Viewpoint – Brazilian Guideline for Myocarditis

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Myocarditis is an inflammatory cardiomyopathy caused by several etiologies, including infectious, post-infectious, autoimmune, and drug-induced diseases. In recent years, COVID-19 has emerged as a considerable etiology of myocarditis, both through direct infection and immune reactions and reactions to specific vaccines against SARS-CoV-2. Tools for diagnosing myocarditis have been consolidated in recent years, with cardiac magnetic resonance imaging being used to important diagnostic, risk stratification, and prognostic evaluation. The disease can result in structural heart damage and severe heart failure. In addition, life-threatening arrhythmias are one of the possible serious complications of this condition. The institution of specific treatment may have prognostic implications. The most recent Brazilian Guideline on Myocarditis provides comprehensive aspects of its diagnosis and treatment.[1]

Diagnosis

The criterion for the diagnostic confirmation of myocarditis defined by the 2013 European and Brazilian Myocarditis Guidelines is the identification of myocardial inflammation by endomyocardial biopsy (EMB).[2,3] This diagnostic criterion, used solely without the option of classifying clinical suspicion, does not mirror clinical practice in the real world, where only a minority of patients in specialized centers are referred for diagnostic investigation through EMB with diagnostic confirmation or exclusion, and most have the diagnosis of clinical suspicion of myocarditis. As an innovation, the 2022 Brazilian Guideline[1] introduces an organizational chart to establish the degrees of suspected diagnosis of myocarditis, which correspond to clinical practice in the real world, where most patients will have a diagnosis of suspected myocarditis rather than confirmation. This organization chart is based on clinical history, myocardial injury biomarkers, electrocardiogram, echocardiogram, and cardiac magnetic resonance, to establish a diagnostic suspicion of myocarditis (Figure 1), which will define different approaches regarding follow-up, treatment, and the need for EMB. Patients with low suspicion of myocarditis have a favorable prognosis with a low risk of developing ventricular dysfunction or cardiovascular mortality, and clinical follow-up is indicated without the need for cardioprotective drugs. Cardioprotective drugs and clinical and ventricular function follow-up by echocardiogram and magnetic resonance imaging are indicated for patients with an intermediate degree of suspicion of miocarditis. Patients with high diagnostic suspicion or with intermediate suspicion with worsening clinical or ventricular function have a worse long-term prognosis, with lower survival, being indicated in this group the EMB for the investigation of the inflammatory activity and the etiological agent to evaluate treatment with immunosuppressants and therapy directed towards the identified etiological factor (Figure 2). With the diagnostic suspicion classification, the new Guideline approaches clinical practice, standardizing the clinical management of most patients with suspected myocarditis and reserving the indication of EMB for those with greater potential for clinical benefit from immunosuppressive therapy.

Another major point of relevance in the 2022 Guideline[1] was the strengthening of the role of CMR in the diagnosis and prognosis of myocarditis. The modification of the Lake Louise diagnostic criteria, with the incorporation of T1 and T2 maps for detecting edema and myocardial fibrosis, favored an increase in the diagnostic accuracy of CMR with a sensitivity of 88% and specificity of 96%, placing CMR as an important tool in assessing the degree of suspicion of myocarditis.[4,5] Using CMR, we can also classify the prognostic risk of patients with myocarditis based on edema, degree of myocardial fibrosis (<17g and 13% of LV mass), and ventricular dysfunction. Through the association of degree of prognostic risk of CMR and degree of diagnostic suspicion, we will define the pharmacological therapeutic approach, indication of EMB, assessment of the risk of sudden death, and indication of a cardioverter defibrillator[1] (Table 1).

The diagnostic investigation of myocarditis of autoimmune origins such as Sarcoidosis and Giant Cells Lupus gained prominence in the 2022 Guideline,[1] which highlighted the increase in diagnostic capacity through detection of inflammatory disease activity, with the use of PET with 18F-FDG, with a sensitivity of 84% and specificity of 83%[6] for the diagnosis of myocarditis due to cardiac sarcoidosis. The analysis of the genetic profile of the myocardial tissue for the research of specific genomes for idiopathic giant cell myocarditis and sarcoidosis increased the diagnostic sensitivity of EMB, avoiding sampling error, which, together with PET with 18F-FDG allow in greater accuracy not only in the diagnostic definition but also disease activity and assessment of response to therapy.

Myocarditis caused by tropical diseases and rheumatic disease is not mentioned in any myocarditis guidelines, despite their high prevalence in several countries. In Brazil, we have a

Keywords

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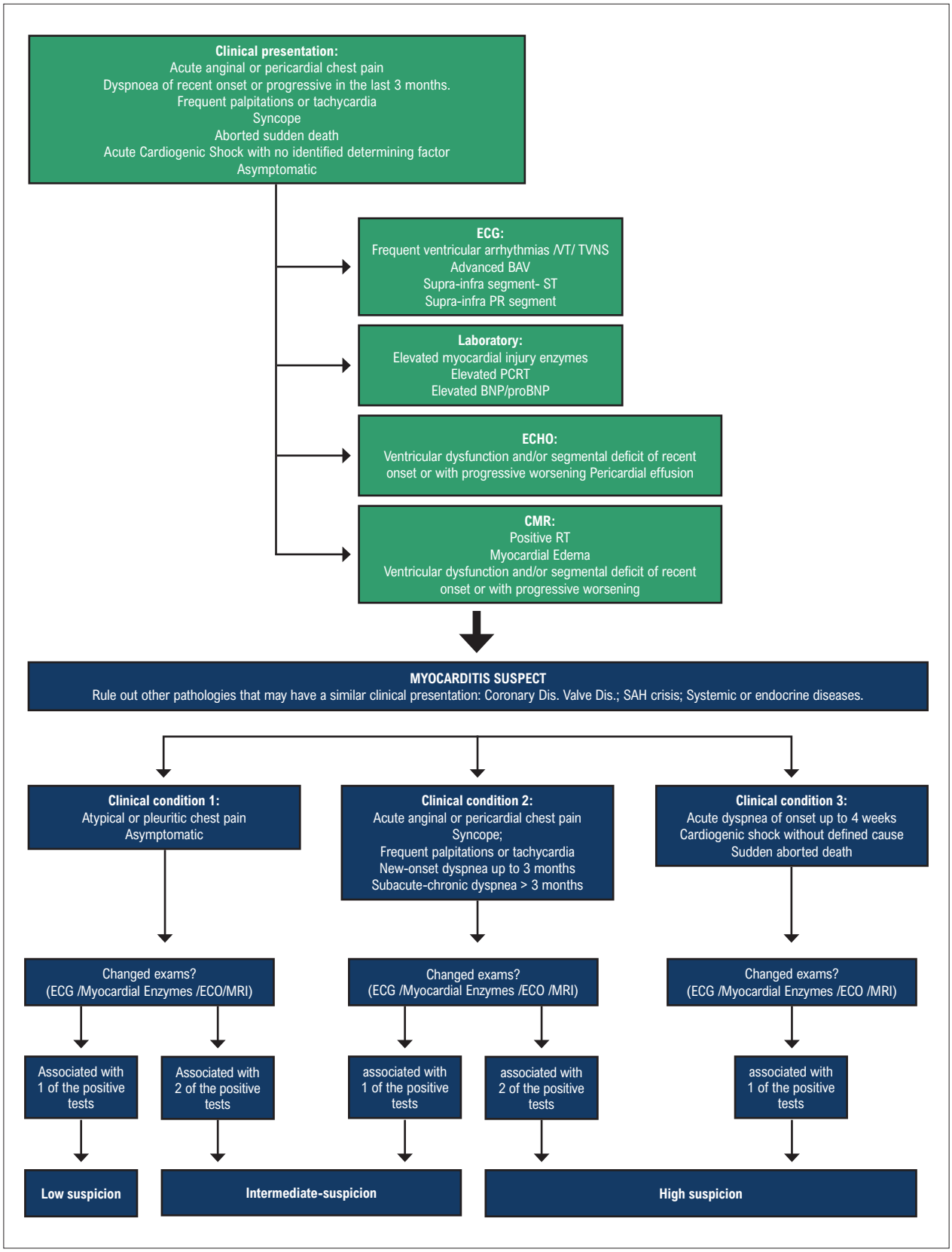

Figure 1 – *Adapted from the stratification algorithm for clinical diagnostic suspicion of myocarditis from the 2022 Brazilian Myocarditis Guideline.*[1] *AVB: atrioventricular block; BNP: B-type natriuretic peptide; ECG: electrocardiogram; ECHO: transthoracic echocardiogram; CMR: cardiac magnetic resonance; PCRT: C-reactive protein.*

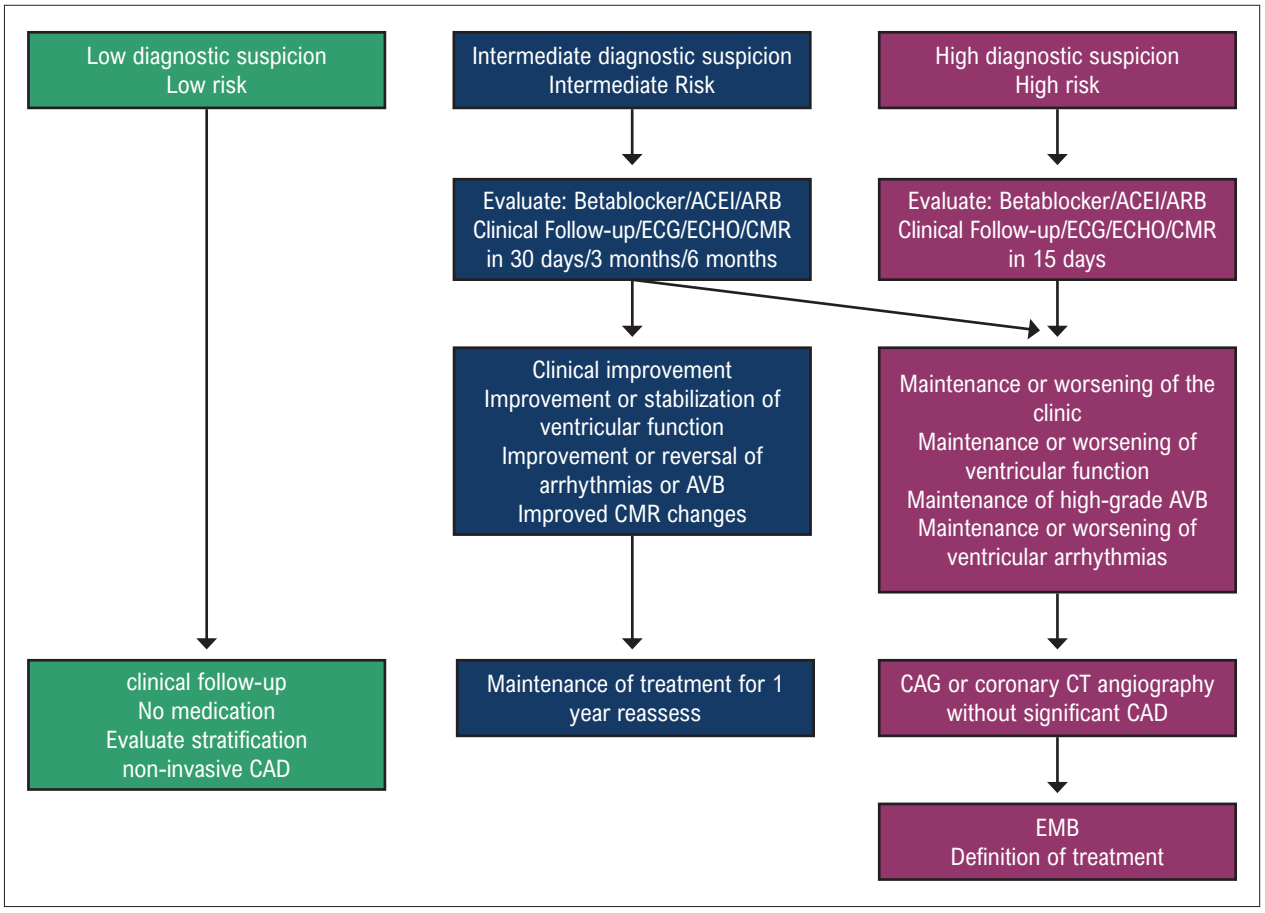

Figure 2 – *Adapted from the therapeutic flowchart of myocarditis based on the degree of clinical suspicion and prognosis of the 2022 Brazilian Myocarditis Guideline.1 AVB: atrioventricular block; EMB: endomyocardial biopsy; CAG: coronary angiography; CAD: coronary artery disease; ECHO: transthoracic echocardiogram; ECG: electrocardiogram; CMR: cardiac magnetic resonance; CT: computed tomography; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers.*

Table 1 – Risk stratification and probability of endomyocardial biopsy indication based on cardiac magnetic resonance parameters

Prognostic risk	CMR parameter	Suggested conduct	Biopsy indication
Low	T1 and T2, without alteration Without ventricular dysfunction	Clinical follow-up	No indication
Intermediary	T1 or T2, positive Non-extensive late enhancement (<17g and 13% of the LV mass) Normal function or slight dysfunction of LV	Clinical follow-up Repeat CMR at 1, 3, and 6 months	Stable: no indication Dysfunction progression: possible indication
High	T1 or T2, positive Extensive late enhancement (>17g or 13% of LV mass), or with involvement of the interventricular septum, and/or moderate or significant LV dysfunction	Clinical follow-up Repeat CMR at 1, 3, and 6 months	Possible indication

LV: left ventricle; CMR: cardiac magnetic resonance.

high prevalence of both pathologies, mainly in the north and northeast of the country and in rural areas, which motivated the 2022 Guideline to establish diagnostic flowcharts and therapeutic approaches for both pathologies; therefore, the only myocarditis guideline with this content.

Myocarditis due to COVID-19 was a widely investigated topic regarding its real prevalence, pathophysiological mechanisms, and therapeutic management. The Guideline provides a simple understanding of physiopathological mechanisms and the alterations of complementary exams

and establishes a practical organization chart of diagnosis and management for SARS-CoV-2-related myocarditis.

Acute Cardiotoxicity by Antineoplastic Therapy, myocarditis related to cancer treatment, has gained importance due to immunotherapy's evolution, specifically immune checkpoint inhibitors. The classic models of cardiotoxicity with ventricular dysfunction are those caused by anthracyclines and cyclophosphamide. As mortality from cardiotoxicity can reach 50%, early and accurate diagnosis is of great importance for reducing cardio-aggression and decision-making on maintaining or discontinuing the antineoplastic agent.[7] The 2022 Guideline aims to provide cardiologists and clinicians involved in cardio-oncology with a guide for prevention, diagnosis, and treatment of cardiotoxicity induced by antineoplastic agents[1] where echocardiogram and CMR are indicated as diagnostic methods of choice with greater sensitivity for early screening of the diagnosis of myocarditis.

Treatment

The Myocarditis Guideline published in 2022[1] brings some innovations concerning the 2013[3] Guideline on the therapeutic regimen that deserve to be highlighted. The first is constructing a therapeutic flowchart based on the degree of clinical suspicion and prognosis. The flowchart helps guide clinicians into the most appropriate therapy in each situation since not all patients will undergo endomyocardial biopsy. Patients with a low risk of myocarditis, without signs of severity or ventricular dysfunction, have a favorable prognosis and can be clinically followed. In patients with intermediate suspicion of myocarditis, initiation of cardioprotective drug therapy such as beta-blockers, converting enzyme inhibitors, or angiotensin receptor blockers is recommended for at least one year in order to preserve ventricular function, with individualized follow-up according to function and arrhythmogenic potential. Finally, patients with a high suspicion of the diagnosis of myocarditis should be evaluated for signs of greater severity and, in the presence of ventricular dysfunction, malignant arrhythmias, or hemodynamic instability, an endomyocardial biopsy is indicated to try to identify etiologies that deserve more aggressive treatment such as giant cell or eosinophilic myocarditis.[8] In situations of instability, using inotropic support and/or short-term devices is recommended to provide support and act as a bridge to the recovery of ventricular function. In this context, invasive monitoring becomes opportune.[8] After performing an endomyocardial biopsy, it is possible to define whether there is myocardial inflammation and investigate the presence of viruses. The inflammation and etiological agent documentation allows adequate therapy for each situation. Three strategies can be used in patients with myocarditis: immunosuppressive agents, antivirals, and immunomodulation.

Immunosuppressive therapy aims to suppress the inflammatory and/or autoimmune response and, consequently, contribute to clinical improvement and ventricular function in conditions such as giant cell myocarditis, eosinophilic myocarditis, or myocarditis secondary to autoimmune diseases (class of recommendation I). Immunosuppressive agents can also be considered in myocarditis with negative viral research in patients who evolve with chronic HF to improve clinical status and LV function, an IIa recommendation according to the Brazilian Guideline. A detailed description of immunosuppressive treatment, which may include corticosteroid pulse therapy, rabbit immunoglobulin, azathioprine or cyclophosphamide, and/or methotrexate for some specific autoimmune etiologies can also be found in the latest update of the Brazilian Myocarditis Guideline.[1,8] Current therapy for patients with myocarditis involves using corticosteroids alone or associated with azathioprine in the presence of inflammation and absence of viral infection. However, viral genome research seems controversial regarding immunosuppressive therapy indications. It is known that the objective is to improve inflammation, and the appropriate scenario is in situations where there is no viral genome and where it has been related to improved ventricular function. On the other hand, there is no strong evidence relating the qualitative finding of microorganisms in cardiac tissue to the development of myocarditis since the viral genome may be present even in normal hearts. In this context, new techniques that document RNA transcription or the number of copies can be promising in the therapeutic decision. Advances in immunosuppression in lymphocytic myocarditis are still needed[1] (Figure 3).

Studies involving antiviral agents have been developed because viral persistence is related to a worse prognosis. Administration of interferon-beta, for example, induced virus elimination in patients with viral myocarditis due to adenovirus or enterovirus and was related to improved survival, functional class, and quality of life. A similar scenario is observed with ganciclovir|valganciclovir in patients with HF symptoms in a clinical situation of myocarditis caused by the human herpesvirus.[6] However, in conditions of BV19 infection, further studies are needed to consolidate the use of nucleoside analogs and antiviral inhibitors of reverse transcriptase to improve clinical outcomes.[1]

Immunomodulation is also a studied strategy for the treatment of viral myocarditis. This strategy includes the use of immunoglobulins and/or immunoadsorption. Intravenous immunoglobulins reduce pro-inflammatory cytokines and increase anti-inflammatory ones. Evidence about the benefits of immunoglobulins in the treatment of myocarditis is still insufficient for the routine recommendation of its use, but there is potential benefit in viral myocarditis due to adenovirus and parvovirus B19. Its use was related to improved heart pump, exercise capacity, functional class, and viral load reduction. The use of immunoadsorption seems to be promising in patients with dilated cardiomyopathy with the presence of antibodies, but there is a lack of evidence to consolidate its therapeutic use in myocarditis.[1]

In addition to specific treatment for myocarditis, cardioprotective strategies should be instituted. Converting enzyme inhibitors and/or beta-blockers for 12 months has potential benefits in patients without ventricular dysfunction. In the presence of ventricular dysfunction, it is essential to institute prognostic-modifying therapies following the recommendations of the Brazilian, American, or European Guidelines for heart failure.[9-11] Such measures may lead to an improvement in ventricular function, and, in this situation,

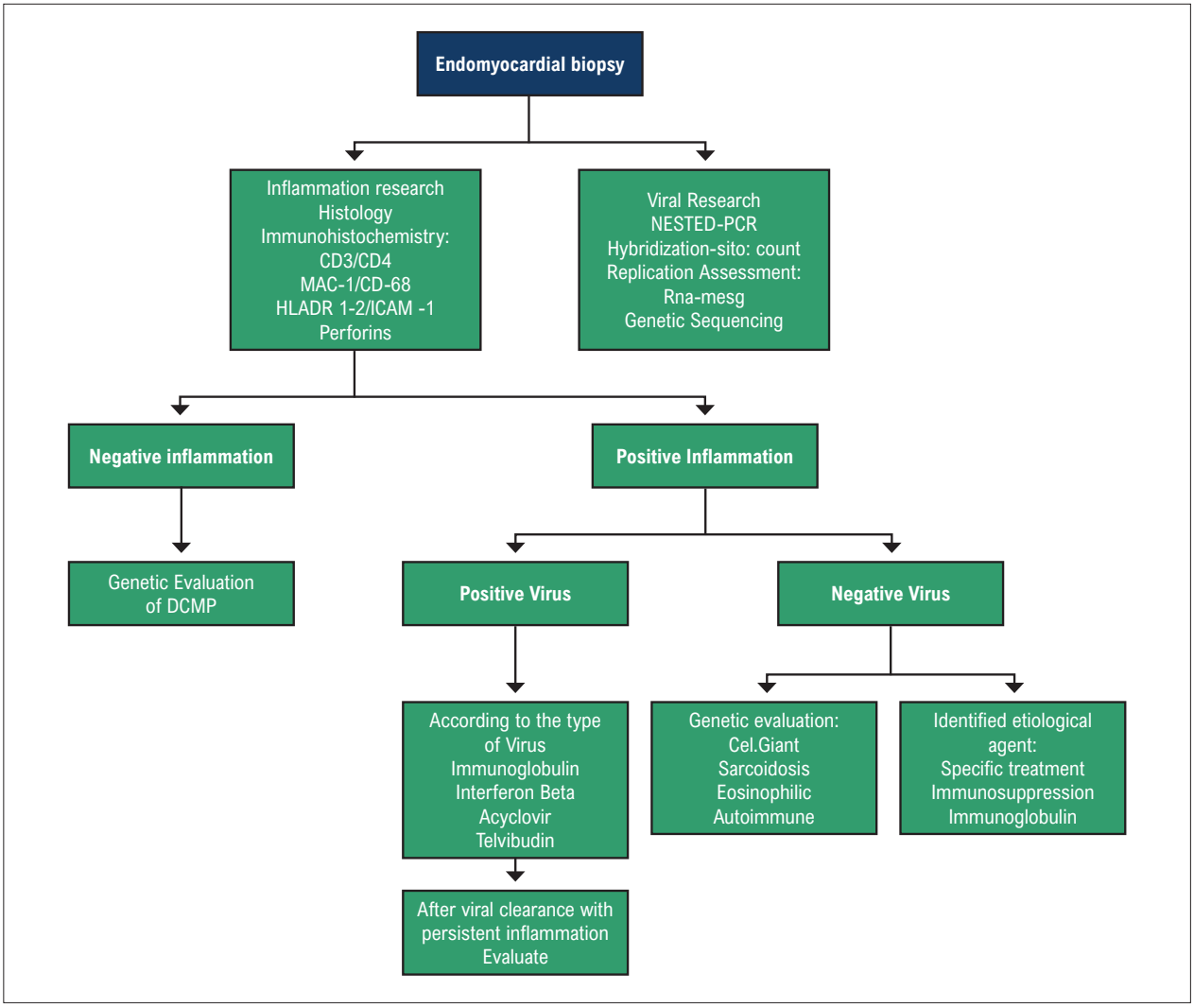

Figure 3 – *Adapted from Myocarditis Therapeutic Flowchart based on BEM results from the 2022 Brazilian Myocarditis Guideline.[1] DCMP: dilated cardiomyopathy; PCR: polymerase chain reaction.*

the maintenance of neurohormonal therapy is recommended since its suspension is associated with a worsening of left ventricular function.[6] Although most patients have a favorable prognosis, a non-negligible percentage of patients may develop hemodynamic instability and cardiogenic shock. In this situation, the use of inotropes, as well as intra-aortic balloon and extracorporeal membrane oxygenation (ECMO), should be considered as a bridge to recovery.[8]

In general, the new Brazilian Guideline on myocarditis addresses the diagnosis and treatment of myocarditis innovatively. It helps clinicians to use it in practice, helping to clarify the diagnosis and define the most appropriate therapy for each clinical scenario.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for important intellectual content: Montera MW, Dan DMD; Acquisition of data; Analysis and interpretation of the data; Statistical analysis and Writing of the manuscript: Montera MW, Dan DMD, Marcondes-Braga FG.

Potential conflict of interest

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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