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BIOMEDICAL SCIENCES

Myocarditis: The Role of Viral and Autoimmune Inflammation in Cardiovascular Pathology

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Abstract

Myocarditis, an inflammatory disease of the myocardium, is a significant contributor to acute and chronic cardiac dysfunction, manifesting as heart failure, arrhythmias, and sudden cardiac death, particularly in younger individuals. Its pathogenesis involves a complex interplay between direct viral injury and immune-mediated mechanisms. Viral myocarditis, commonly caused by coxsackievirus, parvovirus B19, and SARS-CoV-2, results from viral invasion of cardiomyocytes, leading to cell lysis, cytokine release, and activation of innate immunity. Autoimmune myocarditis arises when molecular mimicry or systemic autoimmune disorders, such as systemic lupus erythematosus, trigger sustained immune attacks on myocardial tissue. Clinical presentation is heterogeneous, ranging from mild chest pain to fulminant heart failure, complicating diagnosis. Contemporary approaches emphasize multimodal strategies, integrating cardiac magnetic resonance imaging, biomarker profiling, and selective endomyocardial biopsy to improve diagnostic accuracy. Management combines supportive care—addressing heart failure and arrhythmias—with targeted therapies, including immunosuppressants for autoimmune cases and investigational antivirals for viral etiologies. Emerging technologies, notably artificial intelligence, enhance imaging interpretation and prognostic assessment, while novel therapies aim to prevent progression to dilated cardiomyopathy. Public health challenges include underdiagnosis, disparities in access to advanced diagnostics, and the growing burden associated with post-viral pandemics such as COVID-19. Addressing these requires targeted screening of high-risk populations, equitable access to care, and international collaboration to standardize guidelines. This review synthesizes current knowledge on the viral and autoimmune mechanisms of myocarditis, diagnostic advances, therapeutic strategies, and public health implications, highlighting opportunities for innovation to improve patient outcomes and reduce the global burden of this complex cardiovascular disease.

Keywords: Viral myocarditis, Myocarditis, Autoimmune myocarditis, Cardiac Magnetic Resonance, Dilated cardiomyopathy, SARS-CoV-2 / COVID-19, Artificial Intelligence, Endomyocardial biopsy

Introduction

Myocarditis is an inflammatory condition of the myocardium that significantly contributes to cardiovascular morbidity, often manifesting as heart failure, arrhythmias, and sudden cardiac death, particularly in younger individuals [1]. The disease is driven by diverse etiologies, with viral infections such as coxsackievirus and SARS-CoV-2 directly injuring heart tissue, while autoimmune mechanisms, including systemic lupus erythematosus and post-viral immune responses, trigger myocardial damage through immune-mediated pathways [2, 3]. The complexity of these mechanisms underscores the need for a comprehensive understanding of myocarditis to improve clinical outcomes in affected populations [4].

The diagnostic challenge of myocarditis arises from its nonspecific and variable clinical presentations, such as chest pain, fatigue, and palpitations, which frequently overlap with other cardiac conditions like acute coronary syndrome or pericarditis, leading to frequent underdiagnosis [5, 6]. Recent global health events, particularly the emergence of COVID-19-related myocarditis, have heightened awareness of the disease's potential severity and the critical need for advanced diagnostic tools, such as cardiac magnetic resonance (CMR), to detect myocardial inflammation and guide management [7, 8]. These challenges highlight the importance of integrating clinical suspicion with modern diagnostic modalities to address the often elusive nature of myocarditis [9].

This review synthesizes current knowledge on the pathophysiology, epidemiology, diagnostic ap-

proaches, therapeutic strategies, emerging research, and public health implications of myocarditis, with a focus on its viral and autoimmune origins. By exploring the interplay of these mechanisms and leveraging advancements in non invasive diagnostics and targeted therapies, this article aims to enhance clinical awareness and guide effective management strategies [10]. Ultimately, it seeks to address the global burden of myocarditis by advocating for improved screening, equitable access to care, and ongoing research to mitigate its impact on cardiovascular health.

Pathophysiology of Myocarditis

Myocarditis is characterized by inflammation of the myocardium, driven by a complex interplay of viral and autoimmune mechanisms that result in cardiac injury and dysfunction. Viral infections, such as those caused by coxsackievirus, parvovirus B19, and SARS-CoV-2, initiate direct invasion of cardiomyocytes, leading to cell lysis and the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). This viral-mediated damage triggers an innate immune response, amplifying inflammation and causing further myocardial injury [4, 11]. In contrast, autoimmune myocarditis arises from immune dysregulation, often through molecular mimicry, where viral antigens resembling cardiac proteins provoke T-cell and antibody-mediated attacks on the myocardium. This process is particularly prominent in conditions like systemic lupus erythematosus or post-viral autoimmunity, leading to sustained inflammation and tissue damage [3, 12].

The progression from acute myocarditis to chronic dilated cardiomyopathy (DCM) occurs in susceptible individuals due to persistent inflammation and maladaptive immune responses. In acute phases, viral clearance may fail, or autoimmune reactions may perpetuate, causing ongoing myocyte necrosis and fibrosis. This chronic inflammatory state disrupts myocardial architecture, impairs contractility, and leads to ventricular dilation, a hallmark of DCM [5]. Histopathological analysis via endomyocardial biopsy remains critical for confirming myocarditis, revealing characteristic features such as lymphocytic infiltration and myocyte necrosis, as defined by the Dallas criteria. **Figure 1** illustrates these findings, displaying a myocardial biopsy stained with hematoxylin and eosin, which shows dense lymphocytic infiltration5 within the myocardial interstitium and areas of myocyte necrosis, characteristic of acute myocarditis. The image highlights the inflammatory infiltrate and disrupted myocardial architecture, consistent with the Dallas criteria for myocarditis diagnosis [12].

In severe cases, such as fulminant myocarditis, systemic effects exacerbate the disease's impact. Cytokine storms, driven by excessive release of IL-6, TNF-α, and other mediators, can lead to multiorgan dysfunction, including renal, hepatic, or respiratory involvement. This hyperinflammatory response, often seen in SARS-CoV-2-related myocarditis, may precipitate cardiogenic shock and requires aggressive management [8, 11].

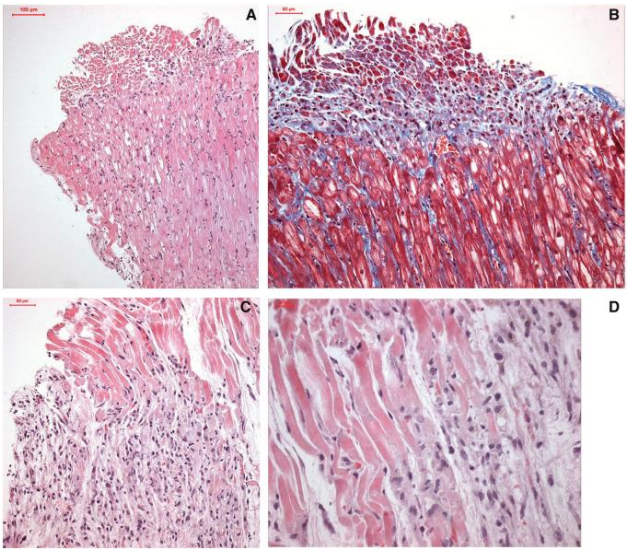

Figure 1: Hematoxylin and eosin–stained myocardial biopsy demonstrating lymphocytic infiltration and myocyte necrosis, diagnostic of myocarditis per Dallas criteria [13].

Understanding these pathophysiological mechanisms is essential for developing targeted therapies and improving outcomes in patients with myocarditis.

Epidemiology and Clinical Manifestations

Myocarditis exhibits a variable global prevalence, with estimates ranging from 10 to 22 cases per 100,000 individuals annually, though true incidence is likely higher due to underdiagnosis [14]. The disease disproportionately affects young adults, particularly those aged 20–40 years, and has gained attention in post-viral settings, such as following SARS-CoV-2 infection, where myocarditis has been reported in 1-4% of hospitalized COVID-19 patients and up to 15% of athletes with prior infection [7, 8]. Post-viral myocarditis, driven by viruses like coxsackievirus, parvovirus B19, and SARS-CoV-2, underscores the role of recent infections in triggering acute myocardial inflammation, particularly in otherwise healthy individuals [3].

Risk factors for myocarditis include younger age, with a peak incidence in adolescents and young adults, and a slight male predominance, potentially due to hormonal or immune response differences [15]. Predisposing conditions, such as autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis), increase susceptibility to autoimmune myocarditis, while genetic factors, including HLA gene variants, may enhance risk in certain populations [5]. **Table 1** delineates the distinctions between viral and autoimmune myocarditis, highlighting differences in etiology, clinical presentation, and diagnostic markers. This table underscores the slight male predominance in both forms, the frequent multiorgan involvement in autoimmune cases, and the distinct biomarker profiles, such as elevated antinuclear antibodies (ANA) in autoimmune myocarditis [3, 4].

Clinical presentations of myocarditis are diverse, ranging from mild, nonspecific symptoms to life-threatening conditions. Acute chest pain, mimicking

Table 1: Comparative Features of Viral and Autoimmune Myocarditis.

Feature	Viral Myocarditis	Autoimmune Myocarditis
Etiology	Viral infection (e.g., coxsackievirus, parvovirus B19, SARS-CoV-2)	Autoimmune diseases (e.g., SLE, post-viral autoimmunity)
Age of Onset	Typically 20–40 years	Variable, often 30–50 years
Sex Predominance	Slight male predominance	Slight male predominance
Cardiac Presentation	Acute chest pain, fulminant heart failure, arrhythmias	Subacute heart failure, ventricular dysfunction
Other Organ Involvement	Rare, may include hepatitis or myositis in severe cases	Frequent, e.g., kidneys (SLE), joints (rheumatoid arthritis)
Electrocardiogram (ECG)	ST-segment elevation, T-wave inversion, arrhythmias	Non-specific ST-T changes, conduction delays
Echocardiogram	Regional/global wall motion abnormalities, reduced EF	Dilated cardiomyopathy, diastolic dysfunction
Biomarker Profile	Elevated troponin, CRP, ESR	Elevated troponin, ANA, dsDNA in autoimmune diseases
Diagnostic Imaging	CMR: myocardial edema, patchy LGE	CMR: diffuse LGE, fibrosis in chronic cases
Confirmatory Tests	Endomyocardial biopsy, viral PCR	Biopsy, autoantibody testing (e.g., ANA, anti-dsDNA)
Prognosis (if untreated)	Variable, may resolve or progress to DCM	Chronic progression to DCM, worse with systemic disease
Available Therapies	Supportive care, antivirals (e.g., interferon-beta)	Immunosuppressants (e.g., corticosteroids, rituximab)

Note: Clinical, demographic, and diagnostic distinctions between viral and autoimmune myocarditis, including etiologies, organ involvement, and diagnostic markers [3, 4].

acute coronary syndrome, is common in viral myocarditis, often accompanied by electrocardiographic changes like ST-segment elevation or T-wave inversion [6]. Heart failure symptoms, including dyspnea and edema, predominate in subacute or autoimmune cases, reflecting ventricular dysfunction. Arrhythmias, such as ventricular tachycardia, and sudden cardiac death are critical complications, particularly in young adults and athletes, where myocarditis accounts for up to 20% of sudden deaths [16]. The overlap of these manifestations with other cardiac conditions poses significant diagnostic challenges, necessitating a high index of suspicion and advanced diagnostic tools.

Diagnostic Approaches

The diagnosis of myocarditis has evolved significantly, transitioning from reliance on invasive endomyocardial biopsy to advanced non-invasive imaging and biomarker assays, improving both accuracy and accessibility. Historically, endomyocardial biopsy was the cornerstone for confirming myocarditis through histopathological evidence, but its invasiveness, sampling errors, and limited availability prompted the development of non-invasive modalities [4]. Cardiac magnetic resonance (CMR) imaging, echocardiography, and serum biomarkers now form the backbone of modern diagnostic strategies, enabling earlier detection and better risk stratification, particularly in settings where biopsy is impractical [9].

Key diagnostic modalities include CMR, which employs the Lake Louise criteria to identify myocardial edema via T2-weighted imaging and late gadolinium enhancement (LGE) for detecting fibrosis or necrosis, offering high sensitivity and specificity for myocarditis [17]. **Figure 2** illustrates a cardiac MRI with T2-weighted imaging showing myocardial edema in the left ventricular free wall, alongside LGE images displaying patchy, non-ischemic enhancement patterns in the mid-myocardium, typical10 of myocarditis. These findings highlight the Lake Louise criteria for diagnosing myocardial inflammation [9]. Echocardiography is widely used to assess ventricular dysfunction and wall motion abnormalities, often revealing regional or global hypokinesis, though it lacks specificity for myocarditis [6]. Biomarkers, such as elevated troponin, C reactive protein (CRP), and natriuretic peptides (e.g., B-type natriuretic peptide), indicate myocardial injury and inflammation but are non-specific, requiring correlation with imaging findings [5]. Endomyocardial biopsy remains the gold standard for histopathological confirmation, identifying lymphocytic infiltration or

viral genomes, but is reserved for cases with inconclusive non-invasive results or suspected autoimmune etiology due to its risks [3].

A structured diagnostic approach is critical to streamline evaluation. **Figure 3** presents a stepwise diagnostic algorithm for myocarditis, beginning with clinical suspicion (e.g., chest pain, arrhythmias), followed by echocardiography to assess wall motion abnormalities, biomarker testing (troponin, CRP), and CMR using Lake Louise criteria. Endomyocardial biopsy is reserved for inconclusive cases or suspected autoimmune etiology [4]. Despite these advances, distinguishing myocarditis from conditions like pericarditis, ischemic cardiomyopathy, or stress-induced cardiomyopathy remains challenging due to overlapping clinical and imaging features, such as chest pain or ST segment changes on electrocardiograms [8]. Non-specific biomarker elevations and variable imaging findings further complicate differentiation, necessitating a multimodal approach integrating clinical, laboratory, and imaging data to ensure accurate diagnosis [18].

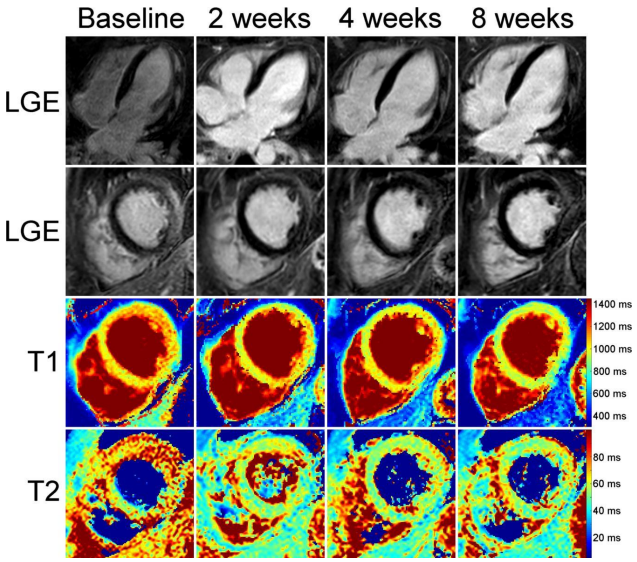

Figure 2: Cardiac magnetic resonance imaging with T1 and T2-weighted imaging and late gadolinium enhancement (LGE) showing myocardial edema and patchy enhancement, characteristic of myocarditis [19].

Therapeutic Strategies

The management of myocarditis encompasses supportive care to address heart failure and arrhythmias, alongside targeted therapies tailored to the underlying etiology, whether viral or autoimmune. Supportive care is critical for stabilizing patients with acute presentations. Diuretics, such as furosemide, are used to manage fluid overload in heart failure, while anti-arrhythmic drugs, like amiodarone, control ventricular or supraventricular arrhythmias, which are common in acute myocarditis [5]. Beta blockers, typically carvedilol or metoprolol, are introduced cautiously in hemodynamically stable patients due to their potential to exacerbate acute heart failure in

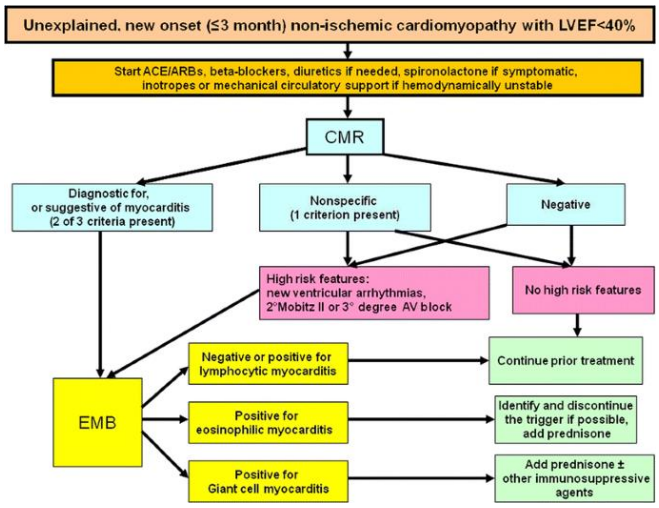

Figure 3: Stepwise diagnostic pathway for myocarditis using clinical suspicion, echocardiography, biomarkers, CMR, and endomyocardial biopsy when indicated [2].

the early phase, but they are beneficial in chronic cases to reduce myocardial stress [6]. In severe cases, such as fulminant myocarditis with cardiogenic shock, mechanical circulatory support, including extracorporeal membrane oxygenation (ECMO) or ventricular assist devices (VADs), may be necessary to bridge patients to recovery or transplantation [3].

Targeted therapies address the specific pathophysiology of viral or autoimmune myocarditis. For viral myocarditis, antiviral agents like interferon-beta have shown limited efficacy in enteroviral infections by inhibiting viral replication, but their use remains investigational and is typically combined with supportive care [3]. Autoimmune myocarditis, often associated with systemic diseases like systemic lupus erythematosus, responds to immunosuppressive therapies. Corticosteroids, such as prednisone, are the cornerstone, reducing immune-mediated inflammation and improving left ventricular ejection fraction in virus-negative cases. Azathioprine is frequently used as a steroid-sparing agent to suppress lymphocyte proliferation, while biologics like rituximab, targeting CD20+ B cells, are effective in refractory cases [20]. **Table 2** summarizes these therapeutic options, detailing mechanisms, indications, and clinical evidence for both viral and autoimmune myocarditis.

Emerging therapies, such as anti-cytokine agents like tocilizumab, show promise in managing cytokine-driven inflammation, particularly in SARS-CoV-2-related myocarditis, though they remain investigational [7]. Complications, including progression to dilated cardiomyopathy, highlight the need for early intervention, while the selective use of mechanical support underscores the importance of individualized treatment plans to optimize outcomes [16].

Emerging Research and Technological Advances

Advancements in artificial intelligence (AI) and novel therapeutic strategies are reshaping the landscape

Table 2: Therapeutic Options for Viral and Autoimmune Myocarditis.

Treatment Class	Therapeutic Agent	Mechanism of Action	Myocarditis Type	Regulatory Status	Key Notes or Trial Evidence
Antiviral Therapy	Interferon-beta	Inhibits viral replication	Viral	Investigational	Limited efficacy in enteroviral myocarditis [3]
Immunosuppressants	Corticosteroids	Reduces immune-mediated inflammation	Autoimmune	Standard of care	Improved LVEF in virus-negative cases [21]
	Azathioprine	Inhibits lymphocyte proliferation	Autoimmune	Standard of care	Used in combination with corticosteroids
Biologics	Rituximab	Targets CD20+ B cells	Autoimmune	Off-label	Effective in refractory autoimmune cases [21]
Anti-cytokine Therapy	Tocilizumab	IL-6 receptor antagonist	Viral or Autoimmune	Investigational	Potential in cytokine-driven inflammation (COVID-19)
Supportive Care	Diuretics, antiarrhythmics	Symptom relief, arrhythmia control	Viral or Autoimmune	Routine use	Beta-blockers poorly tolerated in acute phase
Mechanical Support	ECMO/VAD	Supports cardiac function in fulminant cases	Viral or Autoimmune	Emergency use	Used in fulminant myocarditis with cardiogenic shock

Note: Summary of approved and investigational treatments for myocarditis, including mechanisms, indications, and clinical trial evidence [3, 20].

of myocarditis management, offering potential for earlier diagnosis and targeted interventions. AI-driven diagnostics, particularly convolutional neural networks (CNNs), have shown promise in detecting myocarditis-specific patterns in cardiac magnetic resonance (CMR) and echocardiographic imaging. CNNs analyze complex imaging data to identify myocardial edema, late gadolinium enhancement (LGE), and wall motion abnormalities with high accuracy, reducing reliance on subjective interpretation and improving diagnostic efficiency [21]. **Figure 5** illustrates a CNN model for automated myocarditis detection, comprising multiple panels: (A) an echocardiographic four-chamber view showing regional wall motion abnormalities; (B) a CMR T2-weighted image highlighting myocardial edema; (C) a CMR with LGE showing patchy enhancement; (D) a CNN architecture diagram with input layers processing imaging data; and (E) an output heatmap overlay on CMR, indicating regions of inflammation. This figure demonstrates AI-driven detection of myocarditis-specific imaging patterns [21]

Novel therapeutic approaches are also emerging, targeting the underlying mechanisms of myocarditis. For viral myocarditis, gene therapies aimed at enhancing viral clearance, such as CRISPR-based antiviral strategies, are under investigation to disrupt viral genomes within cardiomyocytes, potentially preventing chronic inflammation [3]. In autoimmune myocarditis, immunomodulatory agents, including next-generation biologics like belimumab, which targets B-cell activating factor, show potential in reducing immune-mediated myocardial damage, particularly in refractory cases [21]. These therapies aim to interrupt the progression to dilated cardiomyopathy, offering hope for improved long-term outcomes.

Despite these advancements, significant challenges persist. AI models require standardization to ensure generalizability across diverse patient populations, as current datasets often lack racial, ethnic, and geographic diversity, limiting their applicability in global settings [21]. Additionally, the high cost of advanced diagnostics, such as CMR, and novel therapies, like gene editing, poses barriers to equitable access, particularly in low-resource regions [14]. Parallels with AI applications in other cardiovascular diseases, such as cardiac amyloidosis, highlight the potential for early detection. In amyloidosis, CNNs have been used to detect amyloid deposits in CMR and echocardiography, enabling earlier intervention, a strategy that could be adapted for myocarditis to improve outcomes through timely diagnosis [17]. Addressing these challenges through collaborative research, diverse data integration, and cost-effective innovations will be critical to translating these advances into clinical practice.

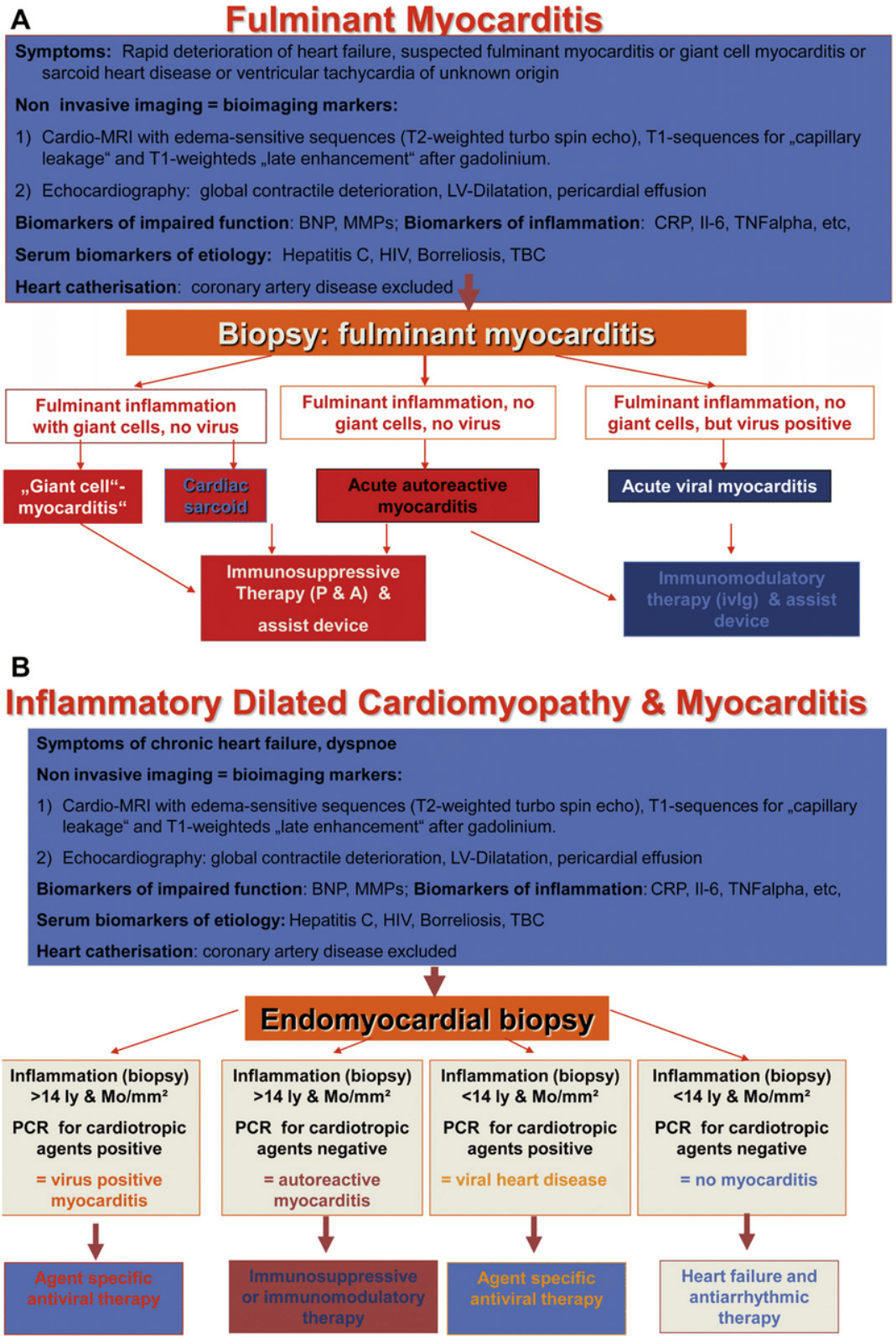

Figure 4: Stepwise diagnostic pathway for myocarditis using clinical suspicion, echocardiography, biomarkers, CMR, and endomyocardial biopsy when indicated [22].

Public Health Implications and Future Directions

Myocarditis poses a significant public health burden, particularly in the context of post viral pandemics like COVID-19, which has highlighted its potential to cause substantial morbidity and mortality. The global incidence of myocarditis, estimated at 10–22 cases per 100,000 individuals annually, is likely underestimated due to diagnostic challenges, with post-viral cases, such as those following SARS-CoV-2 infection [7, 14]. COVID-19-related myocarditis has been reported in 1-4% of hospitalized patients and up to 15% of athletes with prior infection, underscoring the need for heightened surveillance and resource allocation to

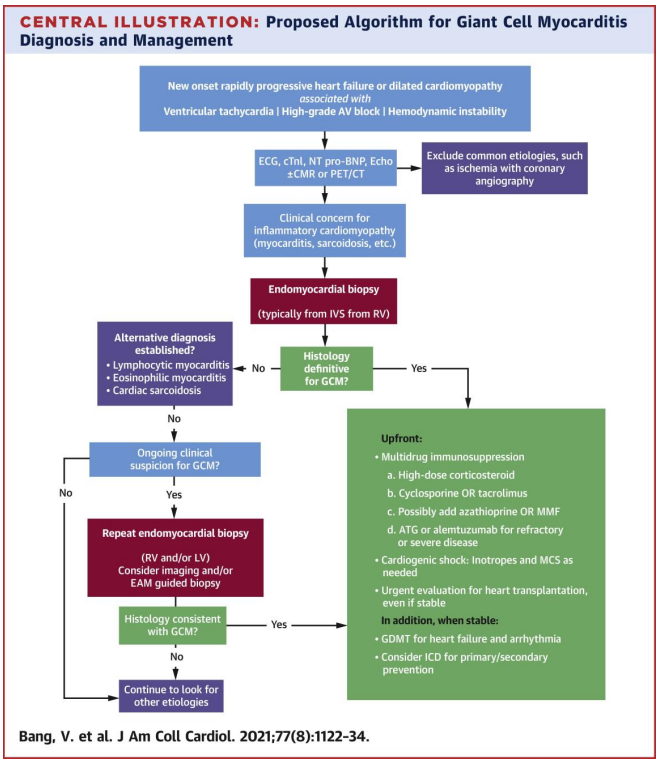

Figure 5: Convolutional neural network (CNN) architecture for detecting myocarditisspecific patterns in CMR and echocardiographic images, with heatmap overlay highlighting inflamed regions [23].

manage the conditions that may arise [8]. The disease's association with sudden cardiac death, particularly in young adults, amplifies its public health impact, necessitating proactive strategies to mitigate its effects [16]. Targeted screening strategies for high-risk groups are essential to reduce myocarditis related morbidity. Young athletes, patients with recent viral infections (e.g., influenza, COVID-19), and those with autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis) are particularly vulnerable due to their increased risk of acute myocardial inflammation or autoimmune-mediated damage [3]. **Table 3** provides a screening checklist for identifying myocarditis in at-risk populations, outlining red-flag features such as unexplained heart failure, recent viral infection, elevated troponin, or CMR findings of myocardial edema. This checklist guides clinicians in prioritizing diagnostic evaluation for high-risk individuals, enhancing early detection and intervention [3, 7].

Disparities in access to advanced diagnostics, such as CMR, and therapies, particularly in low-resource settings, exacerbate the global burden of myocarditis, highlighting the need for equitable healthcare solutions [14]. Future directions include enhanced disease surveillance through national registries to track incidence and outcomes, integration of AI-driven diagnostics into clinical workflows to improve early detection, and development of cost-effective treatments, such as generic immunomodulatory agents [21]. Multidisciplinary collaboration among cardiologists, immunologists, and public health officials is crucial to establish standardized guidelines and improve patient care. By prioritizing screening, surveillance, and equitable access, the public health impact of myocarditis can be significantly reduced, paving the way for better cardiovascular health globally.

Conclusion

Myocarditis remains a critical cardiovascular condition driven by the interplay of viral infections and autoimmune responses, leading to significant morbidity through heart failure, arrhythmias, and sudden cardiac death. Viral pathogens, such as coxsackievirus and SARS-CoV-2, directly damage cardiomyocytes, while autoimmune mechanisms, including molecular mimicry in diseases like systemic lupus erythematosus, perpetuate myocardial inflammation, often progressing to chronic dilated cardiomyopathy in untreated cases. The public health burden, amplified by post-viral pandemics like COVID-19, underscores the urgency of addressing this disease globally.

Advancements in non-invasive diagnostics, notably cardiac magnetic resonance imaging using Lake Louise criteria and AI-driven tools like convolutional neural networks, have revolutionized early detection, enabling timely intervention and improved outcomes. Therapeutic strategies, ranging from supportive care with diuretics and anti-arrhythmics to targeted therapies like interferon-beta for viral myocarditis and rituximab for autoimmune cases, offer tailored approaches to mitigate disease progression [20]. However, challenges such as diagnostic overlap with conditions like ischemic cardiomyopathy, disparities in access to advanced diagnostics, and the high24 cost of novel therapies highlight the need for continued innovation and equitable healthcare solutions.

Looking forward, increased clinical awareness, targeted screening of high-risk groups, such as young athletes and patients with recent viral infections, and equitable access to care are imperative to reduce myocarditis-related morbidity. Ongoing research into gene therapies, immunomodulatory agents, and standardized AI models promises to further transform management, while multidisciplinary collaboration will drive the development of global guidelines and registries. By prioritizing these efforts, the global health community can address the complex challenges of myocarditis, ultimately improving cardiovascular outcomes worldwide.

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Ethics approval and consent to participate

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Table 3: Screening Checklist for Myocarditis in At-Risk Populations.

Category	Red-Flag Feature	Rationale
Demographics	Age 20–40 years, especially males	Higher prevalence in young adults
Cardiovascular History	Unexplained acute heart failure	Suggests fulminant myocarditis
Cardiovascular History	Recent viral infection (e.g., flu, COVID-19)	Common trigger for viral myocarditis
Cardiovascular History	Unexplained arrhythmias or syncope	Conduction system involvement
Systemic Symptoms	Recent fever, myalgia, or fatigue	Indicates possible viral etiology
Systemic Symptoms	Autoimmune disease history (e.g., SLE, RA)	Risk for autoimmune myocarditis
Laboratory Findings	Elevated troponin or CRP without ischemia	Suggests myocardial injury
Laboratory Findings	Positive autoantibodies (e.g., ANA, dsDNA)	Indicates autoimmune etiology
Imaging Findings	CMR: Myocardial edema, patchy LGE	Meets Lake Louise criteria for myocarditis
Imaging Findings	Echocardiography: Wall motion abnormalities	Suggests myocardial dysfunction

Note: Checklist of clinical, laboratory, and imaging red-flag features to guide myocarditis screening in high-risk populations [3, 7].

Competing interests

None of the authors have conflicts of interest to declare.

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