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I BRAZILIAN GUIDELINES ON MYOCARDITIS AND PERICARDITIS



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I BRAZILIAN GUIDELINES ON MYOCARDITIS AND PERICARDITIS

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Myocarditis

1. Epidemiology

The true incidence of myocarditis is difficult to estimate due to factors such as diversified clinical presentation, the continued infrequency of endomyocardial biopsy (EMB) performance, and the lack of sensitive and standardized histological criteria.

Based on autopsy reports, the estimated incidence of myocarditis varies from 0.2 to 12% and depends on the investigated population^{1,2}. The *Myocarditis Treatment Trial* found a myocarditis incidence of 9.6%, confirmed by EMB, in patients with unexplained heart failure³. Recent studies that show a high rate of viral genome presence in adults with left ventricular dysfunction suggest that myocarditis is a main determinant of idiopathic dilated cardiomyopathy⁴.

The prevalence of myocarditis is higher in males, especially in young adults, and it represents a main cause of sudden death in children and adults younger than 40 years old⁵. Pediatric survivors of myocarditis exhibit increased mortality and requirements for heart transplantation over a 12-year span.

Myocarditis might also be present in other types of cardiomyopathy, such as amyloidosis and hypertrophic cardiomyopathy, as well as in patients with acute myocardial infarction, for which it is a factor of poor prognosis^{6,7}.

2. Etiology

Myocarditis can be triggered by several infectious and non-infectious causes, and the most prevalent form occurs secondarily to viral infections (Table 1)⁸.

Viral infections are the most common of the various infectious diseases that can induce myocarditis. The most prevalent cardiotropic viruses include adenoviruses, enteroviruses, parvovirus B19, the herpes simplex virus, the hepatitis C virus (HCV), cytomegalovirus (CMV), and the Epstein-Barr virus. Variations in viral prevalence profiles depend on the investigated geographical area. Adenoviruses, parvoviruses, and herpes viruses are prevalent in Brazil and in Europe, whereas enteroviruses predominate in the United States¹⁰. Multiple viral infections occur in approximately 30% of viral myocarditis cases.

According to autopsy reports, myocarditis is found in more than 50% of human immunodeficiency virus (HIV/AIDS)-infected patients. Non-viral infectious microbial causes of myocarditis include *Clostridium*, *Corynebacterium diphtheria*, *Neisseria meningitidis*, *Streptococcus*, *Listeria*, and *Borrelia burgdorferi* (the etiological agent of Lyme disease)¹¹.

In South America, particularly in some areas of Brazil, Chagas myocarditis, which is caused by the protozoan *Trypanosoma cruzi*¹², is the most prevalent form of myocarditis or dilated cardiomyopathy.

Drugs such as cyclophosphamide, phenytoin, zidovudine, and amphetamines can induce eosinophilic hypersensitivity myocarditis or exhibit direct myocardial toxicity. Eosinophilic hypersensitivity myocarditis must be suspected if peripheral blood eosinophilia or myocardial eosinophilic infiltrates are

observed. Vaccination-induced eosinophilic-lymphocytic myocarditis should also be considered¹³⁻¹⁵.

Autoimmune systemic diseases such as Churg-Strauss syndrome¹⁶ and hypereosinophilic syndrome are associated with eosinophilic myocarditis¹⁷. Although rare, prognoses of giant-cell myocarditis and sarcoidosis might change as a function of early diagnosis and appropriate treatment^{18,19}.

Of the connective tissue diseases, rheumatoid arthritis, dermatomyositis, and systemic lupus erythematosus are associated with the highest rates of myocardial inflammatory activity.

Possible etiological factors of peripartum cardiomyopathy include viral activity, autoimmunity, nutritional disorders, and family origin. The prevalence of myocarditis is variable and could occur in as many as 62% of the patients who were subjected to endomyocardial biopsy. Likely, myocarditis in response to viral infections and autoimmune diseases is due to a higher susceptibility to viral infections during pregnancy and postpartum immune responses to fetal cells^{20,21}.

Table 1: Etiology of myocarditis

Infectious	
RNA viruses	Picornaviruses (Coxsackie A + B, echovirus, poliovirus, hepatitis virus), orthomyxovirus (influenza), paramyxoviruses (respiratory syncytial virus, mumps), togaviruses (rubella), flaviviruses (dengue fever, yellow fever)
DNA viruses	Adenovirus (A 1, 2, 3, and 5), erythrovirus [1 (B19V) and 2], herpesviruses (human herpes virus 6 A/B, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus), retrovirus (HIV)
Bacteria	<i>Chlamydia</i> (<i>C. pneumonia</i> /psittacosis), <i>Haemophilus influenzae</i> , <i>Legionella pneumophila</i> , <i>Brucella</i> , <i>Clostridium</i> , <i>Francisella tularensis</i> , <i>Neisseria meningitidis</i> , <i>Mycobacterium tuberculosis</i> , <i>Salmonella</i> , <i>Staphylococcus</i> , <i>Streptococcus</i> A, <i>S. pneumoniae</i> , <i>tularemia</i> , <i>tetanus</i> , <i>syphilis</i> , <i>Vibrio cholerae</i>
Spirochetes	<i>Borrelia recurrentis</i> , <i>Leptospira</i> , <i>Treponema pallidum</i>
Rickettsia	<i>Coxiella burnetii</i> , <i>R. rickettsii</i> /prowazekii
Fungi	<i>Actinomyces</i> , <i>Aspergillus</i> , <i>Candida</i> , <i>Cryptococcus</i> , <i>Histoplasma</i> , <i>Nocardia</i>
Protozoa	<i>Entamoeba histolytica</i> , <i>Leishmania</i> , <i>Plasmodium falciparum</i> , <i>Trypanosoma cruzi</i> , <i>Trypanosoma brucei</i> , <i>Toxoplasma gondii</i>
Helminths	<i>Ascaris</i> , <i>Echinococcus granulosus</i> , <i>Schistosoma</i> , <i>Trichinella spiralis</i> , <i>Wuchereria bancrofti</i>
Non-infectious	
Autoimmune diseases	Dermatomyositis, inflammatory bowel disease, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, Wegener's granulomatosis, giant cell myocarditis
Drugs	Aminophylline, amphetamines, anthracyclines, catecholamines, chloramphenicol, cyclophosphamide, doxorubicin, 5-fluorouracil, phenytoin, mesylate, methysergide, trastuzumab, zidovudine

Non-infectious	
Hypersensitivity (to drugs)	Azithromycin, benzodiazepines, clozapine, cephalosporins, dapsone, dobutamin, lithium, diuretics, thiazide, methyl dopa, mexiletine, streptomycin, sulfonamides, non-steroidal anti-inflammatory drugs, tetanus toxoid, tetracycline, tricyclic antidepressants
Hypersensitivity	Bee, wasp, black widow spider, scorpion, snake
Systemic diseases	Churg-Strauss syndrome, collagen disease, sarcoidosis, Kawasaki disease, scleroderma
Other	Acute myocardial infarction, hypothermia, transplant rejection, radiation

3. Physiopathology

Viral myocarditis is comprised of acute, subacute, and chronic phases. These temporal and physiopathological stages indicate important diagnostic and therapeutic considerations²².

The acute stage is characterized by the presence of viremia. Myocyte loss due to necrosis occurs as a direct result of viral activity, the cytotoxic effects of inflammatory mediators, and oxidative stress products associated with endothelial dysfunction and ischemia²³. Direct effects result from viral entry into the cells, which is mediated by membrane receptors such as CAR (*coxsackie-adenovirus receptor*) as well as cytoplasmic and nuclear damage²⁴. Viral activity induces a complex immune response that is characterized by a considerable infiltration of inflammatory cells such as natural killer cells and macrophages. The inflammatory response also includes the production of cytokines (interleukin-1 and 2, interferon- γ , and tumor necrosis factor)²⁵ as a mechanism of defense; however, these cytokines can induce myocyte damage in a time and dose-dependent manner. Neutralizing antibodies are not detectable until day 4 post-viral inoculation when the viral titers are extremely high. These antibodies are part of the immune virus clearance response; titers reach peak levels on day 14 and correlate with viral elimination in cardiac tissues (day 10).

The subacute phase lasts from day 4 to day 14 post-inoculation. T lymphocyte infiltration of the myocardium reaches a peak level at 7 to 14 days post-inoculation, and the greatest myocardial cell damage occurs during this period. Additionally, B lymphocyte infiltration appears and gradually increases from the first to the third month²⁶. The humoral immune response plays an important role in the processes of myocardial damage and dysfunction. Direct or indirect myocyte injury releases myosin into the circulation, promoting the release of anti-myosin heavy chain antibodies, and also stimulates CD4+ T lymphocytes, which can perpetuate and amplify cardiac cell damage. CD4+ T lymphocyte-stimulated amplification stimulates the production of anti-myosin antibodies from B-lymphocytes, as well as the cytotoxic activity of CD8+ T lymphocytes. Antibody cross-reactivity between viral antigens and myocardial cells can also contribute to myocyte damage. Sera from myocarditis patients exhibits immunohistochemical motifs that could react with various cardiac myocyte membrane or cytoplasmic proteins²⁷.

The chronic phase extends from day 15 to day 90 post-inoculation and is characterized by intense collagen deposition

in the myocardial interstitium, myocardial fibrosis, and progression to heart dilation, dysfunction and failure^{28,29}.

In addition to direct bacterial effects on myocytes, bacterial myocarditis-related cell damage is caused by the considerable production of toxins (variations in toxicity levels depend on the etiological agent) and intense inflammatory responses, which are characterized by high cytokine levels and infiltration of inflammatory cells such as macrophages and natural killer cells.

In drug-induced myocarditis, sensitivity responses can vary from hours to months. Hypersensitivity is partially explained as a response to chemically reactive components that bind to proteins and promote structural alterations. These particles are phagocytized by defense cells and macrophages, which subsequently present then to T lymphocytes through surface receptor. Cytokines such as interleukin-5 (IL-5), which stimulates eosinophils, are released as part of the delayed hypersensitivity response. IL-5 accumulation promotes high levels of eosinophilic infiltration, increased hypersensitivity responses, and increased myocardial injury. Genetic predisposition seems to favor this type of response.

Hypereosinophilic syndrome is associated with several systemic diseases such as Churg-Strauss syndrome, cancer, and parasitic and helminth infections, as well as vaccinations. Those can trigger an intense inflammatory response in the myocardium that results in cell injury, dysfunction, and heart failure³⁰⁻³².

From a pathophysiological perspective, intense eosinophilic infiltrates (mainly CD69-positive cells) occur in the myocardium and other organs and promote the release of mediators that cause extreme damage to the myocytes, thus resulting in necrosis and loss of the myocardial structure. These aggressive factors include eosinophil-derived neurotoxin, eosinophil cationic protein, and eosinophil protease. Additionally, inflammatory cytokines such as tumor necrosis factor (TNF)- α , the interleukins IL-1, IL-6, IL-8, IL-3, and IL-5, and macrophage inflammatory protein also promote myocyte damage and loss and the progression to myocardial dysfunction³³.

Giant-cell myocarditis is an autoimmune form of myocardial injury that is histologically characterized by the infiltration of multinucleated giant-cells as well as inflammatory T lymphocytes, eosinophils, and histiocytes. However, well-defined granulomas are not always observed. Cytotoxic CD8+ T cells are present in significant numbers and promote intense myocyte injury. This condition is observed in 20% of patients with autoimmune diseases, including Hashimoto's thyroiditis, rheumatoid arthritis, myasthenia gravis, and Takayasu arteritis. The release of large amounts of inflammatory cytokines and oxidative stress mediators causes considerable myocyte damage and results in myocyte loss and fibrotic deposition. The intense damage accelerates the progression of myocarditis and is accompanied by rapid losses of ventricular function and unfavorable clinical prognosis³⁴.

Sarcoidosis is a multisystemic disease of unknown etiology that is characterized by the accumulation of T lymphocytes, mononuclear phagocytes, and non-caseating granulomas in the affected tissues^{35,36}. The lungs are affected in 90% of sarcoidosis patients, and the presence of lung disease is an independent factor that correlates with sarcoidosis-associated morbidity and mortality.

4. Diagnosis

Initially, diagnostic assessment of myocarditis is performed by non-invasive diagnostic methods in response to clinical suspicion of disease. However, a diagnosis must be confirmed by a histological analysis of endomyocardial biopsy samples from the right ventricle. Most clinical cases remain at the level of diagnostic suspicion because only a very small fraction of the patients are subjected to EMB to confirm the presence of inflammatory activity (Figure 1).

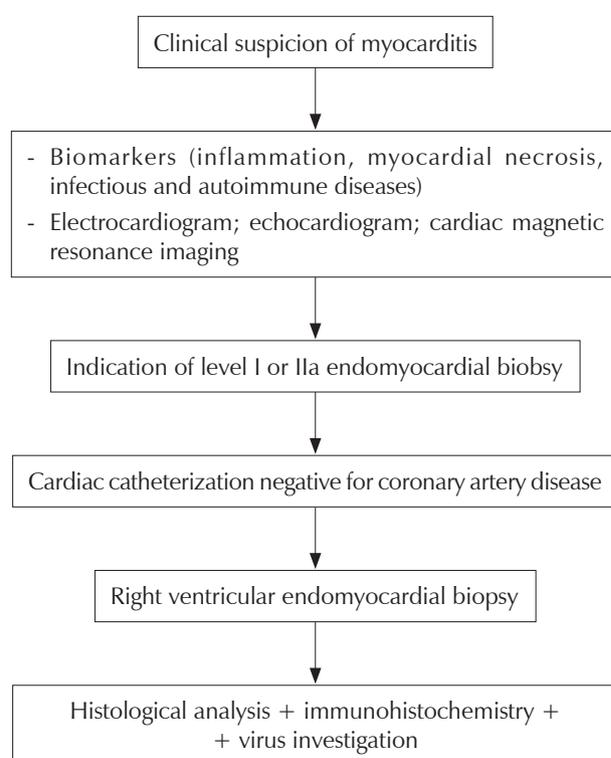


Figure 1 - Flowchart of diagnostic assessment of myocarditis

4.1. Clinical diagnosis

Clinical manifestations of myocarditis are highly variable and range from subclinical forms such as asymptomatic ventricular dilation and dysfunction to acute clinical manifestations such as decompensated heart failure, fulminant myocarditis with cardiogenic shock, chest pain, myocarditis that mimics coronary heart disease, palpitations, syncope or presyncope, and sudden death^{22,37,38}.

Although most cases of myocarditis occur in response to viral infection, respiratory, gastrointestinal, or systemic viral infections are found in only 30% of patients with acute clinical symptoms³⁹.

Acute forms with chest pain can be clinically similar to angina and include characteristics similar those typically observed in acute coronary syndrome, including electrocardiogram alterations and increased levels of myocardial necrosis

markers. Acute myocarditis might also present with similar characteristics to pericarditis when the epimyocardium is affected. Other clinical presentations include acute heart failure, frequent ventricular and atrial arrhythmias, cardiogenic shock, and death^{13,40}.

In newborns and children, myocarditis usually manifests as acute heart failure, sometimes as fulminant heart failure⁴¹, and less frequently as oligosymptomatic dilated cardiomyopathy.

The subacute and chronic forms of myocarditis often manifest initially as dilated cardiomyopathy of recent or indeterminate onset in asymptomatic patients or patients with symptoms of heart failure.

Myocarditis rarely presents with electrocardiographic alterations that indicate variable degrees of atrioventricular conduction disorders that can be associated or not with bundle branch block. More advanced cases exhibit signs of reduced cardiac output due to complete atrioventricular block such as an escape rhythm⁴².

Other symptoms point to more specific forms of myocarditis, including rash, fever, and peripheral eosinophilia, which are suggestive of hypersensitivity myocarditis; dilated cardiomyopathy with thymoma, autoimmune disorders, ventricular tachycardia, or advanced block, which are suggestive of giant-cell myocarditis; and ventricular arrhythmias and advanced block, which might indicate sarcoidosis⁴³.

4.2. Laboratory assessment

4.2.1. Laboratory markers of inflammatory activity

Nonspecific serum inflammatory markers such as the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, and white blood cell counts might be increased or unaltered. Such markers can reflect either the presence of myocardial or pericardial inflammation or the underlying systemic autoimmune or hypersensitivity disease. The detection of increased levels of myocardial necrosis markers depends on the stage of acute myocarditis progression and the extent of inflammatory activity at the time of diagnosis. Unlike coronary syndromes, which exhibit typical increasing/decreasing curves, the levels of myocardial necrosis markers remain at a plateau in myocarditis. Increased (I or T) troponin levels are more common than increased creatine kinase-MB (CK-MB) levels; high levels indicate a worse prognosis (Table 2)^{25-27,33,34}.

4.2.2. Laboratory markers for etiopathogenic investigation

Tests used to investigate the cause of myocarditis depend on the clinical suspicion. As a rule, all patients should be investigated for systemic autoimmune inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, Churg-Strauss syndrome, and celiac disease¹⁰. Viral serological tests often exhibit low sensitivity and specificity and only 4% correlate with myocardial viral infection⁴⁴. Thus, viral serological tests should not be routinely included in diagnostic assessments of myocarditis (table 2). In Brazil, Chagas disease must be routinely investigated in all patients residing in endemic areas due to the high prevalence of infection.

Table 2 – Recommendation of laboratory exams for myocarditis.

Recommendation class	Indications	Evidence level
Class I	Investigation of systemic inflammatory diseases in acute myocarditis	C
Class IIa	Troponin for diagnosis and prognosis of acute myocarditis	B
Class IIa	Nonspecific inflammatory markers (ESR, CRP, white blood cell count) for diagnosis of acute myocarditis	C
Class IIb	Viral serological testing	B

4.3. Electrocardiogram (ECG)

Electrocardiographic alterations depend on the myocardial inflammatory activity stage. As a rule, the ECG diagnostic sensitivity is 47%⁴⁵.

In acute myocarditis, the most common findings are repolarization disorders and atrioventricular block, as well as patterns that suggest coronary ischemia with ST segment elevation or depression (specific area or diffuse); the presence of Q waves indicates a worse prognosis. Supraventricular or ventricular arrhythmias are frequent findings^{27,33}. In the subacute or chronic phases, electrocardiographic signs of chamber remodeling such as ventricular overload and left bundle branch block are common and indicate a worse prognosis⁴⁶.

When the pericardium and myocardium are simultaneously affected (perimyocarditis), the classical electrocardiographic pattern of pericarditis with diffuse ST segment elevation and PR segment depression is commonly observed⁴⁷.

Recommendations for the use of an electrocardiogram in myocarditis are described in Table 3.

Table 3 – Recommendations for the use of an electrocardiogram in myocarditis assessment

Recommendation class	Indication	Evidence level
Class I	ECG on suspicion of myocarditis	C

4.4 Echocardiogram

Echocardiographic findings are nonspecific for myocarditis. The echocardiographic alterations reflect myocardial inflammatory activity and consequences to ventricular function and remodeling; additionally, intraventricular or atrial clots might also be found^{48,49}. Alterations in ventricular contractions might be diffuse or segmental and are indistinguishable from signs of ischemia^{9,50}.

Right ventricular dysfunction is uncommon and its presence is a sign of worse prognosis⁵¹. Fulminant myocarditis is usually accompanied by important systolic dysfunction that is

characterized by normal chamber diameters and sometimes associated with increased septal wall thickness, which denotes myocardial edema^{49,52}. Pericardial effusion in the absence of congestive heart failure suggests pericardial inflammation such as myopericarditis.

Echocardiography plays an important role in the differential diagnosis of myocarditis over other conditions with similar clinical presentations, such as acute valvular heart disease, takotsubo inflammatory cardiomyopathy, and acute myocardial infarction. It also serves as guide for endomyocardial biopsies (Table 4).

Table 4 – Recommendations for the use of an echocardiogram in myocarditis assessment

Recommendation class	Indications	Evidence level
Class I	Echocardiogram for functional assessment	B
Class IIa	Echocardiogram as a guide during EMB	C

4.5. Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) permits the identification of myocardial inflammatory injuries in the acute and subacute phases of myocarditis, as well as scars that are often present in chronic myocarditis. The three main MRI techniques used to characterize myocardial injury in patients with myocarditis are the T2-weighted sequences (*T2 imaging*), early global myocardial enhancement, and the late enhancement technique⁵³.

T2-weighted images permit the assessment of myocardial edema secondary to regional or systemic inflammation in patients with acute myocarditis.

In the early global enhancement technique, images acquired during the first minutes after gadolinium administration represent the areas most affected by inflammatory injury^{54,55}. This assessment measures the signal intensity before and after the injection of gadolinium-based contrast agents and compares the values to the variation of intensity in skeletal muscle tissue within the visual field (e.g. the pectoral muscle). Signal intensity ratios of myocardium to skeletal muscle greater than 4:1 denote inflammation-induced hyperemia and capillary extravasation.

The late enhancement technique permits the assessment of areas with irreversible myocardial injury and thus the identification of necrotic and fibrotic areas in acute or subacute and chronic myocarditis cases, respectively⁵⁶⁻⁵⁸. The late enhancement pattern of distribution in myocarditis and myocardial infarction are very different. In myocarditis, the pattern is often mesocardial and the endocardium is spared; however, the distribution is occasionally epicardial and transmural. The enhanced areas are usually multifocal, heterogeneous, sparse, and not restricted to the coronary territories. However, this pattern of distribution does not occur in every case; some cases exhibit patterns similar to those of coronary disease.

Although each of the abovementioned individual techniques exhibits satisfactory diagnostic accuracy, several studies have shown that optimal results are achieved when the 3 diagnostic criteria are combined⁴⁸. When at least 1 criterion is present, MRI exhibits sensitivity, specificity, positive predictive value (PPV), negative predictive value, and accuracy rates of 88%, 48%, 68%, 68%, and 70%, respectively; when 2 of the criteria are present, the respective rates are 67%, 91%, 91%, 69%, and 78%⁹. The diagnostic accuracy is greater in acute myocarditis cases than in suspected subacute or chronic cases.

MRI is indicated for the diagnostic assessment of patients with suspected acute or chronic myocarditis and also for patients with recent-onset ventricular dysfunction and suspicion of past myocarditis, regardless of manifestation. However, MRI has particular value in cases with increased levels of myocardial necrosis markers and normal coronary arteries according to angiography (acute infarction-like presentation). MRI must be performed as early as possible when myocarditis is clinically suspected. Follow-up tests must be performed 4 and 12 weeks after the acute episode to assess inflammatory progression and remodeling in positive cases. Due to logistical issues that are inherent to the method, MRI is not indicated for the assessment of patients with fulminant myocarditis and hemodynamic instability (Table 5).

Positive late enhancement correlates with worse long-term prognosis in patients with endomyocardial biopsy-confirmed viral myocarditis. The global mortality and heart disease-related mortality rates are higher in such patients, regardless of clinical symptoms and ventricular function. Negative late enhancement correlates with a low risk of sudden death, regardless of ventricular dysfunction and dilation⁵⁹.

Table 5 – Recommendations for the use of MRI in myocarditis assessment

Recommendation class	Indications	Evidence level
Class I	MRI to assess ventricular function, geometry and morphology when acute, subacute or chronic myocarditis is suspected	B
Class IIa	MRI in diagnostic investigation of acute, chronic, and/or suspected past myocarditis	B
Class IIa	MRI as 4- to 12-week follow-up after the acute episode	C
Class III	MRI for fulminant myocarditis with hemodynamic instability	B

4.6. Computed tomography angiography

Computed tomography angiography (CTA) is faster and more widely accessible than MRI, relative to differential chest pain diagnoses. However, disadvantages of CTA include the use of iodinated contrast agents and ionizing radiation⁶⁰. CTA

might provide normal coronary images (when triggered by ECG)⁶¹ and thus rule out ischemia and myocardial infarction.

Additionally, coronary CTA might be used in the differential diagnosis of acute coronary syndrome to exclude significant coronary heart disease in patients who exhibit infarction-like clinical manifestations (chest pain, elevated myocardial necrosis markers, and ECG alterations; Table 6).

Table 6 – Recommendations for the use of coronary tomography angiography in myocarditis assessment.

Recommendation class	Indication	Evidence level
Class IIa	Coronary CTA to rule out severe obstructive coronary disease in the investigation of myocarditis	C

4.7. Nuclear medicine

Nuclear medicine analyses have been used to assess patients with suspected myocarditis for more than three decades⁶². The main applications of such modalities are related to assessments of left ventricular function, the presence of cardiac inflammation, myocarditis subtype identification, and therapeutic responses.

In assessments of cardiac inflammation, myocardial inflammation can be detected by various radionuclide techniques^{63,64}. Of these, gallium-67 scintigraphy is the most widely used and has a 50% sensitivity rate in myocarditis diagnosis. The best results are achieved when gallium-67 scintigraphy is performed within the first three months from the clinical disease onset⁶⁵. The accuracy of gallium-67 scintigraphy is particularly high in some specific forms of myocarditis (e.g. sarcoidosis).

In gallium-positive cases with inflammation, as indicated by endomyocardial biopsy, changes in the marker over time can be used to monitor inflammatory activity and treatment response (Table 7). In some studies, indium-111-labeled monoclonal antibodies could predict myocarditis in myocardial biopsies.

Table 7 – Recommendations for the use of myocardial scintigraphy in myocarditis assessment

Recommendation class	Indication	Evidence level
Class IIb	Gallium scintigraphy for the investigation of myocarditis	B

4.8. Endomyocardial biopsy

Endomyocardial biopsy (EMB) is the gold standard for myocarditis diagnosis, investigations of viral persistence in the myocardium, and other non-inflammatory cardiovascular

diseases. The aim of EMB is to establish a diagnosis of myocardial inflammation with or without viral persistence and thus to define the need for and type of treatment⁶⁶.

In cases of recent-onset heart failure (less than two weeks) with hemodynamic instability that is non-responsive to usual treatment and/or with ventricular arrhythmias or high-grade heart block, EMB is important in investigations of the causal factors that might affect treatment. EMB can indicate a need for immunosuppressant treatment and thus can improve the prognoses of conditions such as giant-cell and necrotizing eosinophilic myocarditis and cardiac sarcoidosis⁶⁷⁻⁶⁹.

Studies have focused on EMB for symptomatic chronic dilated cardiomyopathy with possible viral etiology because antiviral or immunomodulating therapies were found to improve the ejection fraction in patients with symptomatic heart failure after six months of optimized treatment⁷⁰.

Myocarditis can also be induced by some pharmacological agents. EMB plays a crucial role in cases with unclear diagnoses and rapid disease progresses with suspicion of allergic reactions and eosinophilia, as these contribute to a differential diagnosis from other conditions. Due to the invasive nature, EMB is restricted to cases with unfavorable progression and unknown cardiac dysfunction etiology in patients subjected to chemotherapy⁷¹.

Few studies have reported indications of EMB in ventricular arrhythmias of unknown cause. The incidence of histological myocarditis diagnoses in these studies is highly variable. The detection of active myocarditis in a patient with malignant ventricular arrhythmia could theoretically lead to a decision to defer the installation of an implantable cardioverter-defibrillator until the inflammatory activity decreases. Nevertheless, such an approach remains controversial⁷².

The indications of EMB in myocarditis are described in Table 8.

Table 8 – Indications of endomyocardial biopsy

Recommendation class	Indications	Evidence level
Class I	Heart failure (HF) of recent onset (< 2 weeks) without definite cause; non-responsive to usual treatment; hemodynamic deterioration	B
Class I	HF onset between 2 weeks to 3 months without definite cause; associated with ventricular arrhythmias or second- or third-degree atrioventricular block	B
Class IIa	HF onset between 3 months and < 12 months, without definite cause; non-responsive to optimized standard treatment	C
Class IIa	HF due to dilated cardiomyopathy of any duration with suspected allergic reaction and/or eosinophilia	C
Class IIb	Ventricular arrhythmias without definite cause	C

4.8.1. Technique

EMB must be performed in a hemodynamics laboratory by a specialist with procedural experience. Local anesthesia is used, with conscious sedation if necessary, under the continuous supervision of an anesthesiologist.

EMB can be performed safely when guided by direct fluoroscopy, with echocardiographic support^{73,74} to indicate the proper positioning of the bioprobe to avoid puncturing the right ventricular (RV) free wall⁷⁵.

MRI prior to EMB might be helpful to identify focal right or left ventricular lesions and thus indicate sites for sample collection⁷⁶. Although no comparative studies support the recommendation to perform EMB in either the right or the left ventricle (LV), EMB should be performed in the LV only if the full extent of disease is limited to the LV, which in some cases might be determined by MRI.

Samples must be taken from the distal portion of the interventricular septum and apical trabecular area of the RV while avoiding the free wall. The number of collected samples depends on the study aims⁷⁷. In cases of viral myocarditis, 10 samples are needed (six for viral investigation, two for hematoxylin-eosin (HE) staining, and two for immunohistochemical analysis). In cases of infiltrative or storage diseases, six samples are needed (two for HE staining, two for immunohistochemistry, and two for electron microscopy). The samples for HE staining and immunohistochemistry must be stored in 10% buffered formalin and should not be refrigerated. The samples for viral investigation must be collected in Eppendorf® microtubes (without transport solution), placed on dry ice, and quickly stored at -70 °C. The samples for electron microscopy must be placed in Eppendorf® tubes with OCT solution.

4.8.2. Complications

EMB complications are rare; the complication frequencies were 1.7% in a case study of approximately 2,400 patients⁷⁸ and less than 1% in another study of more than 4,000 patients⁷⁹. The use of echocardiogram associated with fluoroscopy resulted in significant reductions in the likelihood of involuntary punctures and subsequent myocardial perforation or coronary injury.

The reported complications include vasovagal syncope, variable grades of atrioventricular (AV) block, perforation of the RV free wall, pneumothorax, perforation of the ventricular septum, puncture site hematoma, intracardiac fistula, retroperitoneal hematoma (femoral access), pericardial effusion, clot displacement, cardiac tamponade, tricuspid chord rupture, and ventricular arrhythmia.

4.9. Pathology

4.9.1. Pathology analysis

The Dallas classic criteria for myocarditis require the presence of inflammatory cells and myocyte necrosis in the endomyocardial biopsy; the absence of necrosis characterizes the so-called borderline myocarditis. The Dallas criteria are widely criticized for a lack of correlation with clinical progression, viral presence and interexaminer variability⁸⁰.

More recently, a suggestion was made to base histological diagnoses of inflammation on lymphocyte and macrophage counts associated with immunohistochemical evaluations of HLA-DR expression⁸¹.

Fulminant myocarditis – The most common cause of fulminant myocarditis is **diffuse lymphocytic myocarditis** with interstitial edema and myocytolysis and good responses to immunosuppressant treatments. A differential diagnosis must be established from giant-cell and necrotizing eosinophilic myocarditis by endomyocardial biopsy due to the prognostic relevance.

Giant-cell myocarditis – Chronic diffuse inflammation with giant cell infiltration that usually occurs in patients that present with other autoimmune diseases.

Necrotizing eosinophilic myocarditis – Very rare condition, with diffuse inflammatory infiltrate where eosinophils predominate and there is extensive necrosis.

Acute myocarditis – Variable degrees of inflammation in an endomyocardial biopsy; usually presents with lymphohistiocytic infiltrates, intracellular and interstitial edema, and focal or diffuse myocytolysis.

Chronic active myocarditis – Frequent form of myocarditis in adults. Endomyocardial biopsy shows active lymphocytic or borderline myocarditis, degenerative fiber changes, and interstitial hypertrophy and fibrosis. Lymphocyte counts might improve diagnostic accuracy as the presence of more than 7 lymphocytes/mm² indicates mild myocarditis, while more than 14/mm² indicates moderate myocarditis. The diagnostic accuracy can be improved by Immunohistochemical.

Storage diseases – Diagnosis requires specific staining techniques to detect amyloid matter, iron, and mucopolysaccharides, among others. Electron microscopy is often helpful for diagnostic confirmation.

Cardiotoxicity – Electron microscopy is critical to the early diagnosis of alterations such as those induced by anthracyclines, which are characterized by extensive myofibrillar lysis, mitochondrial rupture and intramyocyte vacuolization⁸², and injury according to dose progression

4.9.2. Immunochemical histological analysis

To perform immunohistochemical analyses of myocardial tissues, at least two endomyocardial biopsy samples are needed. The samples must be stored in 10% buffered formalin at room temperature and must not be frozen. The diagnostic accuracy of immunohistochemistry for the detection of inflammation in myocarditis is higher than that of the histological criteria. The immunohistochemical assessment is based on the analysis of specific antigen-antibody reactions; for this purpose, mononuclear cells (T and B lymphocytes) and other leukocytes are labeled with specific antibodies to improve both inflammatory cell identification and counts. Immunohistochemistry can also identify the cytokine-induced activation of inflammation through the detection of class I and II histocompatibility antigens (HLA-DR) in the endothelial cells

or interstitium of cardiomyocytes or perivascular cells, as well as the expression of intercellular adhesion molecule (ICAM) receptors on cell surfaces⁸³⁻⁸⁵. Because it detects inflammatory infiltrates as well as cytokine-induced cell adhesion capabilities, immunohistochemistry can identify myocardial inflammation that is distant from the primary infection site, which renders it more accurate than conventional histological analyses for right ventricular endomyocardial biopsy-based myocarditis diagnoses^{86,87}.

The increased myocardial expression of HLA-DR and ICAM might be diffuse or localized and is usually associated with the presence of inflammatory cells (more than two CD3+ T lymphocytes per optical microscopy field (400X), which corresponds to 7.0 cells/mm²)⁸⁸⁻⁹⁰.

A diagnosis of myocarditis can be established from a score that combines HLA-DR expression and inflammatory infiltration^{91,92}.

Score	Criteria
0	Absence or mild presence of HLA-DR in endothelial and interstitial cells
1	Focal presence of HLA-DR in endothelial and interstitial cells
2	Multifocal presence of HLA-DR restricted to the endothelial cells
3	Diffuse presence of HLA-DR in endothelial cells and focal presence in cardiomyocytes
4	Diffuse presence of HLA-DR in endothelial cells and cardiomyocytes

To establish a diagnosis of myocarditis, the HLA-DR positive score must be at least three or the ICAM-1 positive score must be at least two; additionally, the presence of at least 7.0 inflammatory cells/mm² should be observed. Scores from one to three indicate a possible diagnosis of inflammation.

A diagnosis of myocarditis might also be established when lymphocyte counts are at least 14.0 cells/mm². If the count is less than 14 cells/mm², the lymphocyte count might be used for to confirm myocarditis^{37,93}.

Table 9 describes the indications for the use of immunohistochemical analysis in myocarditis.

Table 9 – Indications for the use of immunohistochemistry for myocarditis diagnosis

Recommendation class	Indications	Evidence level
Class I	Immunohistochemistry with class I and II HLA-DR for diagnostic investigation of myocardial inflammation	B
Class I	Immunohistochemistry in the investigation and counting of T and B lymphocyte and macrophage infiltrates	B

5. Treatment

5.1. General and preventive measures: lifestyle, exercise, and diet

The general measures indicated for myocarditis treatment target symptomatic or asymptomatic heart failure (stages B to D). The restriction of dietary sodium intake to two to three g/day is indicated in the absence of hyponatremia and calorie restriction and is a crucial adjuvant in more advanced clinical stages. Fluid restriction to 1,000 – 1,500 ml/day is also recommended during the symptomatic stage.

Smoking and excessive alcohol consumption are contraindicated, and the patients must monitor body weight to avoid both obesity and cachexia. Non-steroidal anti-inflammatory agents should not be used during the acute phase nor in the presence of heart failure^{94,95}. Animal studies showed that aerobic activity during the acute disease phase resulted in increased mortality⁹⁶. Therefore, because myocarditis is a cause of sudden death in young athletes⁹⁷, patients should not perform intense physical exercise for up to six months or longer after the acute phase, depending on the symptoms or the presence of residual effects on ventricular function^{98,99}.

Available prophylactic vaccines (mumps, measles, rubella, poliomyelitis, and influenza) should be administered to reduce rates of myocarditis from the corresponding viruses. Vaccination should not be performed during the active disease phase. Studies in animal models show that influenza vaccination prevents myocardial damage but no studies have been conducted in human beings¹⁰⁰.

Table 10 summarizes the indications of non-pharmacological measures in myocarditis.

Table 10 – Recommendations of non-pharmacological measures in myocarditis

Recommendation class	Indications	Evidence level
Class I	Sodium intake of 2 to 3 g/day in patients with heart failure	C
Class I	Fluid restriction to 1,000-1,500 ml/day in patients with heart failure	C
Class IIa	Body weight monitoring to avoid obesity and cachexia	C
Class IIa	Vaccination when disease is not active	C
Class III	Exercise during and up to 6 months after the acute phase	C
Class III	Use of non-steroidal anti-inflammatory agents in the acute phase and in cases of ventricular dysfunction in the chronic phase	C
Class III	Smoking	A

5.2. General supportive treatment: beta-blockers, ACE inhibitors/ARB, anticoagulants

Modulation of the renin-angiotensin-aldosterone system attenuates the progression of ventricular dysfunction and reduces myocardial fibrosis, necrosis, and inflammation in experimental models^{101,102}. Angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB) are administered to all patients with ventricular dysfunction, even in the absence of heart failure, provided there are no contraindications; ACE and ARB are administered in increasing doses up to the recommended maximum. Maintenance ACE inhibitors/ARB regimens are recommended after ventricular function is normalized. In one study of ACE inhibitor discontinuation, approximately 33% of the patients exhibited new episodes of heart failure versus 5% of patients who did not discontinue the medication¹⁰³. ARB can be used in cases of ventricular dysfunction and intolerance to ACE inhibitors.

The indication for beta-adrenergic blockers in myocarditis arises from the need to reduce the levels of sympathetic activity and noradrenaline and thus to hinder the progression of myocardial dysfunction and improve the prognosis. Beta-blockers are indicated for all patients with ventricular dysfunction and heart failure in increasing doses up to the recommended maximum, provided there are no contraindications. A maintenance regimen of beta-blockers is recommended for at least 1 year after ventricular function is normalized.

The use of oral anticoagulants (OAC) is indicated in patients with myocarditis associated with paroxysmal or permanent atrial fibrillation (AF), intracavitary clots, or a previous history of thromboembolism¹⁰⁴.

Table 11 describes the recommendations of pharmacological measures in myocarditis.

Table 11 – Recommendations of general pharmacological measures in myocarditis

Recommendation class	Indications	Evidence level
Class I	ACE inhibitors and ARB to all patients, except in cases with contraindications	C
Class I	Beta-blockers in ventricular dysfunction	C
Class I	OAC in paroxysmal or permanent AF	C
Class IIa	ACE inhibitors/ARB following normalization of the ventricular function	C
Class IIa	Beta-blockers following normalization of the ventricular function	C

5.3. Specific therapy

5.3.1. Immunosuppression

The aim of immunosuppressive treatment for myocarditis is to suppress inflammatory responses and autoimmune activity, to induce consequent improvements in clinical manifestations and ventricular function, and to reduce mortality. Indications for immunosuppressive therapies require a confirmation of

myocardial inflammatory activity via endomyocardial biopsy and the exclusion of viral presence (Figure 2).

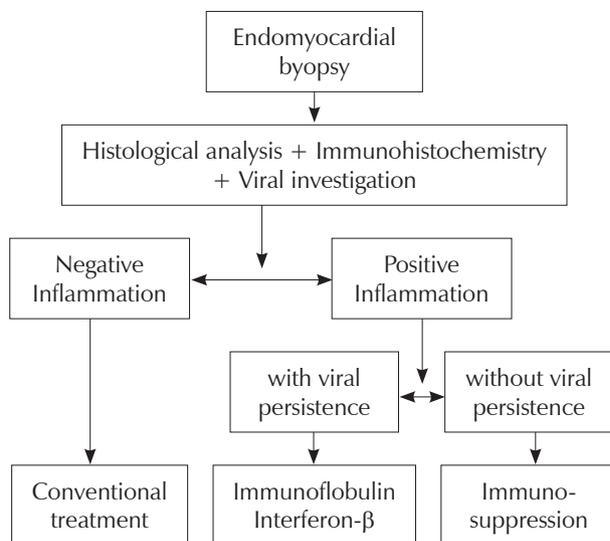


Figure 2 - Therapeutic flowchart for viral myocarditis

Factors such as the spontaneous regression of inflammation, which occurs by approximately 50%. Of cases, the lack of standardization of the diagnostic criteria used in studies, the small number of patients in most trials, the clinical heterogeneity of the investigated populations, and the lack of clinical studies that seek to assess the reduction of mortality alone have resulted in difficulties in analyses of the clinical benefits of immunosuppressant therapy. Clinical studies¹⁰⁵ that assessed survival improvements did not find additional benefits from immunosuppressant therapy when compared to conventional treatments for heart failure. However, those studies had several methodological flaws, including a lack of viral investigation and the exclusive use of the Dallas histological criteria to diagnose myocarditis without immunohistochemical analysis. Because these flaws could compromise the results of immunosuppressive therapies, the potential effects of such therapies on mortality reduction remain unexplored.

In patients with chronic heart failure with active myocarditis and without viral infection, immunosuppressive treatment correlated with clinical improvement, reduction in chamber diameters, improvement of ventricular function, and regression of inflammatory activity (Table 12)¹⁰⁶⁻¹⁰⁹. In cases of autoimmune, eosinophilic hypersensitive, sarcoidosis-related, cyclophosphamide-related (systemic lupus erythematosus) and giant-cell myocarditis, corticosteroids treatment correlated with improvements in clinical manifestations, ventricular function and survival. However, such benefits were reported in studies conducted on small numbers of patients¹¹⁰⁻¹¹².

A combination of prednisone and azathioprine, administered over six months, is the most commonly used

immunosuppressant regimen in patients with post-viral myocarditis (Table 13). Patients receiving immunosuppressant therapy must be closely monitored for side effects that might significantly increase morbidity and mortality.

Table 12 – Indications for the use of immunosuppressant therapy in myocarditis

Recommendation class	Indications	Evidence level
Class I	Myocarditis induced by giant cells, autoimmune diseases, sarcoidosis, and hypersensitivity, associated with ventricular dysfunction.	B
Class IIa	Myocarditis confirmed by EMB with negative viral tests in patients with chronic HF to improve the clinical state and ventricular function	B
Class III	In acute HF, non-responsive to usual treatment	C

Table 13 – Immunosuppressant treatment with prednisone and azathioprine

Prednisone	
First 4 weeks	1 mg/Kg/day
5 to 12 weeks	Reduce dose by 0.08 mg/kg/week
13 to 20 weeks	Maintain dose at 0.3 mg/kg/day
21 to 24 weeks	Reduce dose by 0.08 mg/kg/week
Azathioprine	
1 to 24 weeks	2 mg/kg/day

5.3.2. Antiviral therapy

Antiviral therapy is used to eliminate viruses and prevent viral replication. Available regimens include subcutaneous interferon-β (IFN-β) infusion and intravenous immunoglobulin (IG-IV).

In an experimental model of viral myocarditis in animals genetically modified for IFN-β-deficiency, extensive viral proliferation and intense inflammatory activity were associated with greater ventricular dysfunction and mortality. These results suggest that IFN-β is important to the control of viral infection in myocarditis¹¹³.

Subcutaneous IFN-β infusion in patients with dilated cardiomyopathy and viral persistence (adenoviruses and enteroviruses) is associated with viral elimination and clinical improvements in functional capacity and ventricular function¹⁰⁰. In patients with parvovirus B19-induced myocarditis, IFN-β infusion correlated with reduced viral loads and improved endothelial and ventricular function¹¹⁴. Therefore, IFN-β treatment is an increasingly reliable antiviral treatment option for patients with viral myocarditis.

IG-IV exhibits anti-inflammatory activities and thus reduces immune antiviral responses. It promotes the reduced pro-

inflammatory cytokine activity and exhibits anti-idiotypic properties associated with the reduced production and neutralization of autoantibodies. Additionally, IG-IV exhibits an antiviral activity by reducing viral replication and favoring viral elimination⁹⁹.

The use of IG-IV in recent onset dilated cardiomyopathy was not associated with improved ventricular function when compared to a placebo. However, some methodological flaws might have compromised the results because patients with or without inflammation in endomyocardial biopsies were included; in this study, inflammation was confirmed only in 16% of patients, viral presence was not investigated, and inflammation was diagnosed according to the Dallas criteria⁹⁹.

In adenoviruses and cytomegalovirus (CMV)-induced myocarditis, IG-IV reduced both the viral load and inflammation and consequently improved the clinical state and ventricular function. In parvovirus B19-induced myocarditis, the viral load persisted in 40% of the patients after IG-IV; patients that eliminated the virus exhibited improvements in ventricular function and reduced chamber diameters¹¹⁵. These results suggest that the therapeutic benefit of IG-IV is restricted to myocarditis with active inflammation as assessed by immunohistochemistry and positive virus identification (table 14).

Table 14 – Recommendation of antiviral therapy with immunoglobulin in myocarditis

Recommendation class	Indications	Evidence level
Class IIa	Myocarditis confirmed by EMB and positive testing for adenoviruses, CMV, and parvovirus B19, to improve the clinical state and ventricular function	B
Class IIb	Myocarditis confirmed by EMB and positive testing for adenoviruses, enterovirus, and parvovirus B19 in patients with chronic HF, to improve the clinical state and ventricular function	B
Class III	Use of IG in patients with acute HF, non-responsive to treatment	C

5.3.3. Immunomodulation

Immunomodulation is used to reduce inflammatory and autoimmune responses by removing and modulating the aggressive agents that might be involved in myocarditis pathogenesis.

Immunoabsorption therapy by selective plasmapheresis aims to remove specific autoantibodies and can be used with IG-IV to modulate inflammatory cytokines and autoantibody production. Immunoabsorption is associated with IG-IV-induced reductions myocardial inflammatory activity, improvements in functional class and ventricular function, and longer survival after a five-year follow-up period in patients with chronic inflammatory cardiomyopathy and high serum levels of anti-β1 myocardial adrenoceptor autoantibodies.

Although those results point to the possible benefits of immunoabsorption for patients with autoimmune myocarditis, the number of investigated patients was too small to establish a definitive treatment strategy¹¹⁶.

The anti-inflammatory properties of pentoxifylline include blocking of TNF-α transcriptase and reduced IL-2 and IL-6 levels with consequent reductions in cytokine-induced cardiac damage¹¹⁷.

Pentoxifylline, administered in doses of 1,200 to 2,400 mg/day over six months, resulted in improvements in functional class and ventricular function in patients with dilated cardiomyopathy with chronic heart failure and peripartum cardiomyopathy (Table 15). Those results indicate a beneficial role for pentoxifylline as an adjuvant treatment for chronic inflammatory cardiomyopathy; however, this benefit must be investigated in recent-onset cardiomyopathy and acute myocarditis¹¹⁸⁻¹²¹.

Table 15 – Recommendation for the use of pentoxifylline as an immunomodulator.

Recommendation class	Indication	Evidence level
Class IIb	Use of pentoxifylline in chronic inflammatory or peripartum cardiomyopathy to improve the clinical state and ventricular function	B

6. Special Situations

6.1. Treatment of arrhythmias and prevention of sudden death

During the acute phase of myocarditis, patients can develop tachy- or bradyarrhythmias. Such arrhythmias often disappear after the acute phase and thus only supportive treatment is normally provided.

As a rule, antiarrhythmic treatment is not recommended for asymptomatic atrial and ventricular extrasystoles. Supraventricular tachycardia (SVT), especially atrial fibrillation and flutter, can induce or exacerbate heart failure. The recommended initial approach to symptomatic sustained SVT is restoration of the sinus rhythm by electrical or chemical cardioversion. For cases of recurrent sustained SVT, therapeutic options include catheter ablation and ventricular frequency control.

Cases of asymptomatic nonsustained (NS) ventricular tachycardia (VT) should not be specifically treated. Sustained ventricular arrhythmias should be treated with antiarrhythmic agents after acute electrical reversion. Only amiodarone is available for such treatments because other class I and III drugs are normally avoided in these patients due to the proarrhythmic effects.

Complete atrioventricular (AV) block and symptomatic sinus bradycardia represent indications for temporary stimulation during the acute phase of myocarditis. These conduction disorders are often transient.

As no data exists in the literature about long-term risks for patients with VT or cardiac arrest during the acute phase of myocarditis, management is decided on an individual basis. The implant of a cardiac defibrillator (ICD) is indicated after optimized pharmacological therapy in patients who develop dilated cardiomyopathy during the chronic phase of myocarditis, according to the criteria described in Table 16.

Table 16 – Treatment of arrhythmias and prevention of sudden death in myocarditis

Recommendation class	Indications	Evidence level
Class I	Placement of temporary transvenous pacemaker in patients with symptomatic bradycardia and/or AV block during the acute phase of myocarditis	C
Class I	Beta-blockers in optimized doses to prevent sudden death in patients with myocarditis	A
Class IIa	ICD implant as primary prevention of sudden death in patients with dilated cardiomyopathy during the chronic phase of myocarditis, functional class II-III, LVEF \leq 35%, and at least one year of life expectancy	A
Class IIa	ICD implant as primary prevention of sudden death in patients with dilated cardiomyopathy during the chronic phase of myocarditis (>6 months), functional class III-IV, QRS \geq 150 ms, LVEF \leq 35%, with indication of TRC, and with at least one year of life expectancy	B
Class IIa	Antiarrhythmic treatment with amiodarone in symptomatic NSVT or sustained VT during the acute phase of myocarditis	C
Class III	Physical activity during the acute phase of myocarditis	C
Class III	Indication of ICD in the acute and subacute phase of myocarditis (<6 months)	C

6.2. Fulminant myocarditis

Traditionally, fulminant myocarditis was thought to be the most severe form of acute myocarditis. It is characterized by an acute and extremely fast disease progression with functional class IV congestive heart failure, cardiogenic shock and high lethality in the absence of appropriate hemodynamic support¹²².

In fulminant viral myocarditis, persistently high viral levels usually occur in susceptible individuals in combination with persistent T lymphocyte activation and the production of antibodies that mediate injury responses against myocytes²².

Felker et al. described the characteristics clinical fulminant myocarditis over a long-term follow-up period¹²³. Frequently, in such patients infectious responses were observed during the last four weeks as well as febrile syndromes during the last 12 weeks. The presentation is acute and progressive

and the vast majority of patients exhibit functional class III/IV symptoms at the time of diagnosis. Additionally, the affected patients exhibit higher levels of arterial hypotension and tachycardia and reduced ventricular dilation than those with non-fulminant myocarditis.

Despite the dramatic progression, the prognosis for fulminant myocarditis can be very good if a diagnosis is established early and clinical and hemodynamic supportive treatments are started immediately; eventually, reversion of the ventricular dysfunction and satisfactory late survival rates are observed^{124,125}.

Concerning the specific treatment for myocarditis, identification of causal factors by EMB and histological investigation permits the establishment of specific therapeutic strategies such as immunoglobulin in viral myocarditis cases, immunosuppressants in virus-negative autoimmune myocarditis cases, and corticosteroids in sarcoidosis or giant-cell myocarditis cases. High doses of immunoglobulin were tested and were effective in a case study; however, this result has not yet been confirmed in randomized trials^{126,127}. Inotropic agents and eventually vasopressor drugs should be included in supportive treatment regimens. Immediate failures of pharmacological treatment and fluid replacement indicate a need for hemodynamic support via circulatory assist devices. Frequently used devices such as intra-aortic balloon pumps, percutaneous devices (e.g. TandemHeart and Impella), extracorporeal circulation (ECMO), and paracorporeal artificial ventricles (CENTRIMAG) provide a bridge to recovery or to heart transplantation. Short-term devices are indicated for seven-to-10 days of supportive treatment¹²⁸. If stabilization is not achieved in that time period, ECMO or artificial ventricles might provide additional support and thus increase the odds of ventricular dysfunction recovery¹²⁹.

The indications in fulminant myocarditis are described in table 17.

Table 17: Indications in fulminant myocarditis

Recommendation class	Indications	Evidence level
Class I	Myocarditis induced by giant cells, autoimmune diseases, sarcoidosis, and hypersensitivity.	B
Class I	Hemodynamic support by means of temporary circulatory assist devices when fulminant myocarditis is suspected, and when facing failure of inotropic agents, vasoactive drugs with intra-aortic balloon pump	B
Class I	Priority heart transplant in patients who do not exhibit clinical and hemodynamic improvement in spite of the instituted treatment	B
Class I	Circulatory support with long-term devices when clinical and hemodynamic states do not improve after more than 10 days of temporary support	B
Class I	Performance of EMB in fulminant myocarditis	C

Recommendation class	Indications	Evidence level
Class IIb	Use of IG-IV in patients with clinical manifestations of fulminant myocarditis after confirmation of viral infection via EMB; non-responsive to the initial supportive treatment	B
Class IIb	Indication of immunosuppressant therapy for patients with clinical manifestations of fulminant myocarditis after confirmation of inflammation and viral absence by means of EMB; non-responsive to the initial supportive treatment	B

6.3. Stress (takotsubo) cardiomyopathy

Stress cardiomyopathy diagnoses in emergency care settings have increased in patients with acute ventricular dysfunction. Older postmenopausal women represent the largest risk group (approximately 80% of cases). Cardiomyopathy is frequently triggered by intense physical or emotional stress, financial losses, or natural disasters and sometimes by stress from other diseases. The prognosis of stress cardiomyopathy is good; the in-hospital mortality rate is 2% and normally, cardiac function is fully recovered in two to four weeks¹³⁰.

The main clinical findings are chest pain, dyspnea, and syncope. Electrocardiographic alterations occur frequently and include segment ST depression (34 to 56%), pathologic Q waves, inverted T wave with QT interval prolongation, and nonspecific repolarization disorders. Cardiac troponin levels are often elevated and small increases in troponin conflict with the contractility and hemodynamic disorders¹³¹. Left ventriculography and Doppler echocardiography show apical ballooning with dyskinesia or akinesia, which affects 50-67% of the left ventricle and is associated with hyperdynamic basal segments. Gadolinium-contrast MRI is helpful to distinguish stress cardiomyopathy from AMI and myocarditis because myocardial edema and late enhancement are absent. The right ventricle is affected in 25% of the cases. The main acute complications are heart failure, ventricular tachycardia, thromboembolism, mitral regurgitation, and cardiogenic shock.

Stress cardiomyopathy has a good long-term prognosis, which sometimes contrasts with the significant hemodynamic impairment revealed upon clinical assessment. Treatment regimens provide clinical-hemodynamic support to permit spontaneous myocardial recovery. Beta-blockers, ACE inhibitors and diuretics can be used in the absence of arterial hypotension or signs of low cardiac output. Hemodynamic support in patients with arterial hypotension requires the cautious use of inotropic agents such as dobutamine, and vasopressor drugs must be used in cases with refractory hypotension. Mechanical hemodynamic support via an intra-aortic balloon pump is indicated when the clinical-hemodynamic state does not improve. ECMO can be used in patients who progress into refractory shock, due to the transient nature of this condition.

The indications for the diagnosis of takotsubo cardiomyopathy are described in Table 18.

Table 18 – Indications for the diagnosis of takotsubo cardiomyopathy

Recommendation class	Indications	Evidence level
Class I	Coronary angiography in patients with suspected diagnosis of takotsubo cardiomyopathy, chest pain, and segment ST elevation	C
Class I	Transthoracic echocardiogram in the initial diagnostic assessment of suspected takotsubo cardiomyopathy	C
Class I	MRI to confirm diagnosis of takotsubo cardiomyopathy when there is disagreement between segmental alterations and coronary anatomical injury	C

6.4. Chagas myocarditis

Chagas disease is endemic in Latin America¹³². Chagas myocarditis might present as acute myocarditis during *de novo* *Trypanosoma cruzi* infection via several transmission pathways, including vertical transmission as chronic myocarditis in the later stages of post-infection progression. Furthermore, Chagas myocarditis can be secondary a reactivated infection during immunodeficient states, particularly HIV infection or after the use of immunosuppressants.

The manifestation of acute myocarditis depends on the degrees of cardiac involvement and systemic disease and thus varies from symptomatic forms (sinus tachycardia, low QRS voltage, conduction disorders, QT interval alterations, signs of altered ventricular repolarization, arrhythmias, biventricular function impairment, acute heart failure) to subclinical forms, in which a diagnosis depends on clinical suspicion¹³. Acute myocarditis must always be considered in patients who reside in endemic areas or in whom transmission could occur through vectors or other forms such as oral, congenital and blood transfusions. Acute myocarditis might be associated with signs of systemic infection, such as fever and hepatosplenomegaly, as well as signs of parasitic entry in cases of vector-mediated transmission. Reactivated *Trypanosoma cruzi* infections associated with immunodeficient states might present as acute myocarditis, but the systemic manifestations might be more variable and affect the skin (chagoma and erythema) and the bone marrow and induce meningoencephalitis, fever and hepatosplenomegaly. Biopsy-based differential diagnoses between reactivation and rejection-induced myocarditis can be difficult¹³³. The congenital form might present with jaundice, skin hemorrhage, and neurological signs, particularly in premature newborns. The presence of acute inflammation and apoptosis and lack of significant fibrosis is indicated by lesions in anatomical pathology examinations. Diagnosis is based on the presence of the parasite in the myocardium; alternatively, detection of the parasite in the bloodstream provides a sound basis for diagnosis. Blood smears and xenodiagnosis are commonly used to determine the presence of the parasite. In Brazil, treatment of the acute and reactivated forms is based on specific drug regimens such as benznidazole in doses of five to 10 mg/kg/day over 30 to 60 days in adults

and 15 mg/kg/day in children, and it is highly successful. Allopurinol also successfully treated reactivated disease.

Chronic myocarditis can be found in chronic Chagas disease, which can manifest after a long latency period because acute infection, alone or combined with another disorder, can present as chronic or acute heart failure, arrhythmia, sudden death, and pulmonary or systemic embolism^{134,135}. The signs and symptoms are typical of cardiomyopathy, with an eventual higher incidence of bradycardia and conduction disorders that particularly affect the right bundle branch. The prognosis for this form of cardiomyopathy is poor when compared to other forms¹³⁶. The potential mechanisms involved in the pathogenesis of this form include neurogenic and microvascular injury, apoptosis, chronic inflammation, fibrosis, parasite persistence, and autoimmunity¹³⁷. Currently, parasitic persistence is indicated as an important trigger of Chagas chronic myocarditis¹³⁸. However, other agents might also influence the development of chronic myocarditis¹³⁹. During the chronic phase of Chagas disease, when the clinical diagnosis is highly suggestive and based on compatible epidemiological data, positive serological tests, and typical manifestations of heart failure or other cardiac disorders, an endomyocardial biopsy is usually not performed and other methods may be used¹⁴⁰. Heart failure might result in BNP elevation and a more intense pro-inflammatory process^{141,142}. Specific treatments for the forms without heart failure are controversial and contraindicated in forms with heart failure^{143,144}. The treatment regimens are identical to those used for other forms of both compensated and decompensated heart failure¹⁴⁵⁻¹⁴⁸. Previously, some surgical procedures were considered to be potentially favorable but were later forsaken¹⁴⁹⁻¹⁵¹. In the terminal stage, heart transplantation or the use of circulatory assist devices¹⁵⁶ is indicated to improve the quality of life and survival¹⁵²⁻¹⁵⁵. Although transplantation requires special monitoring due to the higher number of comorbidities, including neoplasia and the reactivation of infection, the outcomes are better for this form of myocarditis than for other forms⁵⁷⁻¹⁶¹.

The indications for the diagnosis and treatment of Chagas myocarditis are described in Table 19.

Table 19 – Indications for the diagnosis and treatment of Chagas myocarditis

Recommendation class	Indications	Evidence level
Class I	Serological tests (2 different techniques) for the diagnosis of Chagas myocarditis in children older than 7 months old	C
Class I	Investigation of <i>T. cruzi</i> (through endomyocardial, skin, or other affected organ biopsy) in cases of reactivation of Chagas myocarditis	C
Class I	Specific treatment with benznidazole in cases of reactivation of Chagas myocarditis	C
Class IIa	Treatment with allopurinol in the absence of ventricular dysfunction in patients with reactivated Chagas myocarditis	C
Class IIb	Routine serological testing to diagnose reactivation of <i>T. cruzi</i> infection	C

7. Prognostic assessment

The natural progression of myocarditis varies in a cause-dependent manner, and clinical and hemodynamic data can contribute to a determination of prognosis (Table 20)¹³.

There are several clinical and pathological forms of myocarditis, and endomyocardial biopsies not only serve to establish diagnoses but might also contribute to prognostic assessments. This is primarily accomplished through the identification of the specific forms of myocarditis such as fulminant, giant-cell, chronic active and eosinophilic myocarditis and sarcoidosis. Clinical and pathological findings might help to distinguish, for example, fulminant lymphocytic from acute lymphocytic myocarditis, with important prognostic implications (table 1)¹⁶². The onset of fulminant lymphocytic myocarditis is clearly indicated by a severe hemodynamic compromise approximately two weeks after a viral prodrome. Despite the initial severity, the odds of ventricular function recovery are high and thus the overall prognosis is good when treatments establish a satisfactory level of vital support (eventually using inotropic agents or mechanical circulatory assistance)¹⁶³.

Previously, the low sensitivity and exclusive use of the Dallas criteria did not permit a strong correlation between histological findings and clinical progression in patients⁴⁵. Currently, indications of viral presence might contribute to predictions of clinical outcomes. In one observational study of 59 biopsy samples that were collected from 48 children with clinical and histological myocarditis or dilated cardiomyopathy diagnoses, viral presence as detected by polymerase chain reaction (PCR) correlated with a poorer prognosis that resulted in heart transplantation or death¹⁶⁴.

The impairment of right ventricular function is also frequently predictive of death or a requirement for heart transplantation⁷⁶.

Table 20 – Correlations of clinical scenarios and prognosis in myocarditis

Clinical scenario	Prognosis
Syndrome similar to acute myocardial infarction with normal coronary arteries	Good when lymphocytic myocarditis is diagnosed via biopsy
Heart failure with hemodynamic compromise	Good in fulminant lymphocytic myocarditis, but therapeutic support may require inotropic therapy or mechanical circulatory assistance.
Heart failure with LV dilation and new ventricular arrhythmias, advanced block, or non-response to usual treatment in 1 to 2 weeks	Poor; high risk of death or required heart transplantation when giant-cell myocarditis is found on biopsy. Requirement for pacemaker or defibrillator increases when sarcoidosis is found.
Heart failure with LV dilation, without ventricular arrhythmias or advanced block	Good during the first few years, but risk of late disease progression into heart failure and cardiomyopathy when the viral genome persists
Heart failure and eosinophilia	Poor

* Adapted from de Cooper LT Jr. Myocarditis. *N Engl J Med*. 2009 Apr 9; 360(15):1526-38.29

Pericarditis

1. Epidemiology

There are no official reports of epidemiological data relative to pericardial disorders in Brazil. Additionally, the available data in the international literature are scarce and are influenced by the characteristics of each institution. Data from emergency departments indicate that 5% of patients with chest pain in whom acute coronary insufficiency is ruled out¹⁶⁵ and 1% of patients with ST segment elevation have acute pericarditis¹⁶⁶.

Pericardial effusion and cardiac tamponade appear more frequently in response to tuberculosis or neoplasms. The frequencies of these findings due to other causes are lower in pericarditis.

2. Classification

Pericarditis is an inflammatory process of the pericardium in response to multiple causes. It can manifest as primary or secondary disease. Although it is usually benign and self-limited, pericarditis can be associated with pericardial effusion or constriction, which result in increased morbidity^{167,168}. Pericarditis is classified according to clinical progression and presentation as^{153,169}:

- Acute pericarditis
- Chronic pericarditis
- Pericardial effusion and cardiac tamponade
- Constrictive pericarditis
- Recurrent pericarditis

3. Etiopathogenesis

Pericarditis has both infectious and non-infectious causes (Table 21). Viral pericarditis is the most common form of pericardial infection and is due to direct viral activities or to the corresponding immune response. The viruses most commonly associated with pericarditis are enteroviruses, echoviruses, the Epstein-Barr virus, herpes simplex virus, influenza virus, and cytomegalovirus; the latter most frequently affects immunodeficient and HIV-positive individuals¹⁷⁰. In seropositive individuals, pericarditis can be caused by infectious, non-infectious, or neoplastic (Kaposi's sarcoma, or lymphoma) diseases and can occasionally progress to myopericarditis²⁵.

Generally, bacterial pericarditis presents with pericardial effusion. It can occur in response to conditions such as pneumonia or empyema, through hematogenous dissemination, or after heart or chest surgery and can be induced by a wide variety of bacterial species. Although the frequency of tuberculous pericarditis (TBP) decreased in response to the effective control of pulmonary tuberculosis (TB), it can still be found, particularly among HIV-infected individuals^{171,172}.

Pericardial autoimmune involvement is found mainly in cases of systemic lupus erythematosus, rheumatoid arthritis, scleroderma, polymyositis and dermatomyositis.

Post-infarction pericarditis might occur early (e.g. within the first three days after acute myocardial infarction

(pericarditis epistenocardica)) and in such cases, can affect the adjacent epicardium and pericardium. Alternatively, it might appear from three weeks to six months after an infarction due to autoimmune activity; such instances are known as Dressler's syndrome. Kidney failure is a common cause of pericardial disease that induces effusion in 20% of patients and can manifest as uremic or dialysis-associated pericarditis. Neoplastic pericarditis occurs in response to tumoral or lymphatic invasion or hematogenous dissemination¹⁶⁷.

Table 21 – Causes of pericarditis

Infectious
Viral (<i>coxsackie</i> , herpes, enteroviruses, CMV, HIV, EBV, varicella, rubella, influenza, etc.)
Bacterial (<i>Pneumococcus</i> , meningococcus, Haemophilus, Chlamydia, Mycobacteria, Mycoplasma, Leptospira, etc.)
Fungal (<i>Candida</i> , Histoplasma)
Parasitic (<i>Toxoplasma</i> , <i>Entamoeba histolytica</i> , etc.)
Autoimmune diseases
Systemic lupus erythematosus, rheumatoid arthritis, rheumatic fever, scleroderma, ankylosing spondylitis, systemic sclerosis, dermatomyositis, polyarteritis nodosa, polymyositis, thrombocytopenic purpura, postcardiotomy syndrome, post-myocardial infarction syndrome, among others
Diseases of adjacent organs
Myocarditis, myocardial infarction, aortic dissection, pulmonary infarction, pneumonia, empyema, esophageal diseases, hydropericardium in heart failure, paraneoplastic syndromes
Metabolic diseases
Kidney failure (uremia), dialysis, myxedema, Addison's disease, diabetic ketoacidosis
Neoplastic diseases
Primary: mesothelioma, sarcoma, fibroma, lipoma and others
Secondary to: lung, breast, stomach, and colon cancer, leukemia and lymphoma, melanoma, sarcoma, among others
Trauma
Direct: penetrating chest wounds, esophageal perforation, foreign bodies
Indirect: non-penetrating chest wounds, mediastinal irradiation
Other situations or syndromes
Pericardial and myocardial injury syndromes, inflammatory bowel disease, Löffler's syndrome, Stevens-Johnson syndrome, giant-cell aortitis, eosinophilic syndrome, acute pancreatitis, pregnancy, among others
Idiopathic

4. Clinical Diagnosis

4.1. Acute pericarditis

Acute pericarditis classically manifests as a febrile syndrome that frequently affects the upper airways and includes chest pain and pericardial friction rub. Chest pain might vary in response to respiration or chest position; additionally, the intensity and duration are variable. The pericardial friction

rub might have one, two, or three sounds and can be transient. Pleural involvement is denoted by a pleural effusion or friction rub. Occasionally, pericarditis is associated with myocarditis, which must be suspected when clinical signs of acute ventricular dysfunction are present.

High-risk markers in acute pericarditis include elevated levels of myocardial necrosis enzymes, fevers higher than 38°C, leukocytosis (high risk for purulent pericarditis), large

pericardial effusion with or without cardiac tamponade, immunosuppression, previous use of oral anticoagulants, and global dysfunction on echocardiogram suggestive of myopericarditis. The presence of these markers indicate a need for hospital admission, more aggressive etiological investigation, and therapeutic optimization^{173,174}.

A flowchart of assessment of pericarditis on admission is shown below (Figure 3).

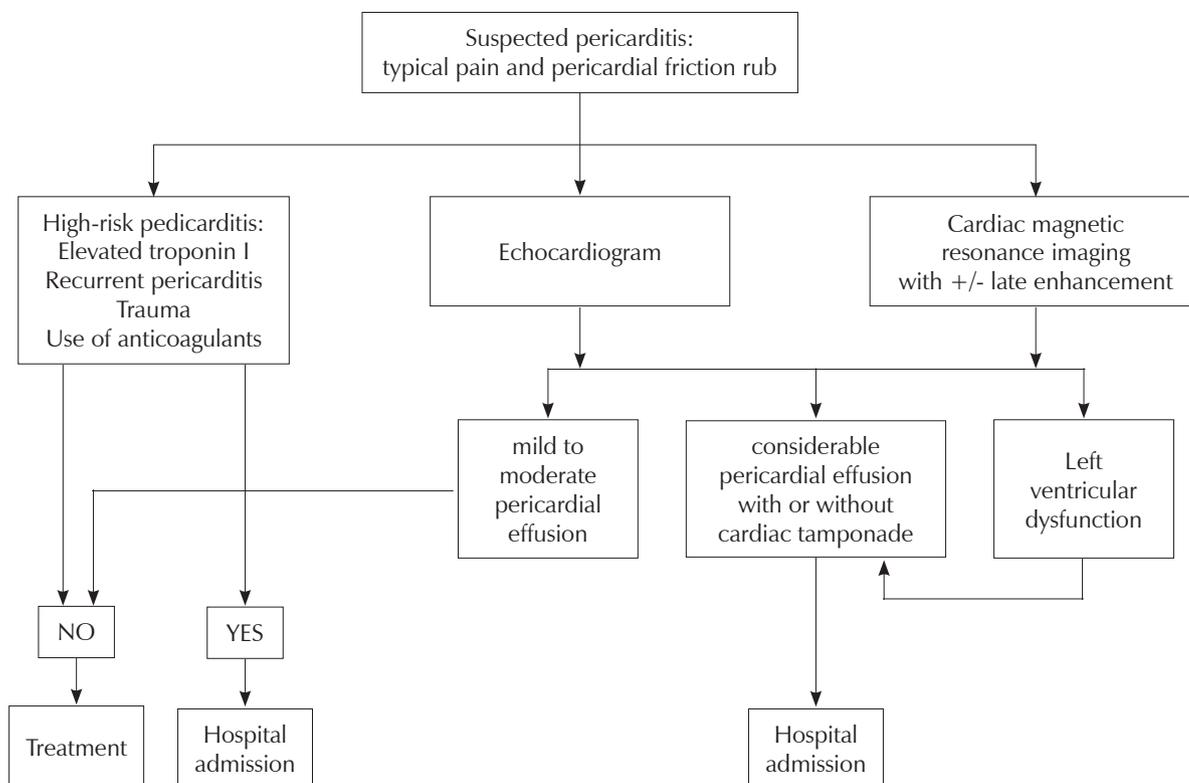


Figure 3 - Flowchart of behavior related to pericarditis on admission

4.2. Cardiac tamponade

The pericardial sac contains a small amount of fluid (30 to 50 ml) that surrounds the heart. If a large amount of fluid accumulates and surpasses the distension capability of the pericardial fibroelastic tissue, the heart chambers are progressively compressed due to the increased intrapericardial pressure, reduced cardiac volume, and greater ventricular interdependence¹⁷⁵.

Tamponade progression depends on the speed of installation and the causal factor; acute cardiac tamponade develops within a few minutes after trauma, heart or aortic rupture, or as a complication of diagnostic and therapeutic procedures (cardiac biopsy, electrophysiological studies, atrial appendage occlusion, interatrial septum occluders, etc.) and results in shock. Subacute cardiac tamponade develops in days to weeks and might be associated with dyspnea and fatigue. Low-pressure (occult) tamponade

occurs in hypovolemic patients with a consequent reduction in intracardiac pressure, which favors extrinsic compression by the pericardial effusion. Regional cardiac tamponade occurs when a localized effusion or hematoma exerts regional compression on one single chamber¹⁶⁸.

Diagnosis of tamponade is clinical and is based on the history and physical evaluation of symptoms such as tachycardia, increased venous pressure, arterial hypotension, and paradoxical arterial pulse.

4.3. Constrictive pericarditis

Constrictive pericarditis should be suspected in symptomatic patients with dyspnea upon exertion and/or fatigue associated with diastolic dysfunction and ascites that is disproportionate to lower limb edema. In such cases, the jugular venous pulse exhibits a prominent “y” descent and Kussmaul’s sign. Additionally, 33% of the cases exhibit a paradoxical arterial pulse.

Transient forms of constrictive-effusive pericarditis (constriction without considerable pericardial wall thickening, usually associated with effusion) can occur within the context of acute pericarditis; these occur more frequently in association with tuberculosis, malignant neoplasms, and hemopericardium.

4.4. Laboratory markers

4.4.1. Markers of disease activity

a) Markers of myocardial necrosis:

High levels of myocardial markers are found in patients with acute pericarditis. Troponin I (TnI) is more frequently elevated when compared to CK-MB because it may be due to peripheral myocarditis rather than viral infection^{176,177}. A retrospective study assessed 55 patients with acute pericarditis and found that TnI was elevated in 27% of the cases¹⁷⁸. A small study suggested that TnI was expressed on the second day after symptom onset and that TnI levels remained high for longer times than CK-MB levels¹⁷⁷. Increased TnI is a marker for associated myocardial impairment (myopericarditis).

b) Markers of inflammatory activity:

Markers of acute inflammatory activity, such as ESR, leukocytosis, and CRP, are elevated in approximately 75% of patients, and normal levels of these markers at the initial assessment do not rule out a diagnosis of pericarditis, especially in patients who use non-steroidal anti-inflammatory agents or have immune affections. The levels of acute phase markers generally return to normal after two weeks; persistent elevation indicates a need for long-term anti-inflammatory treatment and a higher risk for pericarditis recurrence¹⁷⁹. Serial CRP measurements are helpful in diagnoses of acute pericarditis and in assessments of response to treatment.

c) BNP / NT-proBNP:

The levels of B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) might be elevated in pericardial disease^{180,181}. However, there is not sufficient evidence to justify the routine use of these markers in the diagnosis of acute pericarditis.

4.4.2. Markers for etiological diagnosis

A serological assessment to investigate causal factors must include a measurement of thyroid hormones, rheumatologic tests, kidney function tests, and blood cultures if bacterial infection is suspected. Viral analysis via blood serological testing should not be performed because, those not correlate with the pericardial findings. In the presence of significant pericardial effusion, histological and immunohistochemical assessments of the pericardial tissue and fluid must be performed for tuberculosis (adenosine deaminase), neoplasms, viruses, and other factors to significantly increase the likelihood of an etiologic diagnosis¹⁸². In idiopathic recurrent acute pericarditis, low titers of antinuclear antibodies are a common finding and indicate a possible autoimmune pathogenic mechanism¹⁸³.

Table 22 summarizes the main indications for the use of laboratory markers in pericarditis.

Table 22 – Indications for the use of laboratory markers in pericarditis

Recommendation class	Indications	Evidence level
Class I	Measurement of CRP for diagnosis and follow-up in acute pericarditis	B
Class I	Measurement of thyroid hormones, autoantibodies, and assessment of the kidney function for etiologic assessment in acute pericarditis	C
Class IIa	Troponin measurement for diagnosis of acute pericarditis	C
Class IIb	CK-MB measurement for diagnosis of acute pericarditis	C
Class IIb	Measurement of BNP/NTproBNP to help in the differential diagnosis between constrictive pericarditis and restrictive cardiomyopathy	C
Class III	Measurement of BNP/NTproBNP for diagnosis of acute pericarditis	C

4.5. Electrocardiogram

The range of electrocardiographic alterations is quite wide in pericarditis (table 23) and includes abnormalities of the PR and ST segments and rhythm that vary according to the stage of pericarditis. ECG might be normal in up to 6% of cases¹⁸⁴.

In acute pericarditis, the electrocardiographic alterations evolve over the following four stages¹⁸⁵:

Stage 1: diffuse concave upward elevation of segment ST, except in leads aVR and V1, in which it is depressed; peaked T waves with mildly increased amplitude; depression of segment PR, except for lead aVR, in which it is elevated. These alterations are observed in more than 80% of cases^{186,187}.

Stage 2: return of ST and PR segments to baseline and flattening of the T waves.

Stage 3: diffuse inversion of T waves that simulates myocardial ischemia.

Stage 4: return of T waves to baseline, which might occur several weeks or months after the onset.

Rhythm alterations can occur at any stage and can range from sinus tachycardia to various atrial arrhythmias¹⁸⁸.

Low QRS amplitude denotes pericardial effusion; this improves after pericardiocentesis^{189,190}. Alternations in QRS morphology or amplitude denote pericarditis that is associated with a large pericardial effusion and signs of cardiac tamponade¹⁹¹.

The main differential diagnoses suggested by electrocardiographic alterations are acute myocardial infarction, pulmonary thromboembolism, presence of dyskinetic areas, and early repolarization¹⁹².

Differentiation between pericarditis and early repolarization might be established by estimating the ratio of the ST segment onset amplitude to the T wave amplitude (ST/T) in the lead V6. A pericarditis diagnosis is established when the ST/T ratio is equal to or greater than 0.25¹⁹³.

The predominant findings in chronic pericarditis are inverted T waves and low QRS amplitude¹⁹⁴.

Table 23: Indication of electrocardiogram in pericarditis

Recommendation class	Indication	Evidence level
Class I	Electrocardiogram for diagnosis of acute pericarditis	C

4.6. Radiography

Usually, chest radiographs are normal in acute pericarditis cases. Cardiomegaly occurs only when the fluid volume in the pericardial sac is greater than 200 ml. Progressive increases in pericardial effusion, as in cardiac tamponade, result in a globular shaped heart on the chest radiograph¹⁹⁵.

Some studies show that an increased heart silhouette on chest radiographs has moderate sensitivity (70%) but low specificity (41%) for diagnoses of pericardial effusion. There are no studies that assess the sensitivity and specificity of radiography in the diagnosis of pericarditis, but considering that in most cases, pericarditis is not accompanied by pericardial effusion and that this disease has no other specific changes, a diagnosis of pericarditis cannot be established solely on the basis of radiological data¹⁹⁶.

The presence of pericardial calcification, which is easily visualized on chest radiographs, strongly suggests a diagnosis of constrictive pericarditis in patients with heart failure. However, this appears in only 25% of constrictive pericarditis cases (Table 24)¹⁹⁷.

Table 24 – Indications for the use of chest radiographs in pericardial disorders

Recommendation class	Indication	Evidence level
Class I	Chest radiograph as a complementary diagnostic resource when pericardial disorders are suspected	C

4.7. Echocardiogram

Echocardiography is a very useful tool for the diagnosis of pericardial diseases as well as the prognosis and follow-up evaluations of responses to treatment. It has also been used as a guide during pericardial effusion drainage.

As a rule, the echocardiographic findings in acute pericarditis involve pericardial thickening and effusion. However, some cases of acute pericarditis might not exhibit any echocardiographic alterations (e.g. the so-called “acute dry pericarditis”).

4.7.1. Pericardial effusion

Two-dimensional echocardiography permits semi-quantitative assessments of pericardial effusions and hemodynamic repercussions. Small effusions are defined as those that are < 10 mm in size on M-mode and are only visualized behind the left ventricle. Moderate effusions are those that range in size from 10 to 20 mm and extend

around the entire heart. Finally, large effusions are defined as echo-free areas > 20 mm¹⁹⁸. Small effusions are usually only visible behind the left ventricle, whereas the effusions large enough to cause cardiac tamponade can be visualized around the entire heart. The echocardiogram might provide etiological information because it can characterize the nature of the fluid (transudate or exudate) and identify the presence of fibrin (as in tuberculosis), calcium, clots and masses that are suggestive of tumors or cysts; thus, the echocardiogram permits inferences about the etiological diagnosis.

All possible sections of the pericardium must be assessed. When constrictive pericarditis is suspected, the pericardial thickness must be measured; a thickness > three mm on a transesophageal echocardiogram (TEE) indicates a thickened pericardium with sensitivity and specificity rates of 95% and 86%, respectively.

4.7.2. Cardiac tamponade

The usual echocardiographic findings associated with the clinical signs of cardiac tamponade include the dilation of the vena cava with little respiratory variation and diastolic collapse of the free wall of the right ventricle, right atrium, left atrium, and more rarely, the left ventricle. Right atrial collapse is the most sensitive indicator of cardiac tamponade, whereas a right ventricular collapse that lasting for more than one-third of the diastole is the most specific sign. Doppler echocardiograms show increased tricuspid and reduced mitral flow on inspiration and increased mitral flow up to 25% and reduced tricuspid flow on expiration. The findings from Doppler echocardiograms merely represent the echocardiographic expression of a paradoxical pulse.

4.7.3 Constrictive pericarditis

Up to 80% of the cases might exhibit pericardial thickening. However, this is not always detectable on echocardiography, including TEE, and thus other diagnostic methods such as MRI or computed tomography (CT) might be indicated.

The usual findings in pericardial constriction include abnormal motion of the ventricular septum, moderate restrictive flow increases in both atria, and respiratory variations greater than 25% of the mitral flow velocity. These variations are not pathognomonic of pericarditis but also occur in respiratory diseases (chronic obstructive pulmonary disease). However, in respiratory diseases the respiratory variation of the superior vena cava flow is much greater than in pericarditis.

Another useful finding for the diagnosis of constrictive pericarditis, and more particularly to distinguish it from restrictive syndromes, is the presence of e' wave normal velocity on tissue Doppler (> 8 cm/s), which is lacking in restrictive heart disease. It must be stressed that, in cases of pericardial disease, the septal rather than the lateral e' wave must be used, due to the possible influence of the pericardial thickening/effusion on the left ventricular free wall. Additionally, calcification of the mitral ring might reduce the septal e' wave¹⁹⁹. The linear correlation between the E/E' index and the left atrial pressure, which is useful to assess filling pressures in cardiomyopathies, is inverted in constrictive pericarditis (annulus paradoxus). The systemic venous return does not increase with inspiration.

The indications for transthoracic echocardiography in pericarditis are described in Table 25.

Table 25 – Indications for the use of echocardiogram in pericarditis

Recommendation class	Indication	Evidence level
Class I	Doppler echocardiogram for diagnosis of pericardial disorders	B
Class I	Doppler echocardiogram for monitoring pericardiocentesis in pericardial disorders	B
Class I	Doppler echocardiogram for monitoring of pericardial disorders	C

4.8. Cardiac computed tomography (CT)

In acute pericarditis, cardiac CT might show uniform pericardial thickening, pericardial effusion, and some early enhancement of the intravenous contrast agent. The pericardial effusion might be loculated and exhibit septa; eventual observations of gas indicate the presence of microorganisms. The septa also exhibit contrast uptake. The effusion density must be investigated because it is low in transudates (0-10 HU) and high in exudates, hemorrhage, and neoplasms²⁰⁰.

In constrictive pericarditis, cardiac CT can identify pericardial thickening and/or calcification²⁰¹. The normal pericardial thickness is less than two mm and is only properly identified when there is fatty tissue around the pericardium. Thickening can have diffuse or localized effects on the pericardium^{202,203}. Cardiac constriction induced by a thickened pericardium gives the heart a narrow tubular shape. A sulcus is formed when constriction predominates in the fossa ovalis. The atria and vena cava are distended and pericardial effusion and ascites might be observed.

In neoplastic pericarditis, masses in the pericardium, infiltration of the adjacent tissues, impairment of the ventricular margins, and thickened septa that exhibit contrast uptake might be identified in addition to pericardial effusion and leaflet thickening.

Table 26 summarizes the main indications for cardiac CT in pericarditis.

Table 26 – Indications for cardiac CT in pericarditis

Recommendation class	Indications	Evidence level
Class IIa	Acute pericarditis (acute infarction-like presentation, or associated with acute or subacute viral infection; < 3 months)	B
Class IIa	Chronic pericarditis > 3 months	C
Class IIa	Constrictive pericarditis with suspected association with pericardial calcification	B
Class IIb	Constrictive pericarditis without suspected association with pericardial calcification	C

4.9. Magnetic resonance imaging (MRI)

MRI is indicated in the diagnostic assessment of acute and chronic pericarditis (Table 27). It permits quantification of the degree of pericardial thickness and the volume of pericardial effusion. Additionally, the late enhancement technique permits identification of the signs suggestive of myopericardial inflammatory injury¹⁶⁸.

Table 27: Indications for the use of MRI in pericarditis

Recommendation class	Indications	Evidence level
Class IIa	Acute pericarditis (acute infarction-like presentation, or associated with acute or subacute viral infection; < 3 months)	B
Class IIa	Chronic pericarditis > 3 months	B
Class IIa	Constrictive pericarditis with suspected association with pericardial calcification	B
Class IIa	Constrictive pericarditis without suspected association with pericardial calcification	C

4.10. Nuclear medicine

Among the main applications of nuclear medicine for the non-invasive diagnosis of pericarditis, the following stand out: differential diagnosis in patients with chest pain and electrocardiographic changes but without characteristic enzymatic curves, especially when MRI is not available or is contraindicated; diagnosis of pericarditis by active tuberculosis (new evidence indicates the use of [¹⁸F]fluorodeoxyglucose-positron emission tomography, FDG-PET); diagnosis of pericarditis in patients with systemic diseases such as meningitis, pneumococcal sepsis, rheumatoid arthritis, and systemic lupus erythematosus; monitoring of patients with chemotherapy or radiotherapy-induced pericarditis; and the clinical suspicion of pericarditis with diagnostic uncertainty after echocardiogram and MRI^{204,205}.

4.11. Pericardiocentesis and pericardial biopsy

Pericardiocentesis is an invasive procedure used for diagnostic and therapeutic purposes. It is indicated as a life-saving treatment in cardiac tamponade.^{168,195} Pericardiocentesis is further indicated when there is clinical suspicion of post-traumatic hemopericardium, bacterial pericarditis or neoplastic pericarditis (Table 28)²⁰⁶.

In cases of significant but asymptomatic pericardial effusion (> 20 mm at diastole on echocardiogram), pericardiocentesis is indicated for diagnostic assessment and in response to the possibility of sudden progression into cardiac tamponade²⁰⁷.

Pericardiocentesis may be performed at the patient bedside under local anesthesia or in a cat lab via radioscopy. Although the access point may be transthoracic, median or subxyphoid, the latter provides limited exposure to the pericardium, which result in a low success rate²⁰⁸. The pericardial puncture needle must be guided by electrocardiographic monitoring or by imaging methods.

Echocardiogram-guided pericardiocentesis carries a lower risk of complications and a higher rate of success. Additionally, saline injection permits localization of the needle during the procedure²⁰⁹. Once the catheter is introduced, the pericardial cavity pressure must be measured and the fluid aspirated. Relief of symptoms should ensue immediately.

In cases of constrictive-effusive pericarditis, the right atrial pressure remains high after the reduction of the intrapericardial pressure to normal levels in response to pericardial effusion drainage²¹⁰. The pericardial fluid must be subjected to a cytological analysis, a microbiological culture, an investigation of neoplastic cells, a PCR-mediated viral analysis, and measurements of adenosine deaminase according to the suspected etiology (viral, bacterial, tuberculous, fungal or neoplastic). Aortic dissection is an absolute contraindication of pericardiocentesis; relative contraindications include clotting disorders, anticoagulation, platelet counts below 50,000/mm³, and small, posterior or loculated effusions.

To increase the diagnostic sensitivity of pericardiocentesis, new diagnostic and therapeutic strategies such as video pericardioscopy, which allows for large pericardial excision and wider exposure of the pericardial cavity, were developed²¹¹.

Furthermore, pericardial biopsy is indicated in the diagnostic investigation of patients with persistent pericarditis that is refractory to clinical treatment and lacks a definitive diagnosis. Biopsy might play an adjuvant role in therapeutic pericardial drainage for recurrent cardiac tamponade or large effusions that present with significant clinical symptoms.

Pericardial biopsy can also be performed by pericardioscopy, which indicates the sites for sample collection^{212,213}. Pericardial biopsy was shown to improve diagnostic accuracy for pericarditis due to neoplastic disease, tuberculosis and bacterial infection^{214,215}.

The presence of pericardial effusion favors biopsy via pericardioscopy and improves the likelihood of diagnosis, compared to pericarditis without associated pericardial effusion. The specimens must be subjected to histological (two fragments) and immunohistochemical (two fragments) analysis, as well as viral analysis by PCR (four to six fragments), which affords greater viral detection capability than viral analysis of the pericardial effusion fluid²¹⁶⁻²¹⁸.

Figure 4 represents a flowchart of the approach to pericardial effusion and the indications for pericardiocentesis and pericardial biopsy.

Table 28 – Indications for the use of pericardiocentesis with pericardial biopsy

Recommendation class	Indications	Evidence level
Class I	When tuberculosis, neoplasms, bacterial, or fungal etiology is suspected	B
Class I	Associated with video pericardioscopy to increase the diagnostic sensitivity	B
Class IIa	In the diagnosis of significant but asymptomatic pericardial effusion	B

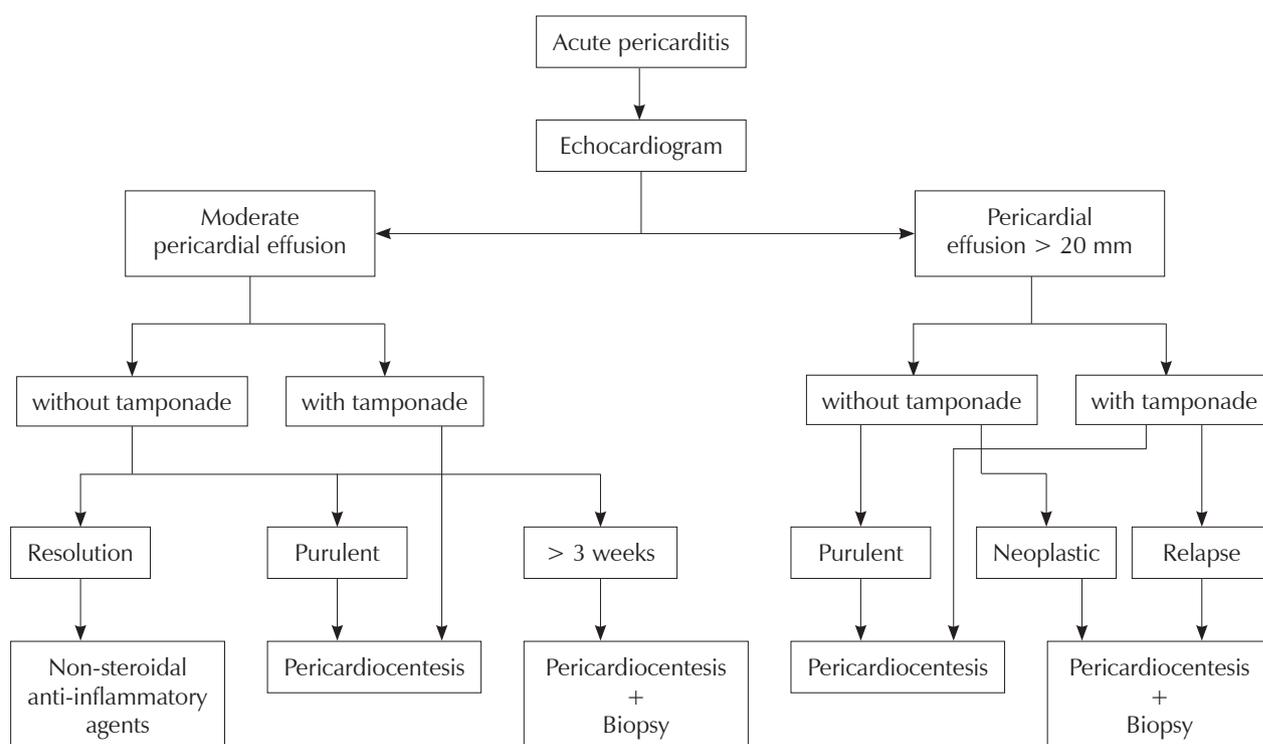


Figure 4 - Flowchart of indications for the use of pericardiocentesis and pericardial biopsy

4.12. Histological analysis

The histological status can be classified according to etiologic categories. In this regard, tuberculosis is the most frequent cause of pericarditis. It is believed that some viruses induce self-limited pericarditis. In cases with considerable inflammation, there is an exuberant proliferation of reactive mesothelial cells with nuclear atypia, which require a differential diagnosis from neoplastic infiltration. Immunohistochemistry is useful because it achieves differentiation with markers for epithelial and mesothelial cells^{212,219}.

Fibrinous pericarditis – characterized by variable degrees of thickness due to edema, mild inflammatory infiltrates, and surface fibrin with collagen thickness and granulation tissue in more chronic cases. Occasionally, there is an exuberant proliferation of mesothelial cells.

Fibrinous purulent pericarditis – characterized by neutrophilic infiltrates, which sometimes form abscesses among fibrin and cell remnants on the serous surface. The etiological agent is frequently found.

Unspecific chronic pericarditis – characterized by lymphohistiocytic infiltrates that are associated with variable degrees of fibrosis. It is believed to be associated with viral infections.

Hemorrhagic pericarditis – is associated with acute pericarditis and exhibits significant hemorrhage. The main causes are tuberculosis, neoplastic infiltration and heart surgery.

Granulomatous pericarditis – The main causal agent is tuberculosis but atypical mycobacteria and fungi such as *Histoplasma* and *Candida* must also be considered. Caseous necrosis is common in tuberculosis and can evolve to constrictive pericarditis.

Constrictive pericarditis – results from scars induced by previous pericarditis. It is characterized by considerable fibrous thickening and adhesions between the visceral and parietal leaflets. Extensive calcification or plaques of calcification are occasionally present.

Post-myocardial infarction pericarditis and Dressler's syndrome – proximity to necrotic myocardium might trigger post-myocardial infarction pericardial inflammation. When this process occurs at a later timepoint, it is called Dressler's syndrome. The histologic appearance corresponds to unspecific chronic pericarditis.

Table 29 summarizes the indications for the use of immunohistochemistry in the diagnosis of pericarditis.

Table 29 – Indications for immunohistochemistry in the diagnosis of pericarditis

Recommendation class	Indications	Evidence level
Class IIa	Immunohistochemistry with class I and II HLA-DR in the diagnostic investigation of epimyocardial and pericardial inflammation	B
Class IIa	Immunohistochemistry to investigate and count epimyocardial and pericardial T and B lymphocyte and macrophage infiltrates	B

5. Treatment

Hospitalization is desirable in most cases of pericarditis to investigate the etiology, monitor the signs and symptoms of cardiac tamponade, and begin a non-steroidal anti-inflammatory drug (NSAID) and symptomatic treatment regimen. NSAIDs are the primary treatment drugs; ibuprofen is the most widely used because it seldom exhibits side effects and induces favorable effects on the coronary flow when used in high doses.

Treatment with systemic corticosteroids must be restricted to connective tissue disorders, autoimmune diseases and uremic pericarditis. Intrapericardial application of corticosteroids bypasses the systemic side effects, is highly effective in the withdrawal of prednisone, ibuprofen and colchicine^{220,221}, and should be introduced early. Recovering patients should be monitored for possible recurrence or constriction.

Heparin is recommended under close supervision in cases that require anticoagulants.

5.1. Non-steroidal anti-inflammatory agents and colchicine

NSAIDs are the pharmacological agents of choice for the treatment of idiopathic and viral pericarditis. Treatment is administered mainly to relieve pain and resolve inflammation^{222,223}.

NSAIDs must be administered in anti-inflammatory doses; for example, acetylsalicylic acid (ASA) at 500 to 750 mg every six or eight hours over seven to 10 days, followed by a gradual reduction of 500 mg per week over three weeks; ibuprofen at 400 to 800 mg every six to eight hours over 14 days; or indomethacin at 75 to 150 mg/day. Indomethacin should be avoided in cases of post-myocardial infarction pericarditis because it impairs healing of the infarcted area^{224,225}.

The normal length of NSAID treatment is approximately 14 days and can be monitored using serum levels of CRP as a marker of inflammatory activity. Tapering off of NSAID therapy must be gradual and slow to decrease the odds of recurrence²²⁶. All patients must use proton-pump inhibitors (PPI) to protect the gastric mucosa.

Colchicine was shown to be effective as an adjuvant treatment for pain relief and prevention of recurrence after an 18-month follow-up in acute pericarditis cases^{220,227}. It is used in doses of 0.5 mg, given every 12 or 24 hours to patients who weigh less than 70 kg, for three months after the first event and six months in cases of recurrent pericarditis^{228,229}. According to some studies, in more severe and recurrent forms, colchicine should be given for 12 to 24 months after the last event, followed by a gradual withdrawal^{230,231}.

The main adverse effect of colchicine is diarrhea, which affects approximately 8% of patients. Less frequent effects are associated with hepatotoxicity, myotoxicity and bone marrow suppression. Thus, colchicine should be avoided in patients with severe kidney failure, liver dysfunction, blood disorders and gastrointestinal motility disorders²³²⁻²³⁴.

5.2. Immunosuppression

The use of corticosteroids to suppress inflammation usually induces a dramatic improvement of the clinical state and inflammatory response in pericarditis. Nevertheless,

the following clinical and physiopathological features that limit the clinical efficacy of these agents must be taken into consideration: treatment with corticosteroids favors the recurrence of pericarditis and a possible explanation is that some recurrences may be provoked by acute or chronic viral infections, and corticosteroids could promote viral replication, or through the phenomenon of autoimmune recurrence; the cause of pericarditis should be identified to predict the response to treatment and determine the treatment regimen; and when viral pericarditis is suspected, viral presence should be ruled out through an analysis of the pericardial fluid and endopericardial biopsy before administering corticosteroids²³⁵.

Corticosteroids are indicated for the treatment of idiopathic acute pericarditis cases that do not respond to non-steroidal anti-inflammatory agents and colchicine. This indication also applies to cases of pericarditis due to autoimmune disease, connective tissue diseases or uremia. The recommended dose is one mg/kg body weight over a two to four week period. To avoid autoimmune recurrences and consequent reactivation of pericarditis, corticosteroids should be tapered off slowly and colchicine should be given at a dosage of one mg/day^{168,228}.

Intrapericardial corticosteroid use was shown to induce considerable clinical improvement and low recurrence rates of pericarditis after a one-year follow-up period. The advantage of this route of administration is that bypasses the side effects of systemic corticosteroid administration and prevents the recurrence of pericarditis. The therapeutic regimen for this purpose involves the use of triamcinolone, 300 mg every 12 hours in combination with colchicine, over a six month period. All patients were subjected to pericardial and epimyocardial biopsies to investigate the state of inflammation and rule out viral infection or other etiological agents. The limitations of this procedure derive from its invasive nature^{221,236}.

The first feature that requires attention in recurrent pericarditis cases is the investigation of the possible causal factor, which may include an inadequate therapeutic regimen, inadequate dosing, rapid withdrawal from corticosteroids, viral replication due to corticosteroid use, reinfection, and the reactivation of autoimmune or connective tissue disease. If none of those factors are identified, corticosteroids can be used in patients who present with frequent crises and severely impaired clinical conditions. Thus, prednisone at a dose of 1-1.5 mg/kg is recommended over a four week period with a slow taper off over three months. In patients with frequent recurrences, azathioprine at a dose of 75-100 mg/day or cyclophosphamide might be combined. Additionally, colchicine must be included in the therapeutic regimen to reduce the odds of recurrence^{206,237}.

The use of low doses of prednisone (0.2 – 0.5 mg/kg/day over four weeks) exhibited the same therapeutic efficacy a dose of one mg/kg/day with lower incidences of side effects²³⁸.

5.3. Antiviral therapy

Viral pericarditis can be induced by several viral species. Diagnosis is established after a positive viral assessment in the epimyocardial and pericardial tissue, as well as in the pericardial fluid. The aim of antiviral therapy is not only to induce the improvement of symptoms and remission of

disease but also to avoid disease recurrence. Several antiviral regimens are currently being tested. These include the use of hyperimmunoglobulin (four ml/kg on days zero, four, and eight; two ml/kg on days 12 and 16) to treat CMV-induced pericarditis, interferon- α (2.5 millions IU/m², per subcutaneous route, over three weeks) for Coxsackie B-induced pericarditis, and intravenous immunoglobulin (10 g on days one and three) for adenovirus and parvovirus B19-induced pericarditis. Although the rationale for the use of immunoglobulin is the same as for viral myocarditis, randomized trials are still needed to establish the efficacy of this therapeutic strategy^{239,240}.

Table 30 – Indications for the use of anti-inflammatory, immunosuppressant and antiviral therapies in pericarditis

Recommendation class	Indications	Evidence level
anti-inflammatory in acute pericarditis		
Class I	Aspirin or ibuprofen in 14 days for the treatment of acute pericarditis	A
Class I	Colchicine in 3 months for the treatment of acute pericarditis and 6 months for the treatment of recurrent pericarditis	A
Immunosuppression in acute pericarditis		
Class I	Prednisone in cases non-responsive to NSAIDs and colchicine in the absence of infection by viruses or other agents confirmed by epimyocardial and pericardial biopsy	B
Class I	Prednisone in the absence of infection by viruses or other agents confirmed by epimyocardial and pericardial biopsy in the following clinical situations: autoimmune pericarditis, connective tissue diseases, or uremic pericarditis	B
Class IIa	Prednisone in patients with recurrent pericarditis without identified causal factor in the absence of infection by viruses or other agents confirmed by epimyocardial and pericardial biopsy	C
Class IIa	Azathioprine in patients with recurrent pericarditis despite use of prednisone	B
Class IIb	Triamcinolone per intrapericardial route in auto-reactive pericarditis in the absence of infection by viruses or other agents confirmed by epimyocardial and pericardial biopsy	B
Antiviral agents in acute pericarditis		
Class IIb	Use of immunoglobulin in viral pericarditis	C

5.4. Treatment of cardiac tamponade

Cardiac tamponade is treated by pericardial drainage to reduce intrapericardial pressure and thus improve the patient hemodynamic condition. A rapid crystalloid infusion might be indicated to improve perfusion and stabilize the patient hemodynamic state prior to pericardial drainage, whereas amines or atropine are used when bradycardia is present.

Pericardial drainage might be performed by percutaneous puncture and catheter placement, open surgical drainage with or without pericardiectomy (pericardial window), or video-assisted pericardioscopy²⁴¹. Pericardiocentesis with a catheter must be guided by echocardiography, which permits identification of the best site and pressure angle, thus reducing the risk of complications and increasing the rate of success²⁴². Catheter drainage might occur over a few days, and the catheter should not be removed until the drainage rate is below 20 – 30 ml/24 hours.

The advantage of surgical drainage is that it permits the performance of a pericardial biopsy. It is recommended in cases of effusion relapse following catheter drainage as well as for clots or effusion that are located in sites not accessible by the percutaneous route¹⁹⁷.

5.5. Surgical treatment of pericardial diseases

Pericardial constriction syndrome is treated by pericardial excision. Pericardial resection can be a technical challenge due to the presence of dense adherences and calcifications that might penetrate into the myocardium. In most centers, the procedure is performed through a median sternotomy and might eventually require extracorporeal circulation²⁴³. The aim of this procedure is to rid the ventricles of the densely adhered pericardium. Special attention must be given in cases with epicardial coronary vessel dissection. The goal is to resect the pericardium from phrenic nerve to phrenic nerve and posteriorly around the entry of the vena cava and pulmonary veins. Although a complete resection will restore the pressure-volume curve²⁴⁴, it is not possible in all cases, particularly in cases of constrictive radiation-induced pericarditis. The surgical mortality may be as high as 10 to 20%^{245,246}. Long-term survival is lower in patients with a history of previous heart surgery, especially those with constrictive radiation-induced pericarditis^{247,248}.

Table 31 summarizes the indications for the use of surgical treatment for pericardial diseases.

Table 31 – Indications for the use of surgical treatment in pericardial diseases

Recommendation class	Indications	Evidence level
Class I	Pericardiocentesis or open pericardial drainage in patients with cardiac tamponade	C
Class I	Pericardiectomy in patients with symptomatic constrictive pericarditis refractory to clinical treatment	C
Class IIa	Pericardial window in recurrent pericardial effusion	C

6. Special situations

6.1. Chronic kidney disease

Severe chronic kidney disease (CKD) is a common cause of pericardial disease, including pericarditis and pericardial effusion.

Several factors contribute to the development of pericardial diseases under this condition, which are generally described as two forms, uremic and dialysis-associated pericarditis²⁴⁹.

Uremic pericarditis occurs in approximately 10% of patients before or immediately after the onset of dialysis²⁵⁰. The pathophysiology is poorly understood and seemingly does not bear any relationship to the underlying cause of CKD (except for systemic lupus erythematosus and scleroderma), although it is related to urea concentrations. Generally, it is easily resolved with continued dialysis therapy.

Dialysis-associated pericarditis occurs in approximately 15% of the patients who undergo hemodialysis and less often among patients who undergo peritoneal dialysis. It is mainly associated with hypervolemia and inappropriate dialysis; therefore, fluid correction and adequate dialysis are of paramount importance²⁵¹.

The clinical and laboratory manifestations are similar to those of non-uremic patients with similar pericardial diseases, except for chest pain, which occurs less often in individuals with terminal CKD, and the lack of electrocardiographic alterations that are typical of acute pericarditis due to the absence of myocardial inflammation^{252,253}.

Most patients respond promptly to dialysis and the pericarditis is resolved in approximately one to two weeks¹. Pain and inflammation can be managed with NSAIDs or corticosteroids, both of which are less effective in patients who are refractory to dialysis. In such cases, colchicine has shown some benefit²⁵⁵. The use of heparin during dialysis treatment should be controlled. Uremic pericarditis seldom progresses into pericardial constriction.

Patients who progress into pericardial tamponade or develop symptomatic volume-persistent pericardial effusion should be treated by pericardiocentesis combined with intrapericardial corticosteroid instillation (triamcinolone 50 mg every six hours over three days)²⁵⁶. Pericardiectomy is indicated for cases of recurrent pericarditis with persistent pain that is refractory to anti-inflammatory treatments²⁵⁷.

6.2. Postpericardiectomy syndrome

Postpericardiectomy syndrome (PPS) occurs in approximately 10 to 15% of the patients who are subjected to surgical heart and/or pericardial trauma and can occur days or even months after the trauma (80% within the first month)²⁵⁸. PPS is thought to have a mixed pathophysiology, in which surgical trauma causes primary inflammation, followed by the development of an autoimmune response (heart anti-sarcolemma antibodies)²⁵⁹.

The vast majority of patients exhibit pleuro-pericardial involvement, such as a fever that appears after the first postoperative week (without evidence of systemic or focal infection), pleuritic chest pain, and a new pleural effusion or aggravation of a pre-existing effusion. Less frequent findings include pericardial friction rub (one-third of patients) and typical electrocardiographic alterations²⁶⁰. Progression into pericardial tamponade or constrictive pericarditis is less common, but hospitalization is usually of longer duration in PPS cases, and PPS is associated with early recurrence and hospital readmission.

The use of aminocaproic acid (valvular or combined coronary and valvular surgery) during surgery has been reported as a predisposing factor for PPS. A recent study found that female gender and pleural incision behave as independent risk factors²⁶¹.

Primary prevention with short courses of colchicine treatment seems to be particularly useful²⁶², whereas there is no evidence to support the use of methylprednisolone or acetylsalicylic acid²⁶⁰.

Treatment of acute PPS is similar to that of acute pericarditis and includes the use of non-steroidal anti-inflammatory agents and colchicine over weeks or months until the effusion is resolved; colchicine is also indicated for recurrences^{229,263}. The alternatives described for refractory cases include oral corticosteroids (three to six months) or pericardiocentesis with an intrapericardial instillation of triamcinolone.

6.3. Neoplasms and radiotherapy

6.3.1. Neoplasms

Pericardial effusion is a severe complication of malignant tumors. Metastatic disease is much more common than primary tumors, and the most common cause is lung cancer, followed by breast cancer, melanoma, lymphoma, and leukemia²⁶⁴.

The clinical course is usually benign. Symptomatic cases can exhibit complaints that range from chest pain and dyspnea to a severe progression into cardiac tamponade²⁶⁵. Very often, the differential diagnosis of effusion is difficult; therefore, a definitive diagnosis is based on a cytological analysis of the pericardial fluid.

Therapeutic options for the immediate relief of symptoms are percutaneous or surgical drainage. Several strategies have been suggested to prevent recurrence, including local sclerosis, pericardial window, systemic and/or local chemotherapy, and radiotherapy²⁶⁶. Intrapericardial sclerosis with bleomycin was shown to have modest benefits when compared to pericardial drainage alone²⁶⁷. Surgical drainage seems to be the best option for lung adenocarcinoma metastases²⁶⁸.

6.3.2. Radiation-induced pericarditis

Radiation-induced pericarditis can occur acutely during radiotherapy treatment or several years after the end of therapy. Patients may exhibit few symptoms, or clinical manifestations might be masked by the underlying neoplastic disease. Effusions might be hemorrhagic or serous, and can progress with formations of adhesions and constriction. Pericarditis must be treated in a conservative manner in asymptomatic cases. Pericardiocentesis is indicated to facilitate a diagnosis and for patients with cardiac tamponade. Pericardiectomy is indicated for patients who progress into pericardial constriction; the surgical mortality rate is high, whereas the five-year survival is low²⁶⁹.

6.4. Tuberculous pericarditis

Tuberculous pericarditis (TBP) occurs in 1-4% of the individuals affected by pulmonary tuberculosis (TB)^{270,271}; TB accounts for 7% of cardiac tamponade cases¹⁷¹.

TBP exhibits four stages of progression: dry, effusive, absorptive and constrictive²⁷². The mortality rate of untreated

TBP is approximately 85%. Pericardial constriction occurs in approximately 30 – 50% of cases²⁷³.

The clinical presentation of TBP is quite variable and may include acute pericarditis with or without effusion, silent cardiac tamponade, persistent fever, acute, subacute, effusive, or chronic constrictive pericarditis, and pericardial calcification²⁷⁴.

Although the onset of TBP is insidious, it can also begin suddenly and dramatically in 20 – 25% of cases²⁷¹. Echocardiogram is the best method to confirm the presence of a pericardial effusion. Diagnosis is established upon the identification of *Mycobacterium tuberculosis* in the pericardial fluid and/or tissue and/or the presence of caseous granulomas in the pericardium.

In TBP, the pericardial fluid has a high protein concentration and highly variable leukocyte counts (from 700 to 54,000 cells/ml). The findings are unspecific and the bacillus is found on direct examination in only 40 to 60% of the patients subjected to pericardiocentesis²⁷⁵. The specificity of the tuberculin test also exhibits poor predictability in areas of high TB incidence. The skin tuberculin test yields false-negative results in 25-33% of patients and false-positive results in 30-40% of elderly patients²⁷⁶.

Pericardial fluid culture has a modest sensitivity rate and a specificity rate of 100%²⁷⁷. Increased adenosine deaminase (ADA) activity levels and interferon- γ concentrations in the pericardial fluid have high diagnostic sensitivities and specificities²⁷⁸.

Polymerase chain reaction (PCR) is another method that can detect *Mycobacterium tuberculosis* in the pericardial fluid, as it is able to quickly identify mycobacterial DNA in the pericardial fluid²⁷⁹.

The interferon- γ test (IGT) is approved for use in peripheral blood but not in other fluids such as the pleural and pericardial fluids. It is not known whether IGT of the pericardial fluid has significant advantages over ADA.

Perimyocardial TB involvement is also associated with high anti-myosin and anti-myolemmal antibody titers²⁸⁰.

Pericardial biopsy permits fast diagnosis and exhibits higher sensitivity than pericardiocentesis (100% vs. 33%). The mortality associated with this type of biopsy, as reported in studies with a rigid endoscope, was 2.1%²⁸¹ and 3.5%²⁸²; mortality was due to anesthetic induction in patients with very large pericardial effusion volumes.

6.4.1. Treatment

Several combinations of anti-TB drugs with different treatment durations (6, 9 and 12 months) have been used²⁸³. Only patients with confirmed or highly probable TBP must be treated. Attempts to prevent constriction in chronic pericardial effusions of indefinite etiology with anti-TB agents were unsuccessful²⁸⁴.

Steroid use remains controversial. A meta-analysis of patients with constrictive-effusive TBP suggests that a combined treatment of anti-TB drugs and steroids might correlate with reduced mortality and a reduced need for pericardiocentesis or pericardiectomy^{285,286}. Pericardiectomy

is indicated when constriction develops in spite of the combination therapy.

The pharmacological treatment for all patients with TBP (and other forms of extrapulmonary TB) is comprised of an initial four-drug regimen (Table 32).

Table 32 – Therapeutic doses and management of tuberculous pericarditis

Medication/procedure	Dose/indication
Isoniazid	300 mg PO once daily
Rifampin	600 mg PO once daily
Pyrazinamide	15 to 30 mg/kg/day
Ethambutol	15 to 20 mg/kg PO once daily
Prednisone	1 – 2 mg/kg/day can be administered simultaneously with anti-TB drugs over 5 to 7 days, with progressive tapering off over 6 to 8 weeks
Following 2 months	Discontinue 4-drug regimen and maintain 2 drugs (isoniazid and rifampin) to complete 6 months of treatment
Pericardiectomy	When pericardial constriction and/or tamponade develop in spite of combined therapy

The initial treatment phase usually involves a daily regimen; the various options are described in table 33²⁸⁷.

Table 33 – Preferential options for the initial treatment of tuberculous pericarditis

Option 1	Daily isoniazid, rifampin, pyrazinamide and ethambutol over 8 weeks, followed by isoniazid and rifampin 5 times per week over 18 weeks. *Selected patients (HIV-negative, negative smear after 2 months of treatment, without cavitory disease) might be given isoniazid and rifampin, or isoniazid and rifapentine once per week. * Consult a TB specialist when patients exhibit symptoms or a positive smear or culture after 3 months of treatment.
Option 2	Daily isoniazid, rifampin, pyrazinamide and ethambutol for 2 weeks, and then twice per week.* Give the same drugs over 6 weeks (by DOT) and then isoniazid and rifampin twice per week over 16 weeks (by DOT). Consult a TB specialist when patients exhibit symptoms or a positive smear or culture after 3 months of treatment.
Option 3	Isoniazid, rifampin, pyrazinamide and ethambutol three times per week* (by DOT) over 6 months.* Consult a TB specialist when patients exhibit symptoms or a positive smear or culture after 3 months of treatment.
Option 4	Daily Isoniazid, rifampin, pyrazinamide and ethambutol for 8 weeks or 5 times per week* (this regimen has evidence level C and must only be used when options 1, 2, and 3 are not available) followed by isoniazid and rifampin daily, five times per week*, or twice per week* over another 31 weeks.

* All regimens used twice or three times per week must be performed as directly observed therapy (DOT). Adapted from the American Thoracic Society/ Centers for Disease Control/Infectious Diseases Society of America²⁸⁷.

6.5. Bacteria and fungi

Although purulent pericarditis has high morbidity and mortality rates, it occurs rarely in adults²⁸⁸. Predisposing conditions include previously existing pericardial effusive disease, recent heart surgery or recent chest trauma, chronic kidney disease, immunosuppression, alcohol abuse, rheumatoid arthritis, and malignant neoplasms. Fungal etiology is even more rare and usually appears in patients with fungal infections at other sites²⁸⁹.

The most common clinical presentation is an acute infectious illness; chest pain and pericardial friction rub are infrequent. Anemia, leukocytosis, electrocardiographic and radiological alterations might be present; however, the echocardiogram is one of the most widely used methods to detect and quantify pericardial effusions. Other diagnostic modalities that can be used are CT and MRI²⁹⁰.

Diagnostic suspicion is based on the clinical presentation and presence of pericardial effusion via echocardiogram. Diagnostic confirmation depends on the performance of pericardiocentesis with Gram staining and culture of the pericardial fluid, in addition to investigations of fungi and TB. Gram-positive bacteria are the most prevalent (64.2%), followed by Gram-negative microorganisms (27.7%) and fungi (1.4%)^{291,292}.

Treatment includes pericardial drainage by pericardiocentesis and antibiotics. The initial regimen must target staphylococci and can be replaced later according to the culture results. In the case of multiloculated effusions by septa, the use of thrombolytic agents might be considered, particularly streptokinase in three doses of 500,000 IU, administered every 12 hours^{293,294}. Pericardial drainage via pericardiectomy is the procedure of choice for persistent and recurrent forms¹⁶⁸.

The indications for the diagnosis and treatment of purulent pericarditis are described in table 34.

Table 34 – Indications for the diagnosis and treatment of purulent pericarditis

Recommendation class	Indications	Evidence level
Class I	Diagnostic pericardiocentesis is conducted when purulent pericarditis is suspected	B
Class I	Pericardiectomy for the treatment of purulent pericarditis	B
Class I	Use of antibiotics preferentially guided by the findings on pericardiocentesis, for the treatment of purulent pericarditis	A
Class IIa	Non-steroidal anti-inflammatory for the treatment of purulent pericarditis	B
Class IIa	Colchicine for the treatment of purulent pericarditis	B
Class IIa	Intrapericardial thrombolytic agent for the treatment of purulent pericarditis with multi-loculated pericardial effusion and much fibrin deposition	C
Class IIa	Pericardiectomy for the treatment of the recurrent and persistent forms of purulent pericarditis	B

Recommendation class	Indications	Evidence level
Class IIa	Oral corticosteroids in the treatment of persistent forms of purulent pericarditis to attenuate the symptoms	C
Class IIb	Corticosteroids in the treatment of purulent pericarditis	C

6.6. Autoimmune diseases

Systemic autoimmune processes can induce pericarditis²⁹⁵, and this disorder occurs in patients with rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, polymyositis, mixed connective tissue disease, seronegative spondylitis, Sjögren's syndrome, systemic vasculitis, Behçet's syndrome, granulomatosis with polyangiitis, and sarcoidosis, among others.

The clinical presentation varies from an asymptomatic finding to acute pericarditis; cardiac tamponade is less frequent. Cases of transient constrictive pericarditis have also been reported²⁹⁶. Progression to chronic constrictive pericarditis is rare. Management of the usual forms is directed at the underlying cause.

An isolated form of autoimmune pericarditis was described after a systematic search for evidence of auto-aggression and was confirmed by lymphocytic predominance or the presence of anti-sarcolemma autoantibodies²⁹⁷ in the pericardial fluid. The presence of viruses or other infectious agents is excluded (no IgM against cardiotropic viruses in the pericardial fluid, and negative PCR for those same agents) in addition to systemic or neoplastic diseases.

Treatment is the same as for acute pericarditis and pericardial effusion associated with treatment of the underlying disease (table 35).

Intrapericardial administration of triamcinolone at a dose of 300 mg/m²/24 hours in 100 ml of normal saline solution proved to be efficacious for the relief of symptoms and prevention of recurrence while avoiding the side effects of systemic corticosteroids²⁹⁸.

Table 35 – Indications of treatment for autoimmune pericarditis

Recommendation class	Indications	Evidence level
Class I	NSAIDs for the initial treatment of autoimmune pericarditis	B
Class I	Colchicine for the treatment of autoimmune pericarditis relapse	B
Class I	Systemic corticosteroids in low doses for the treatment of refractory cases of autoimmune pericarditis (non-responsive to NSAIDs or colchicine)	B
Class I	Surgical indication of refractory pericardial effusion due to chylothorax following heart surgery	B
Class IIa	Possible intrapericardial use of corticosteroids in refractory cases	B
Class III	Systemic corticosteroids in high doses for the treatment of refractory cases of autoimmune pericarditis	B

6.7. Chylopericardium and hypothyroidism

Chylopericardium is the pericardial accumulation of the matter drained by the thoracic duct due to a fistula, complications of mediastinal surgery, cardiovascular surgery, chest trauma, mediastinal tumors or congenital anomalies of the thoracic duct²⁵⁰.

In such cases, the pericardial fluid has a milky white, opalescent appearance and high triglyceride (5 - 50 g/L), protein (22- 60 g/L) and fat concentrations. Magnetic resonance T1- and T2-weighted images provide data that permit a definitive diagnosis²⁹⁹.

However, sometimes it is difficult to distinguish chylopericardium from other causes of pericardial effusion. In such instances, surgical exploration of the pericardium is required to establish a diagnosis.³⁰⁰ Treatment depends on the cause of chylopericardium and the amount of pericardial fluid. When the cause is chest or heart surgery and there are no signs of cardiac tamponade, treatment might merely consist of an occasional puncture and a medium-chain triglyceride-based diet³⁰¹. Cases refractory to conservative treatment might require a surgical pericardioperitoneal shunt or an alternative ligation of the thoracic duct when its location can be established³⁰².

Pericardial effusion is a relatively common occurrence in hypothyroidism and affects 30 to 80% of advanced and 3 to 6% of early cases³⁰³. Although very rare, cardiac tamponade is a possible complication and might be indicated by an unexpectedly fast heart rate in a patient with hypothyroidism and low QRS voltage³⁰⁴.

Treatment of pericardial effusion is easily achieved by the overall treatment of hypothyroidism (table 36).

Table 36 – Indications for chylopericardium and hypothyroidism

Recommendation class	Indications	Evidence level
I	Surgery in refractory cases of chylopericardium following heart surgery	B
I	Treatment of pericardial effusion in hypothyroidism with thyroid hormone replacement	B

6.8. Post-myocardial infarction pericarditis

There are two forms of pericarditis manifestation after AMI. One occurs early and is known as pericarditis epistemonocarda or peri-infarction pericarditis; the other occurs late and is known as post-infarction pericarditis or Dressler's syndrome. Currently, the incidence of both forms is decreasing^{305,306}. Peri-infarction pericarditis is defined by pericardial pain and pericardial friction rub and usually appears two or three days after the establishment of a transmural AMI. The electrocardiographic signs are difficult to identify because they overlap those of AMI. Persistent inverted T waves or the return of T waves to baseline levels might indicate pericarditis. The clinical course is benign and patient prognosis is not affected by this complication.

Post-infarction pericarditis occurs in approximately 5 to 6% of the patients subjected to thrombolysis and usually appears during the second week but can also manifest several months after AMI. It should be suspected in any patient who presents with pleuropericardial chest pain. Pericardial friction rub is not always present. A differential diagnosis between pericarditis and recurrent angina may be difficult; however, close attention to the patient history and serial electrocardiographic assessments can help to elucidate a diagnosis. Most cases have a benign course; however, because this form of pericarditis is associated with large infarctions, the overall long-term mortality rate is higher³⁰⁷.

Rare complications include hemopericardium, cardiac tamponade, and constrictive pericarditis. Treatment regimens target pain, which usually responds well to non-steroidal anti-inflammatory drugs. Nevertheless, treatments remain largely empirical due to a relative lack of controlled clinical trials^{308,309}. Furthermore, the duration of treatment is not well established. However, despite such shortcomings, we suggest the following regimens: ibuprofen, at doses of 1,600 – 3,200 mg/day for up to two weeks, is the first-line drug because it increases coronary flow and exhibits the lowest incidence of side effects^{224,310}; ASA, at doses of 2 to 4 g/day over two to five days, exhibits the same efficacy as ibuprofen. In patients with refractory and recurrent symptoms, colchicine, at a dose of 0.5 mg twice per day, is preferable to oral corticosteroids, which should be used only in low doses (prednisone 0.2 – 0.5 mg/kg/day)^{223,311,312}.

6.9. HIV

Pericardial disease is the most frequent clinical manifestation of cardiovascular disease in patients with HIV/AIDS. Pericardial effusion occurs in approximately 20% (range: 10 to 40%) of patients, and 4% has large effusion³¹³⁻³¹⁶. Two-thirds of the cases are caused by infection or neoplasia; the latter correlates with poorer prognosis³¹⁷.

The clinical manifestations of pericarditis in HIV/AIDS patients are similar to those of pericarditis by other causes. *M. tuberculosis* is frequently found in HIV-infected patients³¹⁸⁻³²³; however, negative tuberculin tests do not rule out a diagnosis. Additionally, although pericardial biopsy is more sensitive than pericardial fluid smears and cultures, it might not indicate caseous granuloma positivity. The incidence of CMV-induced pericarditis is also higher in HIV-infected individuals^{324,325}.

The treatment of pericarditis in HIV-infected patients is both symptomatic and preventive. When the effusion is symptomatic, recurrent, or chronic and viral infection is confirmed, specific treatment must be instituted²⁴².

Cardiac tamponade occurs in 33 to 40% of cases, and immediate drainage is needed. When the pericardial effusion is large and has no established etiology, empirical anti-TB treatment is indicated³²⁶⁻³²⁸.

6.10. Pericarditis following trauma and aortic dissection

6.10.1 Posttraumatic pericarditis

Posttraumatic pericarditis occurs after accidental or iatrogenic wounds. The most severe cases progress to

pericardial effusion and tamponade and require emergency surgical treatment. Closed or penetrating chest or heart wounds with myocardial contusions can cause pericarditis. However, this form of pericarditis has little clinical significance and might develop days or months after the heart or chest injury. Inflammation seems to be due to production of antibodies in response to the myocardial injury. Pericarditis after heart surgery is reported to occur in 20% of myocardial revascularization procedures and can appear days to several months after intervention.

Iatrogenic pericarditis is rare; it occurs in less than 0.2% of percutaneous interventions. The procedures most frequently associated with pericarditis are percutaneous mitral valvuloplasty, transseptal puncture, coronary artery transection following angioplasty, endomyocardial biopsy, implantation of pacemaker electrodes in the right ventricle, and epicardial electrode implantation.

Injury-induced pericarditis also occurs in cases of chest or mediastinal radiation for the treatment of several types of neoplasms, especially Hodgkin disease, non-Hodgkin lymphomas and breast carcinoma. The odds of developing pericarditis are associated with the radiation source, dose, fractionation, duration, volume of exposure and field of application, as well as patient age. Radiation-induced pericarditis can occur during the course of treatment or months to several years afterwards^{167,168}.

6.10.2. Pericarditis by aortic dissection

Pericardial effusion occurs in 17-45% of patients with aortic dissection and in 48% of autopsies of aortic dissection fatalities³²⁹. Dissection of the ascending aorta is commonly complicated by a potentially fatal hemopericardium. Diagnosis is usually established by transeophageal echocardiogram, chest tomography, or cardiac and aortic resonance³³⁰.

Pericardiocentesis is contraindicated due to the risk of increased bleeding and aggravation of the dissection. Patients must be subjected immediately to aortic corrective surgery and pericardial drainage³³¹.

6.11. Recurrent pericarditis

Recurrent pericarditis usually occurs 18 to 20 months after the initially resolved episode. It appears in approximately 15-32% of cases and manifests in two forms, intermittent (asymptomatic intervals without treatment) and incessant pericarditis (symptoms return every time treatment is discontinued)^{168,254}. The mechanisms involved in the development of recurrence are inadequate treatment with non-steroidal anti-inflammatory agents or corticosteroids (dose, duration), inappropriate corticosteroid use that permits viral replication, viral reinfection, and reactivation of autoimmune disease.

Colchicine is the safest and most efficacious therapy for the avoidance of recurrent pericarditis, particularly when NSAIDs or corticosteroid treatment failed to prevent recurrence³³².

Corticosteroid treatment is indicated in patients with frequent recurrence or important clinical manifestations. When responses to corticosteroids are inappropriate, azathioprine

or cyclosporine may be administered concomitantly²⁰⁶. A main determinant of recurrence is rapid corticosteroid withdrawal; withdrawal should be done over a period of at least three months.

Pericardiectomy is indicated in cases with frequent, highly symptomatic, and treatment-refractory recurrence³³³⁻³³⁵.

Table 37 summarizes the indications for the treatment of recurrent pericarditis.

Table 37 – Indications for the treatment of recurrent pericarditis

Recommendation class	Indications	Evidence level
Class I	Colchicine in 6 months for the treatment of recurrent pericarditis	B
Class IIa	Aspirin or ibuprofen for the treatment of recurrent pericarditis	B
Class IIa	Colchicine for the treatment of post-myocardial infarction pericarditis	B
Class IIb	Pericardiectomy for the treatment of recurrent pericarditis and for refractory and highly symptomatic cases	B
Class IIb	Systemic corticosteroids for the treatment of recurrent pericarditis following failure of NSAID and colchicine treatment	C
Class IIb	Use of other immunosuppressant agents (azathioprine and cyclosporine) for recurrences due to autoimmune or collagen diseases	C

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