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New perspectives on paediatric acute myocarditis: A comprehensive review

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Abstract

Acute myocarditis is a rare but significant inflammatory condition of the heart muscle, particularly impacting the paediatric population. Despite advancements in diagnostic tools and therapeutic approaches, the understanding and management of paediatric acute myocarditis remain challenging. This review aims to synthesize current knowledge, focusing on the epidemiology, pathophysiology, clinical presentation, diagnostic strategies, and treatment modalities. Furthermore, we will explore emerging perspectives, including the role of novel biomarkers, advanced imaging techniques, and evolving therapeutic interventions. Acute myocarditis (AM) is a condition caused by inflammation that impacts the heart muscle. It is distinguished by its sudden onset and wide range of clinical presentations. This condition has a significant global impact, particularly on children and young adults. The lack of discernible onset patterns or predictable progression presents a substantial risk to survival, as it may result in the development of severe heart failure and malignant arrhythmias.

A characteristic of myocardial remodeling, myocardial fibrosis is becoming an increasingly acknowledged factor to negative results in cases of acute myocarditis. The complex relationship between viral infections, dysregulated immune reactions, and genetic susceptibility has been brought to light by developments in molecular and immunological techniques. At present, a definitive consensus regarding the diagnosis or continuous follow-up of pediatric patients is lacking. Endomyocardial biopsy (EMB), which was previously regarded as the benchmark diagnostic method, has been enhanced by the efficacy of cardiac magnetic resonance imaging (CMRI) techniques. In light of the intricate procedural intricacies and consequential complications, it is imperative to consider non-invasive alternatives without delay. Within this framework, biomarkers arise as auspicious candidates due to their ability to assess cardiac remodeling and inflammatory processes, thereby furnishing insightful observations regarding the severity, progression, and efficacy of treatments. Therapeutic approaches that target the particular immune pathways or components linked to the underlying causes have demonstrated potential for improved results in these instances. Acute myocarditis in pediatric patients continues to present a complex clinical dilemma, requiring a thorough comprehension of its pathophysiology, assessment, and treatment. The objective of this review is to examine recent developments in knowledge regarding the pathophysiology, diagnosis, and treatment of acute myocarditis in pediatric patients.

Keywords: Myocarditis, pediatric, heart dysfunction, pathophysiology

Introduction

Paediatric acute myocarditis is an inflammatory disease of the myocardium with diverse etiologies, including viral infections, autoimmune responses, and toxic exposures. It can lead to significant morbidity and mortality, necessitating prompt recognition and management. The clinical spectrum ranges from mild, self-limiting illness to fulminant heart failure and sudden cardiac death. This review examines recent advancements in understanding the disease's pathogenesis, diagnostic modalities, and therapeutic strategies, providing a comprehensive overview for clinicians and researchers.

Acute myocarditis (AM) is an inflammation myocardial injury distinguished by its recent onset (Less than one month), which gives rise to a wide array of clinical manifestations that frequently present diagnostic challenges. The absence of distinct initiation patterns and capricious progression of this condition can have an adverse effect on prognosis by causing malignant ventricular tachyarrhythmias and advanced heart failure^[1]. Worldwide, there have been reports of AM prevalence ranging from 10.2 to 105.6 cases per 100,000 individuals, which equates to an estimated 1.8 million cases per year^[2].

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Nevertheless, the precise incidence and prevalence rates among pediatrics are probably underestimated as a result of a considerable number of cases not requiring medical intervention. Clinically, acute myocarditis accounts for approximately 0.05% of hospitalizations, with an 81% prevalence among male adolescents. 3. The age distribution exhibits a bimodal pattern, with high points occurring at 1 year and 16 years. Conversely, the most severe manifestations are noted in the first year of life, persisting until the age of 4, and are most prevalent among adolescents. Histological examinations reveal that the prevalence of myocarditis ranges from 0.12% to 12%⁵. It is worth mentioning that AM is responsible for as much as 46% of dilated heart diseases and around 4% of cases of heart failure, of which a portion is linked to an unfavorable prognosis^[1, 6, 7]. A transition has occurred in the age categories most significantly impacted by myocarditis-related fatalities, from children and adolescents to adults, due to the critical responsibility of hospitals in the management of this condition^[8]. Determining whether newly identified heart failure or arrhythmias in the pediatric population are caused by an infectious stimulus or preexisting cardiac conditions can be a difficult task^[9, 10]. At the moment, a universally accepted diagnostic approach for minors does not exist.

The utilization of endomyocardial biopsy (EMB) for histological verification is constrained by its high-risk profile and low specificity^[11, 12]. Cardiac magnetic resonance imaging (CMRI), a sophisticated imaging technique, may encounter challenges such as the need for profound anesthesia in young children and, in certain instances, restricted applicability as a result of unstable arrhythmias^[11]. The objective of this review is to examine new and emerging knowledge regarding acute coronary artery disease in pediatric patients.

Epidemiology

The incidence of paediatric acute myocarditis is difficult to ascertain due to its varied presentation and under diagnosis. Studies estimate an incidence of 1-2 per 100, 000 children per year. Viral infections are the most common cause, with enteroviruses, adenoviruses, and more recently, SARS-CoV-2, being notable pathogens. Geographic and seasonal variations are observed, with higher incidences reported

during the winter months correlating with viral respiratory infections.

Pathophysiology: Acute myocarditis involves an initial injury to the myocardium, often triggered by a viral infection. The pathophysiological process includes.

- **Viral Entry and Myocyte Injury:** Viruses enter myocytes through specific receptors, leading to direct cytotoxicity.
- **Immune Response:** The innate immune system recognizes viral particles, activating inflammatory pathways. This includes cytokine release and recruitment of immune cells.
- **Autoimmune Component:** In some cases, the immune response becomes dysregulated, resulting in ongoing myocardial damage even after the viral infection has resolved.
- **Myocardial Dysfunction:** Persistent inflammation leads to myocardial necrosis, fibrosis, and eventually, impaired cardiac function.

Recent research has highlighted the role of genetic predispositions and molecular mechanisms, such as the involvement of toll-like receptors and the balance between pro-inflammatory and anti-inflammatory cytokines.

Immune cells and the molecular mechanisms of the inflammasome: In organisms of greater complexity, inflammation functions as a crucial protective mechanism, comprising the first response of the immune system. The primary purpose of such reaction is to remove harmful stimuli that cause damage, including infectious pathogens, damaged cells, and irritants. As a result, healing procedures can initiate^[13, 14]. This inherent mechanism is essential to every type of myocardial injury^[15]. Considerable insight into the etiology of myocarditis is being obtained using murine models; these discoveries are also relevant to the human condition^[16]. Viral infection is being identified as the primary etiology of myocarditis in children^[17]. Strong evidence supports the notion that viral myocardial stimuli and concomitant pathological host immune responses^[15] play a direct role in this. The complex interaction described manifests itself in a progressive manner, as illustrated in Figure 1.

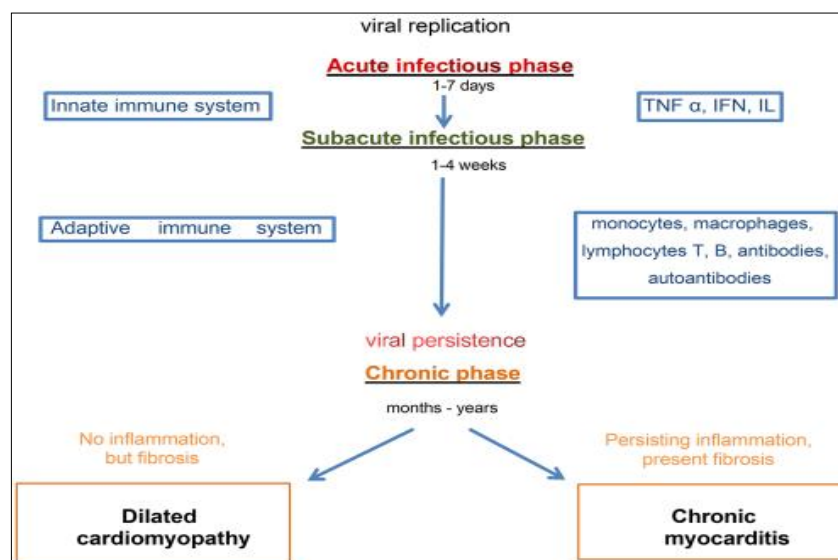


Fig 1: Three-phase model for the pathogenesis of viral myocarditis

Clinical Presentation

The clinical manifestations of paediatric acute myocarditis vary widely, from asymptomatic cases to severe heart failure. Common symptoms include.

- **Mild Cases:** Fever, fatigue, and chest pain.
- **Moderate Cases:** Dyspnea, palpitations, and exercise intolerance.
- **Severe Cases:** Cardiogenic shock, arrhythmias, and sudden cardiac arrest.

Infants often present with non-specific symptoms like irritability, poor feeding, and respiratory distress, making diagnosis challenging.

Diagnostic Strategies

Early and accurate diagnosis of paediatric acute myocarditis is crucial. The diagnostic approach typically involves.

- **Clinical Evaluation:** A thorough history and physical examination to identify potential etiological factors and symptomatology.
- **Laboratory Tests:** Elevated cardiac biomarkers (troponins, NT-proBNP) suggest myocardial injury. Inflammatory markers (CRP, ESR) and viral serologies can support the diagnosis.
- **Electrocardiography (ECG):** ECG findings may show nonspecific changes, but ST-segment elevations, T-wave inversions, and arrhythmias can be indicative.

Imaging

- **Echocardiography:** Useful for assessing cardiac function and excluding structural heart disease. Findings may include ventricular dysfunction and pericardial effusion.
- **Cardiac Magnetic Resonance Imaging (CMR):** The gold standard for non-invasive diagnosis. Late gadolinium enhancement and T2-weighted imaging are sensitive for detecting myocardial inflammation and fibrosis.
- **Endomyocardial Biopsy (EMB):** Considered in uncertain cases or when other diagnoses cannot be excluded. Histopathological analysis can confirm myocarditis and identify specific etiologies.

Emerging Perspectives

Novel Biomarkers

Recent research has focused on identifying novel biomarkers for early diagnosis and prognostication. These include.

- **MicroRNAs:** Small, non-coding RNAs involved in gene regulation. Specific microRNA profiles have been associated with myocarditis.
- **Cytokine Profiles:** Distinct patterns of pro-inflammatory and anti-inflammatory cytokines can help in diagnosing and predicting outcomes.

At present, a consensus has been reached regarding the efficacy of nonspecific circulating biomarkers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), in determining the systemic inflammatory status of myocarditis patients during the acute phase. Nevertheless, these biomarkers do not exhibit specificity with regard to risk stratification, prognosis, or diagnosis^[1]. On the other hand, troponins exhibit greater specificity as prognostic indicators of myocardial injury, specifically in instances of

acute coronary syndrome, and are of considerable importance^[19]. B-type natriuretic peptide (BNP), which is produced under physiological conditions from its precursor N-terminal pro b-type natriuretic peptide (NT-proBNP), enters the circulation in response to systolic or diastolic dysfunction. However, it should be noted that these markers demonstrate relatively modest negative predictive values^[19]. In the course of the three-phase progression of myocarditis, necrosis transforms into extensive fibrosis subsequent to the acute phase; this condition ultimately presents itself clinically as heart failure or sudden cardiac mortality^[1, 18]. Myocardial fibrosis is a critical component in the process of cardiac remodeling. It is distinguished by an overabundance of fibroblast stimulation and an increased production of extracellular matrix (ECM), in conjunction with cardiomyocyte apoptosis^[20]. Persistent cardiac injury, irrespective of its cause, induces the secretion of diverse substances at the cellular level, which facilitate the advancement towards fibrosis^[21, 22]. Cardiomyocytes, which are constituents of the myocardium, are of utmost importance in the maintenance of extracellular matrix (ECM) homeostasis and remodeling of the heart. They facilitate various physiological processes, including apoptosis, cell proliferation, angiogenesis, and cardiomyocyte hypertrophy^[22, 23].

Advanced Imaging Techniques

- **Positron Emission Tomography (PET):** Emerging as a useful tool for assessing myocardial inflammation and metabolic activity.
- **Hybrid Imaging:** Combining PET with CMR or CT to provide comprehensive evaluation of myocardial structure, function, and inflammation.

Genetic and Molecular Insights

- **Genetic Testing:** Identifying genetic predispositions can help in understanding individual susceptibility and tailoring therapies.
- **Molecular Pathways:** Targeting specific inflammatory and immune pathways holds promise for developing targeted therapies.

Immunotherapy and Biological Agents

- **Monoclonal Antibodies:** Therapies targeting specific cytokines (e.g., TNF-alpha inhibitors) are being explored.
- **Cell-Based Therapies:** Using stem cells and regenerative therapies to repair damaged myocardium.

Future Perspective

These prospective therapeutics present novel methodologies for selectively targeting pathways and mechanisms implicated in the fibrotic and inflammatory processes that are linked to myocarditis. An intriguing strategy for addressing autoantibodies that contribute to cardiac inflammation, such as beta (1)-adrenergic receptor (β (1) AR) autoantibodies, involves the concurrent administration of immunoabsorbents via intravenous inoculation.

The treatment approach employs IVIG to modulate the immune response and eliminate autoantibodies, with the dual purpose of diminishing inflammation and enhancing the functionality of the left ventricle. Eplerenone and other aldosterone antagonists, which have been utilized to treat other cardiac conditions, are currently being investigated for

their potential advantages in cardiac remodeling through the inhibition of inflammation and regulation of mast cell gene expression [24]. Additionally, specific cytokine targeting has garnered attention. The potential of anti-mouse IL1 β antibodies to inhibit IL-1 β and fibrotic scar formation, thereby potentially averting aberrant cardiac remodeling [25], has been demonstrated. In a similar vein, there is ongoing research into the potential of Secukinumab, a monoclonal antibody that can neutralize IL-17-induced profibrotic pathways, to treat autoimmune cardiac impairment [26]. Antisense miRNA complements, also known as antagonistic miRNAs, represent an innovative strategy in the treatment of autoimmune myocarditis. The implementation of antagomiR-21a-5p enabled the reduction of myocardial fibrosis and inflammation in experimental models of induced myocarditis [27]. This underscores the potential of therapeutics based on microRNAs (miRNAs) to regulate the expression of genes linked to pathological processes. Ulinastatin, an acid-resistant protease inhibitor that is indigenous to human urine, has garnered clinical attention

for its potent anti-inflammatory characteristics in the treatment of numerous diseases, thereby establishing itself as a feasible substitute for corticosteroids. A noteworthy study [28] has unveiled the protective effects of this substance on cardiomyocytes, demonstrating a substantial enhancement in cardiac performance and a reduction in myocardial damage, particularly when combined with creatine phosphate sodium. The implications of these findings for the treatment of viral myocarditis in pediatric patients are encouraging. Continuous human trials are of the utmost importance in order to verify the effectiveness and safety of these nascent therapies, as well as to enhance their therapeutic capabilities. By targeting and addressing the underlying immune and inflammatory mechanisms, these perspectives have the potential to offer patients with myocarditis more targeted and effective therapeutic options, with the ultimate goal of improving cardiac function and patient outcomes. The accepted treatments and potential future therapies for acute myocarditis are summarized in Table 1.

Table 1: Aspects of proposed therapy in AM, such as acknowledged and prospective therapies, objectives, and achievements. (Reference: 14-28)

Therapy	Target	Drug class/medication	Role
Symptoms-based	Heart failure arrhythmias sudden death risk	Beta-blokers (Carvedilol) Diuretics (Torsemide) Anti-arrhythmias	Antioxidant cardiac remodeling
Aetiology proven-based	Parvo B-19, EBV, CMV, HHV-6 Enteroviruses SARS-CoV 2	IFN β Antivirals (Acyclovir, Ganciclovir, Valacyclovir) Pleconaril, Pocopavir Remdesivir	Improve viral clearance Improve left ventricular function
Pathogenesis-based	Immuno-modulation	Prednisone, Prednisolone IVIG	Improve left ventricular function
Perspectives	Inflammatory / Fibrotic process	Immunoabsorption + IVIG fibrotic process Aldosterone antagonist (Eplerenone) Anti-mouse IL-1 β antibodies Anti-IL-17 monoclonal antibodies (Secukinumab) Ulinastatin + creatine phosphate sodium antisense miRNA complements (antagomiR-21a-5p)	Cardiac remodelling IVIG

Conclusion

Paediatric acute myocarditis remains a complex and challenging condition with significant implications for affected children. Advances in understanding its pathophysiology, improved diagnostic modalities, and evolving therapeutic strategies offer hope for better outcomes. Future research should focus on refining diagnostic criteria, validating novel biomarkers, and developing targeted therapies to improve the management and prognosis of paediatric myocarditis. A variety of techniques are utilized to diagnose myocarditis, but endomyocardial biopsy is the preferred method for validation. Nevertheless, in examining viral aetiology in myocardial samples, alternative diagnostic instruments such as immunohistochemistry and rt-PCR are of considerable importance, particularly in pediatric patients, due to the inherent dangers. Biomarkers have surfaced as auspicious contenders for predictive and diagnostic objectives, aiding physicians in the evaluation of cardiac repair and inflammation. These biomarkers may provide valuable information regarding the severity, progression, and efficacy of a medication. It is imperative to comprehend the fundamental pathogenesis of myocarditis in order to develop efficacious treatments. Various etiologies, including autoimmune reactions and infections caused by viruses,

induce unique inflammatory and immune responses. Targeted therapies, which concentrate on particular immune factors or pathways linked to these etiologies, have demonstrated promise in achieving improved outcomes. Continual investigations aim to develop more accurate diagnostic techniques, efficacious therapeutic approaches, and a more comprehensive comprehension of the intricacies associated with myocarditis. By adopting this all-encompassing strategy, the final result will be enhanced healthcare for patients, improved therapeutic results, and an additional knowledgeable clinical administration of this arduous cardiac condition.

Conflict of Interest

Not available

Financial Support

Not available

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