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MIS-C pathogenesis: immune dysregulation & viral triggers

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Multisystem Inflammatory Syndrome in Children (MIS-C) is a serious condition emerging during the COVID-19 pandemic, strongly associated with prior SARS-CoV-2 infection. Characterized by systemic inflammation affecting multiple organs, MIS-C presents a complex clinical picture including fever, gastrointestinal distress, cardiac dysfunction, and neurological manifestations. Although its exact pathogenesis remains incompletely understood, immune dysregulation is recognized as a central mechanism. This review examines current understanding of MIS-C pathogenesis, focusing on immune dysfunction and viral triggers, particularly SARS-CoV-2. We analyze both innate and adaptive immune responses, cytokine storm dynamics, molecular mimicry, and virus-induced inflammatory cascades. Additionally, we discuss potential immunomodulatory therapeutic strategies and identify future research directions to improve MIS-C management and treatment outcomes.

KEYWORDS

children, MIS-C, immune dysregulation, viral triggers, SARS-CoV-2

1 Introduction

The COVID-19 pandemic has highlighted multisystem inflammatory syndrome in children (MIS-C), a severe condition typically emerging 2–6 weeks after SARS-CoV-2 infection (1–3). While rare hyperinflammatory responses were previously documented in pediatric cases of Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), MIS-C demonstrates a distinct clinical characterized by more pronounced gastrointestinal and mucocutaneous involvement. MIS-C presents with fever, abdominal pain, and rash, and cardiovascular manifestations, posing substantial diagnostic challenges (4–7). Its pathophysiology involves dysregulated hyperinflammatory responses to viral exposure, evidenced by elevated inflammatory markers including C-reactive protein (CRP) and interleukin-6 (IL-6) (8–10). This immune dysregulation likely stems from genetic predispositions interacting with environmental triggers, particularly viral infections. The immune activation pattern shows partial overlap with Kawasaki Disease (KD) but demonstrates distinct cytokine profiles and epidemiological

characteristics (11, 12). The temporal delay between SARS-CoV-2 infection and MIS-C onset supports classification as a post-infectious syndrome rather than direct viral pathology, a crucial distinction guiding therapeutic strategies (6, 13–15).

Clinical management remains challenging without standardized protocols. Current guidelines recommend immunomodulatory therapies including intravenous immunoglobulin (IVIG) and corticosteroids, though variable treatment responses necessitate further investigation through controlled trials (16–18). Emerging research focuses on identifying predictive biomarkers to enable personalized treatment approaches (10, 19–21).

Understanding the interplay between viral triggers and immune dysregulation remains essential for elucidating MIS-C pathogenesis. Continued investigation into immunological mechanisms and therapeutic interventions will be critical for improving outcomes and preparing for future pediatric health emergencies.

2 Clinical manifestations and diagnostic criteria of MIS-C

2.1 Characteristic symptom presentations

MIS-C is a severe inflammatory complication of SARS-CoV-2 infection, with clinical features overlapping KD (19, 22, 23). Key symptoms include persistent fever (present in nearly all cases), rash, conjunctivitis, and gastrointestinal issues such as abdominal pain, vomiting, and diarrhea. Cardiovascular manifestations (e.g., shock) and neurological symptoms (e.g., altered mental status or seizures) may also occur, complicating diagnosis (5, 24, 25). Elevated inflammatory markers—including C-reactive protein (CRP), ferritin, and D-dimer—are common and aid in assessing severity (26–28). Some children exhibit acute respiratory symptoms, potentially leading to misdiagnosis as primary respiratory infections (29).

Epidemiological data reveal significant disparities in MIS-C prevalence across populations. Incidence rates are higher among Hispanic/Latino and non-Hispanic Black children compared to non-Hispanic White children, with variations linked to genetic, socioeconomic, and geographic factors (30–32). Age and gender also influence risk, with peak incidence in children aged 5–12 years and a male predominance (ratio ~1.5:1) (33). These differences underscore the need for population-specific clinical awareness.

Abbreviations: ACE2, Angiotensin-converting enzyme 2; BNP, B-type natriuretic peptide; COVID-19, Coronavirus disease 2019; CRP, reactive protein; CDC, Centers for Disease Control and Prevention; ESR, erythrocyte sedimentation rate; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; KD, Kawasaki Disease; MAS, Macrophage activation syndrome; MIS-C, multisystem inflammatory syndrome in children; MAS, macrophage activation syndrome; PRRs, pattern recognition receptors; RBD, receptor-binding domain; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; WHO, the World Health Organization (WHO); TLRs, Toll-like receptors; TSS, toxic shock syndrome; VIS, Vasoactive Inotropic Score.

Given the symptom overlap with other inflammatory conditions, high suspicion and comprehensive assessment are essential for accurate differentiation. A schematic of MIS-C symptom characteristics is shown in Figure 1.

2.2 Diagnostic approaches

Diagnostic MIS-C relies on clinical evaluation and laboratory testing, based on criteria from the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) (34–36). Key requirements include fever lasting ≥ 24 hours, elevated inflammatory markers (e.g., CRP, erythrocyte sedimentation rate, or ferritin), and involvement of ≥2 organ systems (e.g., cardiovascular, gastrointestinal, or neurological). Providers must exclude alternative causes, such as active infections or other inflammatory syndromes.

Early identification is critical for initiating treatments like intravenous immunoglobulin (IVIG) and corticosteroids. The diagnostic process should account for demographic variations; for instance, higher prevalence in certain populations may warrant adjusted thresholds for inflammatory markers (30, 37). MIS-C typically presents as multi-system inflammation weeks post-SARS-CoV-2 infection, and confirmation involves characteristic markers and organ involvement, as summarized in Table 1.

2.3 Laboratory and imaging evaluations

Laboratory tests are crucial for diagnosing and managing MIS-C. Common findings from these tests often show elevated inflammatory markers, including CRP, procalcitonin, ferritin, and D-dimer, alongside conditions like lymphopenia and thrombocytopenia (38, 39). Additionally, cardiac biomarkers such as troponin and B-type natriuretic peptide (BNP) are frequently elevated, suggesting possible heart involvement (40). Imaging studies, especially echocardiography, are vital for evaluating cardiac function and detecting complications like coronary artery dilation or aneurysms, which pose significant risks in MIS-C cases (41). Chest imaging may also be necessary to check for lung involvement. By integrating clinical observations, laboratory results, and imaging findings, healthcare providers can conduct a thorough assessment of the child's health, which is essential for making informed treatment decisions and monitoring for potential complications. In summary, effectively managing MIS-C requires a comprehensive approach that combines symptom evaluation, laboratory testing, and imaging studies to ensure prompt and effective care for this serious condition.

3 Abnormal immune responses

3.1 Mechanisms of autoimmunity and viral cross-reactivity

Autoimmunity arises from genetic, environmental, and immunological imbalances that disrupt immune tolerance,

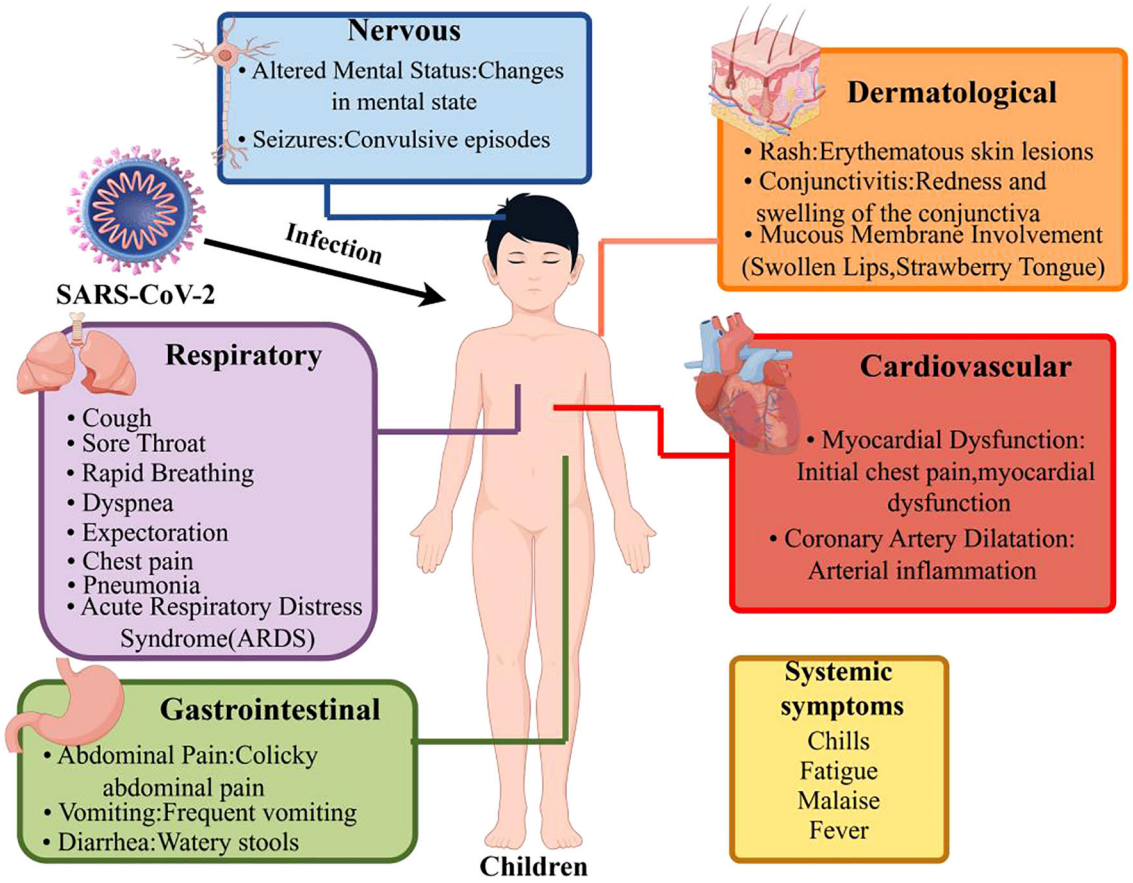

FIGURE 1
Symptom characteristics simulation chart of MIS-C following SARS-CoV-2 infection (By Figdraw). This schematic summarizes the multisystem clinical features observed in children with MIS-C following SARS-CoV-2 infection. The characteristic symptoms involve multiple organ systems: Cardiovascular: Myocardial dysfunction (e.g., chest pain), coronary artery dilatation, and arterial inflammation. Gastrointestinal System: Abdominal pain (often colicky), vomiting, and diarrhea (watery stools). Skin and Mucous Membranes: Erythematous rash, non-purulent conjunctivitis, and mucosal involvement. Neurological System: Altered mental status and seizures. Respiratory System: Respiratory distress, cough, and pneumonia. Systemic Symptoms: Persistent fever, fatigue, myalgia, and chills. This comprehensive depiction highlights the systemic hyperinflammation and heterogeneous presentation in MIS-C, which distinguishes it from other pediatric inflammatory conditions.

triggering activation of self-reactive T and B cells (42). These cells produce autoantibodies and pro-inflammatory cytokines, driving tissue injury and inflammation (43). Infections can exacerbate such responses, as seen in MIS-C, where viral epitopes induce cross-reactivity:

EBV as Primary Driver: The EBV nuclear antigen 2-derived peptide TVFYNIPPMPL is a dominant cross-reactive epitope. TCRVβ21.3+ CD8+ T cells (expanded in 82% of MIS-C patients) show 3.1-fold stronger reactivity to this EBV epitope than non-EBV antigens. Single-cell TCR sequencing confirms MIS-C T-cell repertoires cluster with EBV-specific (not SARS-CoV-2-specific) TCRs, indicating EBV-directed responses are central to cross-reactivity (44).

SARS-CoV-2 as Potential Initiator: Structural models suggested SARS-CoV-2 spike protein superantigen-like activity, but functional studies show limited T-cell activation by SARS-CoV-2 peptides. Pre-pandemic MIS-C cases indicate spike protein is non-essential. Instead, SARS-CoV-2 may dysregulate TGFβ, impairing TCRVβ21.3+ T-cell cytotoxicity against EBV-infected B cells, promoting viral persistence and inflammation (45).

HLA-Mediated Amplification: HLA risk alleles (e.g., HLA-DRB101, HLA-DQB105), present in 19.4% - 23% of MIS-C patients (absent in controls) and enhance presentation of EBV/host molecular mimics, analogous to HLA-B27 in ankylosing spondylitis (46).

Autoantibody Pathogenesis: Autoantibodies targeting endothelial, myocardial, and gastrointestinal antigens contribute to multi-organ damage. Recent studies link specific autoantibody profiles to cardiac dysfunction in MIS-C, highlighting their role in disease severity (47).

Supporting evidence includes 79.7% EBV seropositivity in MIS-C patients (vs. 56% controls) with elevated anti-EBNA2 IgA, and organ-specific inflammation aligning with EBV/host antigen mimicrysites (44). Infections trigger autoreactive lymphocytes via molecular mimicry or epitope spreading, while inflammatory cytokines (e.g., IL-6) further drive the autoimmune, as observed

TABLE 1 Diagnostic criteria and key points of MIS-C.

Diagnostic criteria	Description	Ref.
Fever	Fever is a common symptom of MIS-C, with no specific duration required. Any subjective or documented fever (≥38° C) is sufficient for inclusion.	(19) (22),
Age	MIS-C primarily occurs in individuals under 21 years of age, typically 2-6 weeks after SARS-CoV-2 infection. The average age of MIS-C patients is around 10 years.	(91)
Multi-Organ Involvement	MIS-C involves multiple organ systems, including cardiovascular, gastrointestinal, hematologic, respiratory, and neurological systems. Cardiac dysfunction, such as reduced left ventricular ejection fraction (<55%) or coronary artery dilation, is common.	(19) (39),
Clinical Severity	MIS-C presents with fever, gastrointestinal symptoms, cardiovascular issues, rash, conjunctivitis, abdominal pain, vomiting, diarrhea, and signs of shock. Neurological symptoms such as altered mental status and seizures may also occur.	(19) (22),
Systemic Inflammation	Elevated levels of inflammatory markers such as C-reactive protein (CRP ≥3.0 mg/dL), ferritin, and D-dimer are common in MIS-C patients. The CRP threshold of ≥3.0 mg/dL is required to indicate systemic inflammation.	(25) (26),
Epidemiologic Linkage	MIS-C is epidemiologically linked to SARS-CoV-2 infection, typically occurring 2-6 weeks after the infection.	(19) (30),
Laboratory Evidence of SARS-CoV-2	Laboratory evidence of SARS-CoV-2 infection is typically required, such as positive nucleic acid amplification tests (NAAT), antigen tests, or antibodies. Testing must occur within 60 days before or during hospitalization or after hospitalization.	(19) (31),
Exclusion of Other Diagnoses	The diagnosis of MIS-C requires the exclusion of other possible causes, such as active infections or other inflammatory conditions, including Kawasaki disease and toxic shock syndrome.	(19) (30),

CRP, C-reactive protein; MIS-C, multisystem inflammatory syndrome in children; SARS CoV-2, severe acute respiratory syndrome coronavirus 2.

in lupus and rheumatoid arthritis. Understanding these mechanisms—viral cross-reactivity, HLA restriction, and autoantibody effects—is critical for targeted therapies to restore immune tolerance (46).

3.2 Inflammatory cytokine expression

Inflammatory cytokines balance protective immunity and harmful inflammation (48–50). Autoimmune diseases often disrupt this balance, elevating pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) that correlate with disease severity (51–54). These cytokines sustain the inflammatory cycle by shaping the immune environment and driving immune cell activation and differentiation. For example, in rheumatoid arthritis, persistent cytokine exposure promotes joint damage and systemic complications (55–57). Consequently, targeting cytokine signaling pathways represents a promising therapeutic strategy to restore pro-inflammatory and anti-inflammatory balance in autoimmune diseases.

3.3 Immune cell activation status

Immune cell activation status critically shapes immune responses and significantly influences autoimmune disease onset and progression (58–63). In autoimmune diseases, T cells, B cells, and macrophages often exhibit hyperactivation. For example, CD4+ T helper cells differentiate into pro-inflammatory Th1 and Th17 subsets, releasing cytokines that amplify inflammation and tissue injury. Similarly, B cells produce autoantibodies that further propagate autoimmune pathology. This dysregulation disrupts immune tolerance, activating autoreactive lymphocytes (64–67). Meanwhile, regulatory T cells (Tregs) frequently show impaired function, failing to control inflammatory responses (68–72). Understanding these cellular activation patterns is therefore essential for developing targeted immunotherapies to reestablish immune equilibrium and prevent tissue damage.

4 Virus trigger mechanisms

4.1 Immune response to SARS-CoV-2 infection

The immune response to SARS-CoV-2 involves complex innate and adaptive interactions (73–75). Infection triggers innate immunity via pattern recognition receptors (PRRs) like Toll-like receptors (TLRs), which detect viral components (76, 77). This recognition induces type I and III interferons, creating an antiviral state. However, SARS-CoV-2 evades strong interferon responses compared to SARS-CoV, despite efficient replication (78, 79).

Such evasion delays adaptive immunity, leading to low-affinity antibodies and T-cell hyperactivation that worsen disease outcomes. Additionally, immune dysregulation causes cytokine storms with pro-inflammatory cytokines like IL-6, IL-1β, and TNF-α, resulting in tissue damage and respiratory issues (80–83).

As shown in Figure 2, TLR and RLR hyperactivation drives excessive cytokine production, triggering systemic inflammation and multi-organ injury. Acute infection involves innate cell activation and lymphopenia, which normalizes during recovery. In contrast, MIS-C exhibits delayed, exaggerated immune responses with elevated inflammatory markers and tissue damage.

Epidemiological studies further reveal that MIS-C cases typically peak 2–6 weeks after community surges of SARS-CoV-2 infection, with incidence rates proportional to transmission levels (84–86).This temporal clustering, with cases surging 2–6 weeks post-infection waves, underscores the importance of monitoring infection spread for early MIS-C detection. For instance, surveillance data indicate a direct correlation between regional COVID-19 incidence and subsequent MIS-C outbreaks, highlighting the need for proactive surveillance to detect early signs of the syndrome (87, 88).

4.2 Effects of viral variants

The emergence of viral variants has important implications for how SARS-CoV-2 causes disease and how effective public health measures can be (89, 90). Variants like Delta and Omicron have shown increased transmissibility and the ability to evade immune responses, which complicates how the body reacts to previous infections or vaccinations (91, 92). For example, spike protein mutations in the receptor-binding domain (RBD) enhance ACE2 binding, facilitating host cell entry (93, 94). Pre-existing immunity from other coronaviruses may impair neutralizing antibodies against variants, potentially exacerbating disease (95, 96). Variants' ability to partially escape antibodies challenges vaccine efficacy, highlighting the need for updated vaccines. Ongoing surveillance is crucial to understand impacts on spread, severity, and vaccine effectiveness. These variants may also influence MIS-C incidence proportionally to infection waves, as observed in variant-specific outbreaks (97, 98).

4.3 Virus-induced immune hyperreactivity

Virus-induced airway hyperreactivity, especially from respiratory infections, poses a significant risk to children (99, 100). For instance, infections caused by respiratory syncytial virus (RSV) are linked to a higher likelihood of developing asthma and other chronic respiratory issues later in life (101). The causes of this hyperreactivity are complex, including direct viral effects and

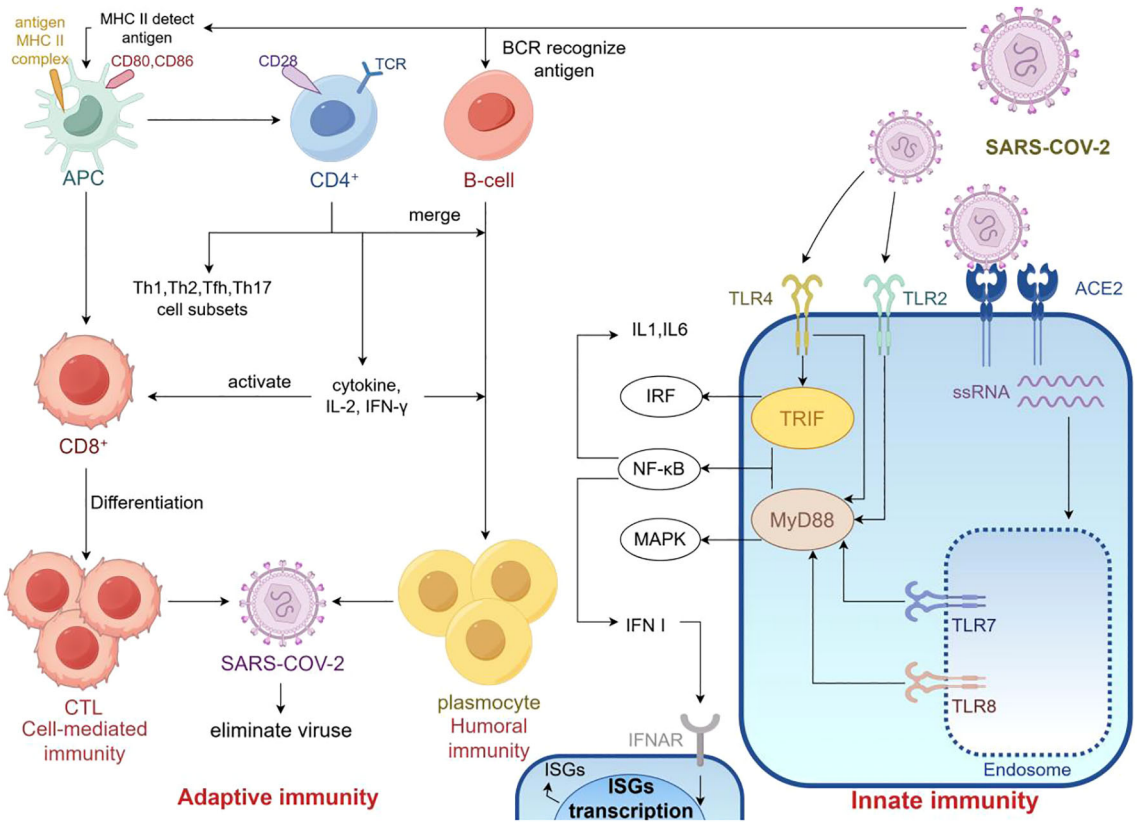

FIGURE 2
Immunological mechanisms in MIS-C (By Figdraw). MIS-C is a severe inflammatory syndrome associated with infection, characterized by aberrant activation of both innate and adaptive immunity. Innate immunity: TLR2 and TLR4 trigger pro-inflammatory cytokine release; TLR7 and TLR8 detect viral ssRNA, activating type I interferons via the MyD88 pathway; type I interferons bind to IFNAR receptor, activating JAK-STAT signaling and inducing interferon-stimulated genes (ISGs) to inhibit viral replication. Adaptive immunity: Antigen-presenting cells (APCs) process viral antigens and present them to naïve $CD4^+$ and $CD8^+$ T cells; activated $CD4^+$ T cells differentiate into subsets such as Th1, secreting cytokines to coordinate immune responses; $CD8^+$ T cells, with $CD4^+$ T cell help, become cytotoxic T lymphocytes that directly kill infected cells; B cells, activated by $CD4^+$ T cells, differentiate into plasma cells that secrete IgM and IgG antibodies through class switching; memory B and T cells are formed to provide long-term immunity. This dysregulated immune activation contributes to the hyperinflammation seen in MIS-C.

resulting immune imbalances. After an RSV infection, airway hyperreactivity notably increases, likely resulting from ongoing inflammation, disruption of the airway lining, and release of inflammatory substances. Furthermore, the interaction between viral infections and the body's immune response can induce a state of heightened airway sensitivity. This increased sensitivity makes the airways more prone to future infections and allergic reactions. This situation underscores the need to better understand the long-term effects of viral infections on respiratory health, particularly in at-risk groups such as infants and young children. Addressing these challenges through preventive strategies, including vaccinations and early interventions, is crucial to reducing the incidence of chronic respiratory diseases associated with viral infections.

4.4 Comparative viral pathogenesis in MIS-C

Specific viruses trigger MIS-C through distinct immunopathological mechanisms. SARS-CoV-2 has the strongest causal link (>95% of cases), supported by temporal clustering, high seropositivity, and tissue viral RNA detection. Key mechanisms include spike protein superantigen-like activity driving TCR Vβ 21.3+ T-cell expansion and cytokine storms (elevated IL-6/IL-10/IFN-γ), plus ACE2-mediated endothelial damage via MMP-9 overexpression (20, 51). Unique features include IFN-I suppression and elevated NETosis markers. EBV shows a moderate association (15-20% of cases), often through reactivation evidenced by EBNA-IgG/VCA-IgM serology (102, 103). It contributes via LMP1-induced NF-κB hyperactivation and CD21+ B-cell depletion, exacerbating macrophage activation syndrome -like pathology with hyperferritinemia in co-infections. Elevated TGFβ in MIS-C impairs T cell cytotoxicity against EBV, leading to reactivation and hyper-inflammation (44). Adenovirus involvement is emerging (5-10% of cases), with hexon protein seropositivity linked to MIS-C (104). It triggers HSP60-mediated molecular mimicry against cardiac antigens and immune complex deposition driving complement-mediated NETosis, often with higher myocarditis incidence (troponin-I >1.0 ng/mL). Common pathways include triphasic immune dysregulation: viral endocytosis (via ACE2/LAT1), delayed IFN-I responses promoting pyroptosis, and TRAIL+ CD4+ T-cell cytotoxicity causing multi-organ damage. Genetic susceptibility (e.g., HLA-DRB1*11:01 allele, conferring 9.3× increased risk) further unifies these mechanisms. Milestones in MIS-C Pathogenesis are shown in Figure 3.

5 Comparisons with other pediatric inflammatory diseases

5.1 Distinguishing MIS-C from sepsis

Differentiating MIS-C from sepsis remains challenging due to overlapping features like fever, gastrointestinal distress, and cardiovascular instability. However, key distinctions exist: MIS-C patients are generally older (median age 10 years vs. 4 years for sepsis) and exhibit prolonged fever with prominent mucocutaneous and gastrointestinal symptoms. Laboratory findings further aid differentiation-sepsis often shows elevated leukocyte counts and procalcitonin, while MIS-C commonly presents with thrombocytopenia, lymphopenia, and hyperfibrinogenemia. Myocardial dysfunction is more severe in MIS-C and can be quantified using the Vasoactive Inotropic Score (VIS) (105). The MISSEP scoring system, with high sensitivity and specificity, assists clinicians in this distinction (16). This differentiation is vital as it informs appropriate treatment strategies; sepsis typically necessitates immediate antibiotic therapy, whereas the management of MIS-C may involve immunomodulatory treatments such as IVIG and corticosteroids.

5.2 Similarities and differences with Kawasaki disease

MIS-C and KD (KD) share clinical features (e.g., prolonged fever, rash, conjunctivitis, mucosal changes, and coronary artery complications), yet their pathogenesis and inflammatory profiles differ fundamentally. KD is a vasculitis treated with IVIG and aspirin, while MIS-C is a post-infectious hyperinflammatory syndrome triggered by SARS-CoV-2. MIS-C demonstrates distinct cytokine patterns, such as elevated CXCL9, rarely seen in KD (106, 107). Management strategies for MIS-C are evolving, potentially incorporating biologics tailored to its unique immunopathology.

5.3 Comparison with other virus-related diseases

MIS-C parallels other hyperinflammatory conditions like macrophage activation syndrome (MAS) and toxic shock syndrome (TSS) in its "cytokine storm" signature and multi-organ involvement (4). However, unlike typical viral infections presenting with respiratory symptoms, MIS-C manifests as systemic inflammation with potential organ failure (108). Its immune dysregulation may be exacerbated by SARS-CoV-2's superantigen-like properties. These distinctions emphasize the need for comprehensive differential diagnosis in pediatric patients with systemic inflammation (98, 109, 110).

6 Future research directions and clinical applications

6.1 Identification of novel biomarkers

Novel biomarkers are critical for advancing MIS-C diagnosis and management. Recent studies highlight immunoglobulin G (IgG) glycosylation patterns—particularly afucosylated spike IgG

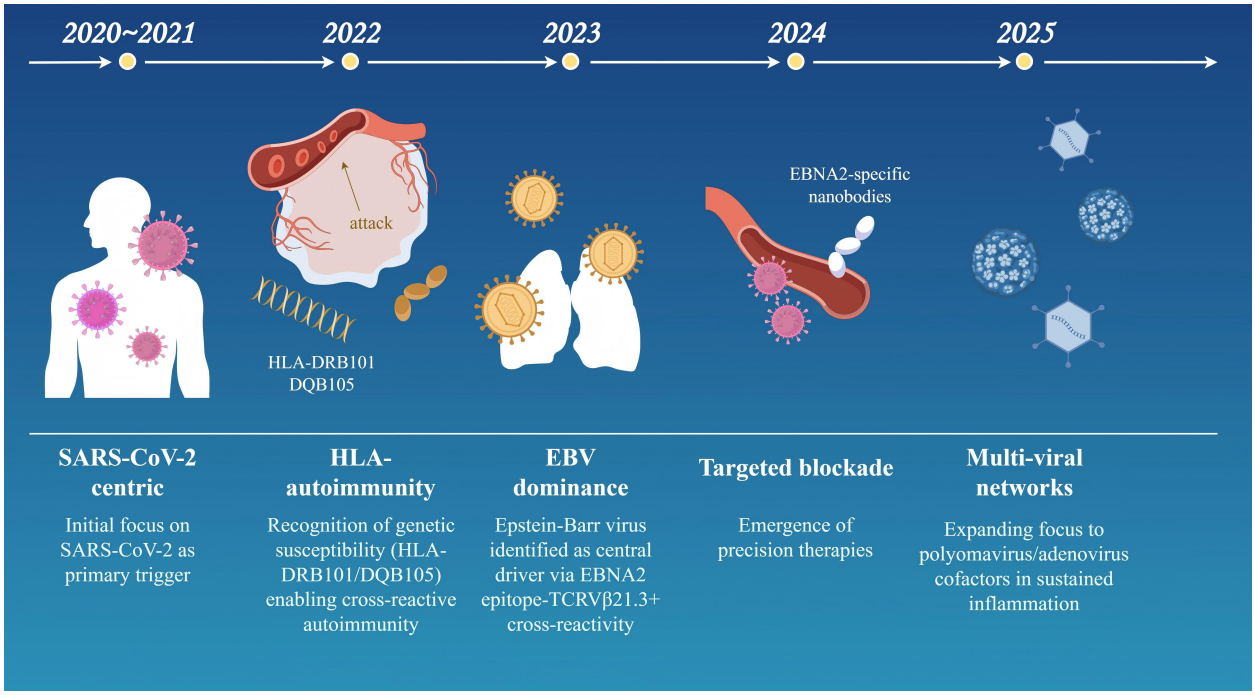

FIGURE 3
Conceptual evolution of MIS-C pathogenesis (2020–2025) (By Figdraw). This timeline model outlines key milestones in the understanding of MIS-C pathogenesis over a five-year period, reflecting shifts in research focus and mechanistic insights: 2020–2021 (SARS–CoV–2–centric phase): Initial emphasis on SARS–CoV–2 as the primary trigger, highlighting viral spike protein interactions and systemic cytokine storms. 2022 (HLA and autoimmunity): Recognition of genetic susceptibility linked to HLA–DRB101/DQB105 haplotypes, facilitating cross–reactive autoimmune responses. 2023 (Epstein–Barr virus dominance): Identification of Epstein–Barr virus (EBV) as a central driver, mediated by EBNA2 epitope cross–reactivity with TCR Vβ21.3+ T cells. 2024 (Targeted therapeutic blockade): Emergence of precision immunotherapies, including EBNA2–specific nanobodies designed to inhibit vascular leakage and hyperinflammation. 2025 (Multi–viral network hypothesis): Expanding evidence for co–factors such as polyomaviruses and adenoviruses in sustaining inflammatory networks and disease severity. The model underscores the progressive elucidation of synergistic viral, genetic, and immunologic factors in MIS-C.

—as promising biomarkers correlating with disease severity and hyperinflammatory responses in MIS-C patients. These glycan modifications may help track disease progression and therapeutic responses. Additional biomarkers involving cytokine/chemokine dysregulation (e.g., IL-6, CXCL9) and T-cell activation profiles are under investigation for early diagnosis and targeted therapy development (20, 106). Future research should prioritize validating large-scale validation of these biomarkers and assess their clinical utility.

6.2 Optimization of treatment strategies

Treatment optimization remains challenging due to MIS-C heterogeneity and variable treatment responses. Current immunomodulatory regimens (e.g., IVIG, corticosteroids) show inconsistent efficacy (111). Emerging strategies combine conventional therapies with novel agents like zonulin inhibitors to address intestinal barrier dysfunction and immune hyperactivation. Personalized approaches accounting for individual immune profiles and organ involvement may improve outcomes. Robust clinical trials evaluating combination therapies and biomarker-guided regimens are urgently needed to establish evidence-based guidelines.

6.3 Impact of vaccination on MIS-C incidence and severity

Vaccination significantly reduces MIS-C risk by modulating SARS-CoV-2-induced inflammatory responses. Multiple studies demonstrate 2-4-fold lower MIS-C incidence among vaccinated children, with attenuated severity in breakthrough cases (112–114). Proposed mechanisms include vaccine-induced neutralizing antibodies limiting viral replication and memory B-cell responses dampening hyperinflammation. Longitudinal data confirm sustained protection against MIS-C post-vaccination, supporting its public health value (115). Ongoing surveillance is essential to evaluate vaccine efficacy against emerging variants and optimize pediatric vaccination strategies.

7 Conclusion

Research on MIS-C has elucidated its complex pathophysiological, focusing on immune dysregulation and viral triggers. As a significant COVID-19 complication, MIS-C presents distinctive challenges in pediatric healthcare, requiring comprehensive understanding of its diverse clinical manifestations and immunological responses. The integration of multidisciplinary

findings reveals that effective management necessitates collaborative approaches spanning immunology, pediatrics, and infectious disease specialties.

MIS-C's heterogeneous clinical presentation—ranging from gastrointestinal to cardiovascular involvement—demands broad diagnostic criteria, while its hyperinflammatory nature underscores the need for targeted immunomodulatory therapies. Current advances not only improve clinical practice but also guide future research directions. Ongoing investigations into immune dysregulation mechanisms remain crucial for developing effective preventive and therapeutic strategies. For instance, biomarker discovery could enable risk stratification and personalized treatment approaches.

Furthermore, insights from MIS-C management inform our understanding of other pediatric inflammatory conditions and enhance preparedness for future emerging pathogens. This collective knowledge strengthens pandemic response capabilities and ultimately contributes to improved global child health outcomes.

Author contributions

TX: Funding acquisition, Investigation, Writing – original draft, Writing – review & editing. JZ: Writing – original draft, Writing – review & editing, Data curation, Methodology. XH: Writing – original draft, Writing – review & editing, Visualization, Formal analysis. XX: Data curation, Resources, Visualization, Writing – original draft, Writing – review & editing. JQ: Formal analysis, Writing – original draft, Writing – review & editing, Methodology. CW: Project administration, Validation, Writing – original draft, Writing – review & editing. YY: Software, Visualization, Writing – original draft, Writing – review & editing. LK: Investigation, Project administration, Writing – original draft, Writing – review & editing. BZ: Writing – original draft, Writing – review & editing, Conceptualization, Visualization.

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Conflict of interest

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