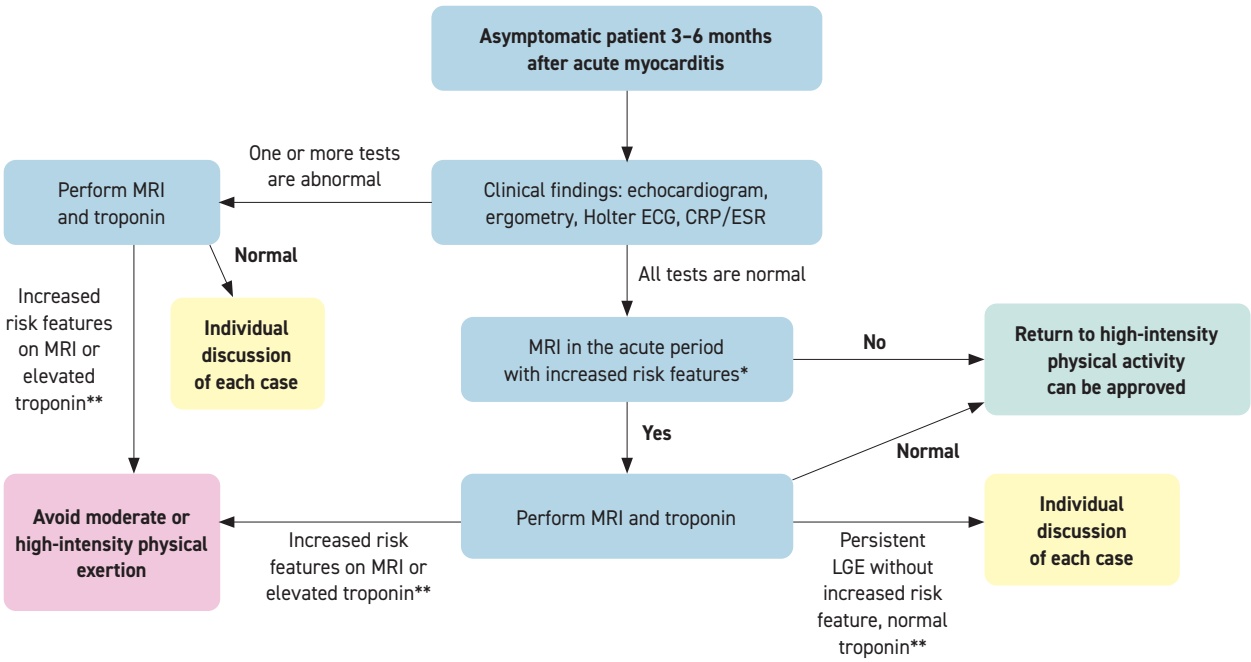
Recovering patients who present with heart failure or who had decreased left ventricular systolic function during the acute phase of the disease should be encouraged to gradually return to activity as part of a cardiac rehabilitation program. In addition, in patients who were engaged in intense physical activ-

Figure 1. Return to physical activity of asymptomatic patients after acute myocarditis

*Features of increased risk in cardiac MRI during the acute period: Extensive LGE or LGE located in the middle of the interventricular septum or extensive inflammatory process

**Features of increased risk on repeat cardiac MRI during follow-up: Extensive LGE or LGE located in the middle of the interventricular septum or persistence of the inflammatory process

CRP = C-reactive protein, ECG = electrocardiogram, EMB = endomyocardial biopsy, ESR = erythrocyte sedimentation rate, LGE = late gadolinium enhancement, MRI = magnetic resonance imaging



ity, guidance by an exercise physiologist should be considered.

The recommendations regarding the return to physical activity in recovering patients with myocarditis secondary to COVID-19 infection and secondary to COVID-19 mRNA vaccination are similar to the guidelines for myocarditis patients due to other causes and depend on the severity of the cardiopulmonary symptoms [37]. In patients recovering from COVID-19 without a diagnosis of myocarditis but with mild cardiopulmonary symptoms, physical exertion should be avoided if the symptoms persist. In patients with severe COVID disease and/or in patients with cardiopulmonary symptoms, or an increase in troponin without a clear diagnosis of myocarditis, an electrocardiogram and an echocardiogram should be performed, and the patient should be referred to a cardiologist, and if needed to a pulmonologist as well, for further evaluation and guidance [37].

CONCLUSIONS

This document provides an up-to-date definition of acute myocarditis categories, a consensus approach to the diagnosis and management of the disease, and a practical guide to all aspects of in-hospital management and following hospital discharge, considering the realities of the Israeli healthcare system. Most cases of myocarditis can be clinically confirmed by combining the clinical presentation, laboratory findings (primarily high sensitivity troponin), and imaging (echocardiography and cardiac magnetic resonance imaging). In an important minority of patients, endomyocardial biopsy is required to establish the diagnosis, define the etiology, and guide patient management. In fulminant myocarditis, including patients with life-threatening arrhythmias or high-grade conduction disturbances, or when immunological etiology is highly suspected, it is reasonable to initiate intravenous steroids prior to performing an endomyocardial biopsy or before receiving the biopsy results. Continuation of immunosuppressive treatment depends on the results of the endomyocardial biopsy and the initial response to steroids. Patients with severe disease should be transferred to a tertiary center where an endomyocardial biopsy can be safely performed and if required, advanced mechanical circulatory support can be provided. Genetic and immune etiologies should be considered, particularly in patients with recurrent myocarditis. A genetic background should be suspected in patients with family history of myocarditis, nonischemic dilated cardiomyopathy, and sudden cardiac death at a young age.

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In any free society, the conflict between social conformity and individual liberty is permanent, unresolvable, and necessary.

Kathleen Norris (1880–1966), American novelist and newspaper columnist

There are no chaste minds. Minds copulate wherever they meet.

Eric Hoffer (1902–1983), American philosopher and author

Capsule

The airway microbiome mediates the interaction between environmental exposure and respiratory health in humans

Exposure to environmental pollution influences respiratory health. The role of the airway microbial ecosystem underlying the interaction of exposure and respiratory health remains unclear. Through a province-wide chronic obstructive pulmonary disease surveillance program, **Lin** et al. conducted a population-based survey of bacterial (n=1651) and fungal (n=719) taxa and metagenomes (n=1128) from induced sputum of 1651 household members in Guangdong, China. They found that cigarette smoking and higher $PM_{2.5}$ concentrations were associated with lung function impairment through the mediation of bacterial and fungal communities, respectively, and that exposure was associated with an enhanced inter-kingdom microbial interaction resembling the pattern seen in chronic obstructive pulmonary disease. Enrichment of *Neisseria* was associated with a 2.25-fold increased risk of high respiratory symptom burden, coupled with an elevation in *Aspergillus*, in association with occupational pollution. The authors developed an individualized microbiome-based health index, which covaried with exposure, respiratory symptoms, and diseases with potential generalizability to global datasets. These results may inform environmental risk prevention and guide interventions that harness airway microbiome.

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Eitan Israeli