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Unveiling the complexity of pediatric acute myocarditis: A multifaceted approach to understanding and managing a challenging syndrome

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Abstract
Pediatric acute myocarditis presents a complex clinical scenario that demands a nuanced understanding of its pathophysiology, diagnostic intricacies, and evolving therapeutic landscape. This comprehensive review synthesizes recent advancements across multiple domains, providing an in-depth analysis of the diverse clinical presentations, underlying causes, diagnostic modalities, and treatment strategies. By examining the latest research findings, we aim to offer a holistic perspective on pediatric acute myocarditis, contributing to the refinement of diagnostic criteria and the development of tailored therapeutic approaches.

Keywords: Paediatric, myocarditis, heart dysfunction, myocardial fibrosis

Introduction
Pediatric acute myocarditis, though rare, poses significant challenges in terms of diagnosis and management. This section provides an overview of the epidemiology and clinical significance of the syndrome, setting the stage for a detailed exploration of recent developments in the field.
Myocarditis is a medical disorder that occurs when there is inflammation in the heart muscle cells, leading to swelling and damage or death of the heart muscle tissue [1]. The precise occurrence is uncertain, although it is probably underestimated, as milder instances may not show any signs or only exhibit limited non-specific symptoms [1, 2]. Multiple investigations have demonstrated a higher prevalence of myocarditis in males, with an estimated occurrence rate ranging from 0.80 to 2.13 occurrences per 100,000 individuals (Table 1). Accurate diagnosis and proper treatment are crucial in paediatric myocarditis, as it continues to be a known factor in sudden cardiac death among children and athletes, with a prevalence of up to 12% in extensive studies, primarily relying on postmortem findings [1-7]. Recently, two more causes of myocarditis have been identified: one is linked to the severe acute respiratory syndrome-Coronavirus 2 (SARS-CoV-2), and the other is associated with myocarditis that occurs after receiving mRNA vaccines. In this study, we examined and condensed the impact of myocarditis, the process of diagnosing myocarditis, and the latest advanced uses of cardiac magnetic resonance (CMR) evaluation of myocarditis in children during the SARs-CoV-2 period. This evaluation is predicated on prior completed research and personal observations, and does not encompass any novel investigations involving human or animal subjects.

Pathophysiology
Advancements in our understanding of the pathophysiological mechanisms driving pediatric acute myocarditis are crucial for targeted interventions. This section delves into the intricate interplay of viral triggers, autoimmune responses, genetic predisposition, and the emerging role of the microbiome. The evolving landscape of immunopathogenesis and its implications for therapeutic strategies will be thoroughly examined.
The primary cause of myocarditis in infants is typically a viral or infectious origin, with parvovirus-19 and human herpesvirus 6 being the most prevalent culprits [1].

Table 1: Summary of myrocarditis in paediatric population

Authors	Years data collected	Type of study	Age of subjects	Gender	Incidence/prevalence	Limitations
Arola A *et al*.	2004-2014	Retrospective study from all hospitals in Finland through a national registry	≤ 15 years	77% male Incidence increases in males after 6 years of age	1.95 per 100,000 incidence	Limited age range
Klugman *et al*	2005	Cohort study evaluating pediatric discharges of 35 children's hospitals that are members of the Pediatric Health Information System	≤ 21 years	56.5% males	0.05% prevalence	Does not evaluate over time
Vasudeva *et al*.	2007-2016	Retrospective serial cross-section study of the National Inpatient Sample database	≤ 18 years	66% males	0.80 per 100,000 incidence	
Witberg *et al*.	2020-2021	Retrospective cohort study in patients who were enrolled in Clalit Health Services and had been vaccinated against SARS-CoV-2	≥16 years	The highest incidence of myocarditis was in males 16 to 29 years old	2.13 per100,000 incidence	Study exclusively Evaluated myocarditis in regards to the SARS-CoV-2 vaccine

Additional, infrequent factors such as immunological responses, medication-induced effects, hypersensitivity reactions, and toxins have also been confirmed [1, 7]. From a pathophysiological perspective, when the pathogen infiltrates the host cell and causes its demise, a series of acute inflammatory cells and substances, including tumour necrosis factor-α, interleukin-1β, interleukin-6, and nitric oxide, are discharged. The innate immune response triggers the release of neutrophils and monocytes from the bone marrow. It is believed that the monocytes are responsible for causing tissue damage [1]. After a few days of infection, the immune system's adaptive response, which involves T- and B cells that target specific antigens, eliminates the virus. However, this immune response also causes additional harm to the heart muscle cells, leading to the advancement of fibrosis. This fibrosis can ultimately result in the formation of cardiomyopathy [1]. Once the inflammation diminishes, the heart may regain its normal function. However, in certain cases, the continued presence of the virus and inflammation can result in negative changes to the structure of the heart's ventricles [1, 8]. This can lead to the development of an illness that is apparent from idiopathic dilated cardiomyopathy.

Multiple investigations have detected a difference among myocarditis caused by SARS-CoV-2 and the separate condition known as MIS-C. MIS-C has a more widespread involvement and a late gadolinium enhancement pattern in the septum, which is not seen in SARS-CoV-2 infection [10]. Patients diagnosed with myocarditis as a result of MIS-C exhibited elevated levels of C-reactive protein, presented with diverse clinical symptoms, and demonstrated faster restoration of left ventricular systolic function comparable to other symptoms of myocarditis [9]. One concern that arises regarding this distinction is if the pathophysiology of myocardial injury observed in MIS-C entails a comparable mechanism of inflammatory cell infiltration and if unfavourable ventricular remodelling can take place.

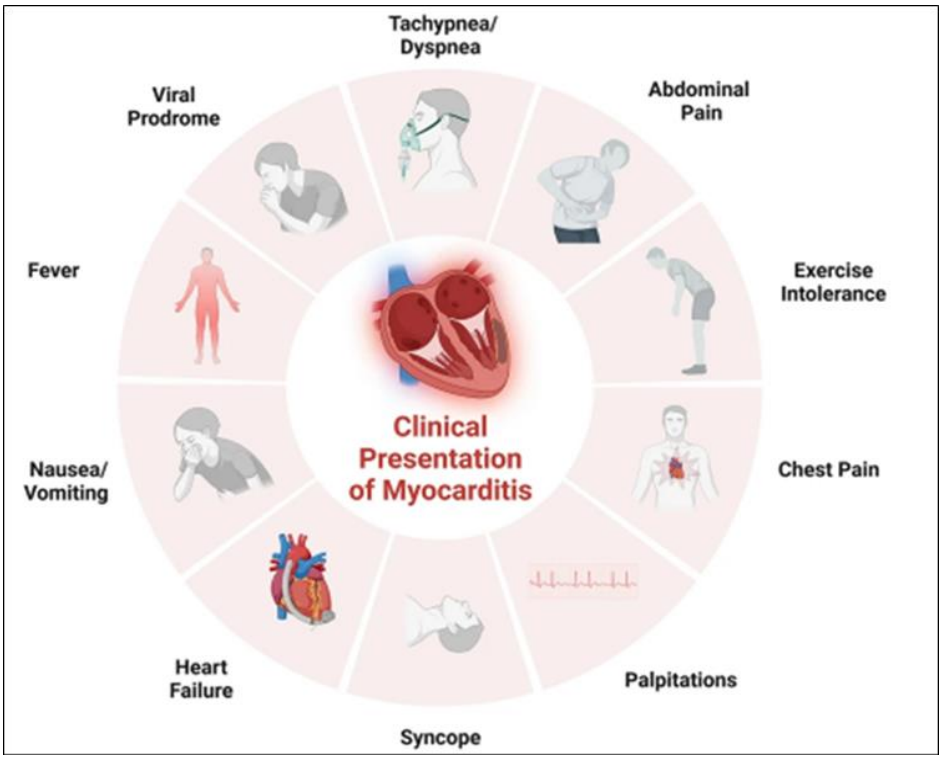

Fig 1: Clinical presentation of acute myocarditis

Diagnostic Modalities

Accurate and timely diagnosis is paramount in mitigating the impact of pediatric acute myocarditis. Here, we delve into the latest diagnostic modalities, emphasizing the role of advanced imaging techniques, endomyocardial biopsy, and novel biomarkers. The section will explore the sensitivity and specificity of these tools, providing a critical evaluation of their utility in diverse clinical scenarios.

When there is suspicion of myocarditis, patients will usually undergo laboratory testing, electrocardiography (ECG), chest radiography, and further non-invasive imaging studies (such as echocardiography, cardiac magnetic resonance imaging (CMR), or cardiac computed tomography). Diagnostic testing and biomarkers can be specific, however they may not be detectable in paediatric patients with myocarditis, posing a challenge for diagnosis. The initial evaluation involves the measurement of cardiac-specific biomarkers, including troponin level, creatinine kinase MB, and BNP/pro-BNP. Some of these biomarkers have been linked to unfavourable outcomes [1]. Additional non-specific laboratory markers of inflammation may be beneficial, however they are not consistently acquired [1]. In children, ECG can reveal several abnormalities. However, major adverse cardiac events (MACE) have been linked to specific anomalies such as a wide QRS-T angle, low voltage, and prolonged QTc [12]. Among all forms of myocarditis, the occurrence of ECG abnormalities is least frequent in MIS-C myocarditis [11].

Clinical Presentations and Subtypes

The heterogeneity of clinical presentations in pediatric acute myocarditis requires a refined classification system. Recent research has identified distinct subtypes based on clinical phenotypes and pathological characteristics. This section comprehensively outlines the spectrum of clinical manifestations, highlighting the importance of recognizing subtle presentations and tailoring therapeutic approaches accordingly.

Chronic myocarditis is characterized by symptomatic inflammation by laboratory evidence and normal ventricular function. Most cases of myocarditis result in recovery; however, dilated cardiomyopathy and sudden death remain risks in a minority of patients following myocarditis [1]. It is not uncommon for pediatric patients to present with clinical signs/symptoms, evidence of myocardial injury (e.g., troponin leak), but stable hemodynamics and normal left ventricular systolic function. Patients are typically admitted for observation and to monitor for progression, with serial trending of troponins and telemetry monitoring. There are conflicting data regarding the prognostic value of peak troponin, with some data showing higher peak troponin correlating with worse outcome [13]. While worse outcomes with ventricular dysfunction at presentation are well established, patients with normal left ventricular systolic function at presentation are also at risk for evolving dysfunction necessitating treatment [14].

Etiology

A thorough exploration of the diverse etiological factors contributing to pediatric acute myocarditis is essential for targeted interventions. Viral triggers, autoimmune mechanisms, and environmental influences will be dissected, with a focus on recent discoveries shaping our understanding of disease causation. The section will also explore the interplay between host genetics and environmental factors, shedding light on personalized approaches to treatment.

Treatment Strategies

Recent advances in therapeutic strategies have the potential to transform the management of pediatric acute myocarditis. Immunomodulatory therapies, mechanical circulatory support, and emerging pharmacotherapies will be critically evaluated. Challenges in treating refractory cases and the potential for precision medicine approaches based on individual patient profiles will be discussed, offering insights into the evolving therapeutic landscape.

The management of myocarditis is tailored to the degree of severity of symptoms and the specific stage of the disease. Both atrial and ventricular arrhythmias should be taken into account and necessitate proper treatment with antiarrhythmic medications, as ventricular arrhythmias are linked to unfavourable prognosis. Instances of presentation with full cardiac block have been documented, however they are infrequent. Temporary pacing is a supplementary method used to manage patients with dysrhythmia. Continuous cardiac monitoring is crucial for inpatients with myocarditis, particularly those with ventricular dysfunction.

In decompensated patients, the administration of milrinone, a phosphodiesterase-3 inhibitor, is commonly used to commence inotropic support. Milrinone enhances ventricular contractility, reduces afterload, and promotes relaxation or lusitropy. Epinephrine, which has both inotropic and vasopressor properties, is specifically used to treat low blood pressure and cardiogenic shock [1]. Calcium chloride and vasopressin can be employed to enhance systemic perfusion. For individuals experiencing sudden and severe inflammation of the heart muscle, known as fulminant myocarditis, or for those whose condition does not respond to medical treatment, it is advisable to promptly explore the use of mechanical circulatory support (MCS) at a specialised facility. This is particularly important for patients who are experiencing a sudden failure of the heart's ability to pump blood, known as cardiogenic collapse. According to paediatric registry data, it has been shown that as many as 23% of patients may require therapy with mechanical circulatory support (MCS) while they are hospitalised. Extracorporeal membrane oxygenation (ECMO) can be rapidly implemented as an immediate and temporary life-saving intervention. Available multicenter data indicate that the process of discontinuing ECMO is generally advantageous for most patients experiencing cardiogenic shock and is linked to enhanced survival rates [1]. Ventricular assist devices (VADs), such as the Berlin Heart EXCOR, are used as a long-term support option for patients who require ongoing assistance and are awaiting a heart transplant [1, 15]. More recent support devices, such as Impella (Abiomed, Danvers, MA, USA), provide an advantage by reducing the stress on the left ventricle by a less invasive percutaneous insertion [1, 17].

Carvedilol, the beta-blocker that has received the most research attention, has been demonstrated to have cardioprotective effects in animal studies and promotes ventricular remodelling [15]. This approach is observed at numerous paediatric centres. A retrospective multicenter research conducted on paediatric patients admitted with myocarditis revealed that 64% of patients who did not have heart transplantation were prescribed heart failure drugs at

discharge. The most often prescribed medication was an ACE-I, followed by a beta-blocker [16]. Intravenous immunoglobulin (IVIG) has been used as an immunologic therapy for treating myocarditis.

Conclusion: The review concludes with a forward-looking exploration of future research directions. From harnessing the potential of emerging technologies to developing innovative treatment modalities, this section outlines avenues for collaborative research and translational efforts. Myocarditis is an uncommon inflammatory disorder that affects children. It is important to diagnose and manage this condition promptly in order to predict outcomes and assess the level of risk. SARS-CoV-2 is the most recent pathogen responsible for myocarditis, and the long-term consequences of this condition are yet unknown. Cardiac MRI is a valuable method that does not require surgery and enables the evaluation of ventricular function and tissue properties. Advanced approaches, such myocardial strain, can assist in making acute and long-term treatment decisions. Although myocardial injury and inflammation may be resolved, it is still advantageous to conduct long-term multimodality evaluation to detect the possible occurrence of heart failure and major adverse cardiovascular events (MACE). In essence, this comprehensive review aims to provide a detailed and up-to-date resource for clinicians, researchers, and healthcare professionals invested in understanding and managing pediatric acute myocarditis. By synthesizing recent advancements, we aspire to contribute to the refinement of diagnostic criteria, the identification of novel therapeutic targets, and the improvement of overall outcomes in this complex and challenging clinical entity.

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