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CLINICAL AND IMMUNOLOGICAL FEATURES OF VIRAL RESPIRATORY INFECTIONS IN CHILDREN WITH COMORBID CONDITIONS: A LITERATURE REVIEW

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Abstract

Background: Viral respiratory infections are a leading cause of pediatric hospitalization and healthcare strain worldwide. While healthy children typically experience mild or self-limiting clinical courses, patients with underlying chronic conditions face a significantly higher risk of severe lower respiratory tract disease, mechanical ventilation, and mortality.

Aim: To analyze recent scientific literature on the clinical course, immunological mechanisms, complications, and risk factors of viral respiratory infections in children with comorbid conditions.

Methods: A narrative review was conducted using PubMed, Scopus, Web of Science, WHO, CDC, and UNICEF databases, focusing exclusively on peer-reviewed literature published from 2021 to 2026.

Results: Chronic comorbidities such as bronchial asthma, obesity, type 1 diabetes mellitus, malnutrition, anemia, congenital cardiovascular defects, neurological impairments, and primary or secondary immunodeficiencies alter host structural and cellular defense mechanisms. Immunologically, these conditions are associated with delayed or blunted type I/III interferon responses, leading to uncontrolled intracellular viral replication. This delayed clearance triggers a secondary, dysregulated immune response characterized by the hyperactivation of pro-inflammatory cytokines ((IL-1}\beta$, (IL-6), (TNF}-\alpha$). Clinically, this manifests as accelerated progression from upper respiratory symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS), or post-viral hyperinflammatory states like Multisystem Inflammatory Syndrome in Children (MIS-C).

Conclusion: Children with comorbidities experience unique, severe clinical trajectories driven by systemic immune dysregulation. Comprehensive risk stratification using specific biomarkers ((CRP), procalcitonin, ferritin, D-dimer) and multiplex PCR testing is essential. Management requires early antiviral

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interventions, optimized supportive care, and strict adherence to universal immunization guidelines.

Keywords

viral respiratory infections, children, comorbid conditions, COVID-19, influenza, RSV, immune response, cytokines, clinical features, complications.

Introduction

Viral respiratory infections represent a substantial global burden, remaining the leading cause of morbidity, clinical consultations, and acute hospitalizations within the pediatric population. The clinical and epidemiological spectrum of pediatric respiratory disease is driven by a diverse array of highly transmissible pathogens, including coronavirus disease 2019 ((COVID-19)) caused by severe acute respiratory syndrome coronavirus 2 ((SARS-CoV-2)), seasonal influenza viruses (types A and B), respiratory syncytial virus ((RSV)), human adenoviruses, parainfluenza viruses, and rhinoviruses. While a vast majority of immunologically robust, otherwise healthy children experience uncomplicated, self-limiting upper respiratory tracts signs, the clinical trajectory changes significantly when these infections occur in children with underlying comorbid conditions.

The presence of comorbidities—encompassing chronic pulmonary diseases like bronchial asthma, metabolic dysregulations such as obesity and type 1 diabetes mellitus, nutritional deficiencies, baseline anemias, structural cardiovascular anomalies, and static or progressive neurological conditions—fundamentally undermines the pediatric host's functional reserves and immunological integrity. Accumulating evidence from the last five years indicates that these vulnerable subgroups have higher rates of lower respiratory tract involvement, intensive care unit allocations, and mechanical ventilation requirements.

The critical need to evaluate these populations stems from observations of profound, pathogen-mediated immune dysregulation. Rather than facilitating targeted viral clearance, infections in comorbid children frequently trigger a dysregulated hyperinflammatory cascade, often referred to as a "cytokine storm," causing systemic tissue injury. Consequently, a comprehensive review of the distinct clinical presentations, diagnostic features, and immunological abnormalities in this population is vital. This analysis is necessary for establishing evidence-based risk-stratification criteria, improving diagnostic precision, and refining targeted therapeutic protocols to reduce the global burden of pediatric respiratory disease.

Aim of the Review

To analyze recent scientific literature on the clinical course, immunological mechanisms, complications, and risk factors of viral respiratory infections in children with comorbid conditions.

Materials and Methods

This study was designed and executed as a structured narrative literature review to synthesize current evidence on pediatric viral respiratory infections and co-occurring chronic conditions. To compile a high-quality, scientifically robust body of literature, an electronic database search was performed using PubMed, Scopus, Web of Science, and the official databases of the World Health Organization ((WHO)), the Centers for Disease Control and Prevention ((CDC)), and (UNICEF). The search strategies relied on combinations of Medical Subject Headings ((MeSH)) terms and Boolean operators, including: ("viral respiratory infection" OR "influenza" OR "RSV" OR "COVID-19") AND ("children" OR "pediatric") AND ("comorbidities" OR "asthma" OR "obesity" OR "immunodeficiency") AND ("immune response" OR "cytokines").

Strict inclusion and exclusion criteria were maintained to ensure the temporal relevance and clinical reliability of the synthesized data. The inclusion criteria limited the selection exclusively to peer-reviewed original research articles, systematic reviews, meta-analyses, consensus clinical guidelines, and official epidemiological reports published within the last 5 years, spanning from 2021 to 2026. Only studies evaluating pediatric cohorts (aged 0 to 18 years) with clearly documented comorbid conditions and primary viral respiratory etiologies were reviewed. Conversely, the exclusion criteria filtered out outdated studies published prior to 2021, case reports with insufficient sample sizes, non-peer-reviewed preprints, abstracts from unindexed conferences, and articles lacking detailed clinical, laboratory, or immunological data. Through this approach, an evidence-based narrative was compiled.

Main Body

General Characteristics of Viral Respiratory Infections in Children

The pediatric respiratory tract is highly susceptible to an extensive array of viral pathogens due to its unique anatomical and immunological characteristics. The primary causative agents driving global pediatric respiratory disease include (RSV), influenza A and B, (SARS-CoV-2), human adenoviruses, rhinoviruses, and parainfluenza viruses. Transmission occurs predominantly via the inhalation of airborne respiratory droplets generated during coughing and sneezing, or via indirect contact with contaminated fomites followed by self-inoculation of oral, nasal, or conjunctival mucosa.

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The clinical expression of these infections exhibits profound age-dependent variations. Neonates and young infants frequently manifest systemic signs such as poor feeding, lethargy, and apnea, alongside localized lower airway inflammation such as bronchiolitis. In contrast, older children more commonly present with classic upper or lower respiratory syndromes, including rhinorrhea, pharyngitis, tracheobronchitis, and pneumonia. The global disease burden is exceptionally high, accounting for millions of pediatric emergency department visits annually, placing an immense socioeconomic strain on healthcare delivery networks.

Role of Comorbid Conditions

Comorbidities act as major destabilizing factors that alter the natural history of viral respiratory infections in children. Iron deficiency and nutritional anemias compromise cellular oxygenation and hinder proper lymphocyte proliferation, thereby weakening basic mucosal immunity. Bronchial asthma and chronic bronchitis involve pre-existing mucosal inflammation, baseline hyperresponsiveness, and impaired mucociliary clearance, which facilitate deeper viral invasion and provoke acute bronchospastic exacerbations.

Metabolic conditions, most notably pediatric obesity and type 1 diabetes mellitus, introduce a state of chronic, systemic low-grade inflammation and immune cellular dysfunction, reducing the production of protective anti-viral interferons. Malnutrition deprives the bone marrow and secondary lymphoid organs of vital amino acids and micronutrients necessary for robust antibody production. Furthermore, children affected by congenital or acquired cardiovascular diseases, static or progressive neurological disorders (e.g., cerebral palsy, which impairs the cough reflex), and primary or secondary immunodeficiency states possess virtually no physiological reserve, leading to rapid, uncompensated decompensation during acute viral insults.

Clinical Features

The clinical presentation of viral respiratory tract infections in children with comorbidities is characterized by accelerated progression, overlapping syndromes, and heightened severity. While healthy children exhibit localized, manageable symptoms, comorbid children display prominent, high-grade pyrexia (fever) that is frequently refractory to conventional antipyretics, alongside a persistent, distressing cough. As the infection descends into the lower respiratory tract, clinical signs of dyspnea and severe respiratory distress rapidly become apparent. This is objectively evidenced by tachypnea, intercostal and subcostal retractions, nasal flaring, grunting, and a progressive drop in peripheral oxygen saturation ($SpO_2 < 92\ \%$).

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Extrapulmonary manifestations are also significantly more prevalent in this subpopulation; gastrointestinal symptoms such as intractable vomiting, severe diarrhea, and abdominal pain often complicate fluid status, while neurological manifestations including febrile or non-febrile seizures, altered mental status, and encephalopathy highlight systemic viral impact. The divergence between mild, moderate, and severe forms is dictated by the velocity of respiratory failure onset and the degree of secondary multi-organ dysfunction.

Immunological Mechanisms

The immunopathogenesis of severe viral respiratory disease in children with comorbidities centers on a fundamental failure of immune homeostasis. Under physiological conditions, the innate immune response recognizes viral pathogen-associated molecular patterns (PAMPs) through toll-like receptors, triggering the rapid secretion of type I and type III interferons ((IFN}-\alpha$, (IFN}-\beta$, (IFN}-\lambda$) to suppress viral replication. In comorbid children, this initial innate response is frequently blunted or delayed. This delay permits unhindered intracellular viral replication, which subsequently induces widespread epithelial cell necrosis and triggers an uncontrolled, secondary recruitment of inflammatory monocytes and neutrophils.

This dysregulated cellular influx drives an intense activation of the adaptive immune response, but instead of targeted clearance, it often culminates in an aberrant hyperinflammatory state characterized by excessive cytokine activation. Pronounced elevations in interleukin-1 beta ((IL-1}\beta$), interleukin-6 ((IL-6)), tumor necrosis factor-alpha ((TNF}-\alpha$), and chemokines systematically disrupt endothelial integrity, promote microvascular thrombosis, and cause severe alveolar-capillary membrane damage. This immune dysregulation is exacerbated by pre-existing chronic inflammation or metabolic derangement, rendering the child highly vulnerable to inflammatory tissue injury.

COVID-19 in Children with Comorbid Conditions

Although (SARS-CoV-2) infection typically causes mild disease in the general pediatric population, the clinical reality is profoundly altered for children with pre-existing chronic diseases. In these high-risk patients, acute (COVID-19) frequently presents as severe, bilateral interstitial pneumonia requiring high-flow nasal cannula support or invasive mechanical ventilation. Key risk factors for severe outcomes include adolescent obesity, poorly controlled type 1 diabetes, congenital heart defects with compromised hemodynamics, and severe neurodevelopmental delay.

Laboratory investigations in these children reveal profound lymphopenia, striking leukocytosis, and marked elevations in systemic inflammatory markers. A

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critical and life-threatening post-(COVID) complication is Multisystem Inflammatory Syndrome in Children ((MIS-C)). (MIS-C) is a hyperinflammatory phenomenon that manifests several weeks after the initial viral insult, presenting with prolonged fever, myocardial dysfunction, coronary artery aneurysms, and acute gastrointestinal distress, requiring aggressive management with intravenous immunoglobulins ((IVIG)) and high-dose corticosteroids.

Influenza and RSV in Children with Comorbidities

Seasonal influenza and (RSV) inflict substantial damage on pediatric cohorts with underlying medical complexities. In children with bronchial asthma, congenital heart disease, or chronic lung disease of prematurity (bronchopulmonary dysplasia), (RSV) infection swiftly transitions from simple upper respiratory congestion to severe, necrotizing bronchiolitis and extensive viral pneumonia. Concurrently, influenza strains trigger widespread desquamation of airway epithelial cells, markedly increasing the risk of secondary bacterial superinfections, most notably by *Streptococcus pneumoniae* and *Staphylococcus aureus*.

The clinical course in these children is marked by a significantly elevated risk of developing acute respiratory distress syndrome ((ARDS)), which sharply increases the rates of pediatric intensive care unit ((PICU)) admission and prolongs hospital stays. These severe trajectories highlight the absolute critical need for robust preventive strategies, including universal annual influenza vaccination for all children over six months of age with comorbidities, and the timely administration of long-acting monoclonal antibodies (such as nirsevimab or palivizumab) to safeguard infants at high risk for severe (RSV) disease.

Laboratory and Diagnostic Features

Accurate, rapid laboratory evaluation and risk stratification are indispensable when managing viral respiratory infections in children with comorbidities. A complete blood count ((CBC)) often reveals distinct diagnostic patterns, such as absolute lymphopenia, which correlates with severe viral replication and immune exhaustion, or marked neutrophilia, which strongly suggests bacterial superinfection. Systemic acute-phase reactants are critical tools for monitoring disease progression; C-reactive protein ((CRP)) and procalcitonin ((PCT)) show minimal elevations in uncomplicated viral states but rise sharply during bacterial coinfections or systemic hyperinflammatory syndromes.

Furthermore, intracellular and metabolic storage markers such as ferritin and D-dimer serve as valuable prognostic indicators; elevated ferritin levels reflect macrophage activation syndrome and tissue necrosis, while rising D-dimer levels signal widespread microvascular endothelial damage and activation of the coagulation cascade. Direct measurement of specific cytokine markers (e.g., (IL-6),

(TNF}-\alpha$) provides a window into the intensity of the immune response. At the center of modern etiological diagnostics is the deployment of qualitative and quantitative polymerase chain reaction ((PCR)) testing and multiplex respiratory panels, which allow for the simultaneous, highly sensitive identification of multiple viral and atypical bacterial targets from a single nasopharyngeal swab.

Complications

The progression of viral respiratory infections in children with comorbidities is frequently punctuated by severe, life-threatening complications. The most common lower respiratory complication is severe, confluent pneumonia, which can rapidly progress to acute respiratory failure requiring invasive respiratory support. If the dysregulated localized inflammatory response escapes into the systemic circulation, it can induce a state of cardiovascular collapse, profound hypotension, and refractory sepsis, culminating in multi-organ dysfunction syndrome ((MODS)).

Furthermore, the acute viral insult acts as a major stressor that triggers severe exacerbations of the child's underlying chronic conditions, such as precipitating status asthmaticus in asthmatic children, or inducing diabetic ketoacidosis ((DKA)) in patients with type 1 diabetes. Long-term post-infectious complications are also substantial; these include the development of bronchiolitis obliterans, a permanent reduction in baseline pulmonary function parameters, prolonged muscular wasting, and chronic post-viral fatigue syndromes that severely impair the child's long-term developmental trajectory and overall quality of life.

Prevention and Management

The clinical management of viral respiratory infections in children with comorbid conditions demands an aggressive, multidisciplinary, and highly structured proactive approach. Early diagnosis represents the critical first step, achieved through immediate clinical screening and rapid molecular multiplex (PCR) testing at the first sign of respiratory symptoms. Proactive prevention centers on comprehensive, up-to-date immunization, including annual influenza vaccines and updated (COVID-19) boosters for the child, their immediate family members, and healthcare providers to establish a protective cocoon effect. When indicated, targeted antiviral therapies should be initiated as early as possible within the therapeutic window, such as utilizing oseltamivir for confirmed influenza infections or Paxlovid (nirmatrelvir/ritonavir) for eligible high-risk pediatric (COVID-19) cases, alongside monoclonal antibodies for (RSV) prophylaxis.

The foundation of in-hospital management remains meticulously calibrated supportive treatment, consisting of titrated humidified oxygen therapy, non-invasive positive pressure ventilation, strict fluid and electrolyte balance monitoring, and the judicious use of broad-spectrum empiric antibiotics if

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secondary bacterial superinfection is suspected. Continuous clinical monitoring of high-risk children via pulse oximetry, cardiac telemetry, and serial biomarker checks ensures timely escalation of care. Ultimately, these clinical efforts must be supported by public health prevention strategies, including robust school-based infection control policies, public hygiene education, and accessible pediatric vaccination campaigns.

Tables

Table 1. Major comorbid conditions associated with severe viral respiratory infections in children

Comorbid Condition	Possible Mechanism of Increased Risk	Clinical Significance	Preventive Approach
Bronchial Asthma / Chronic Bronchitis	Pre-existing mucosal inflammation, airway hyperresponsiveness, impaired mucociliary clearance.	Triggers status asthmaticus, severe bronchospasm, and high risk of secondary bacterial pneumonia.	Optimization of controller therapies (ICS), annual influenza vaccination, pneumococcal immunization.
Pediatric Obesity	Chronic low-grade systemic inflammation, compromised diaphragmatic excursion, altered T-cell responses.	Increased risk of severe interstitial pneumonia, ARDS, and prolonged mechanical ventilation.	Weight management counseling, early antiviral therapy initiation, prioritized seasonal vaccination.
Type 1 Diabetes Mellitus	Hyperglycemia-induced impairment of neutrophil phagocytosis, compromised cellular immune defense.	Rapid metabolic decompensation, high risk of diabetic ketoacidosis (DKA) during acute viral stress.	Strict glycemic control during illness, continuous glucose monitoring, mandatory immunizations.
Congenital Cardiovascular Defects	Baseline pulmonary hypertension, altered pulmonary hemodynamics, limited cardiac reserve.	Rapid development of congestive heart failure, severe hypoxemia, uncompensated	RSV immunoprophylaxis (monoclonal antibodies), annual influenza and COVID-19

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Comorbid Condition	Possible Mechanism of Increased Risk	Clinical Significance	Preventive Approach
		metabolic acidosis.	vaccination, close fluid tracking.
Neurological Disorders (e.g., Cerebral Palsy)	Impaired swallow and cough reflexes, respiratory muscle hypotonia, chronic microaspiration risk.	High prevalence of aspiration pneumonia, progressive atelectasis, acute hypoxemic respiratory failure.	Chest physiotherapy, airway clearance techniques, positional rotation, comprehensive vaccination.
Primary/Secondary Immunodeficiencies	Defective antibody production, impaired T-cell or NK-cell cytotoxicity, delayed viral clearance.	Disseminated viral disease, chronic unremitting viral shedding, high rate of opportunistic coinfections.	Intravenous immunoglobulin (IVIG) therapy, strict protective isolation, prophylactic anti-infectives.

Table 2. Laboratory markers used in the assessment of viral respiratory infections in children

Marker	Clinical Meaning	Changes in Severe Disease	Diagnostic or Prognostic Value
Complete Blood Count (CBC)	Reflects systemic cellular immune response and bone marrow activation.	Profound absolute lymphopenia, significant leukocytosis with a pronounced left shift.	High diagnostic value for differentiating primary viral processes from secondary bacterial superinfections.
C-reactive Protein (CRP)	Acute-phase reactant synthesized by the liver in response to IL-6 stimulation.	Markedly elevated ($>50\text{--}100\text{ mg/L)) in severe hyperinflammatory states or bacterial coinfections.	Excellent prognostic tool for tracking therapeutic responses and identifying systemic tissue damage.
Procalcitonin	Specific biomarker	Remains low in isolated	Extremely high

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Marker	Clinical Meaning	Changes in Severe Disease	Diagnostic or Prognostic Value
(PCT)	induced primarily by bacterial endotoxins and systemic cytokines.	viral infection; rises sharply ($>0.5\text{--}2.0\text{ ng/mL}$) during bacterial superinfection.	diagnostic value for guiding rational antimicrobial stewardship and antibiotic de-escalation.
Serum Ferritin	Intracellular iron storage protein that acts as a prominent inflammatory marker.	Exhibits exponential increases in cytokine storm syndromes and macrophage activation states.	Strong prognostic indicator for severe systemic inflammatory response syndrome (SIRS) and mortality risk.
D-dimer	Fibrin degradation product indicating activation of the systemic coagulation pathway.	Significantly elevated in severe COVID-19, MIS-C, or disseminated intravascular coagulation (DIC).	Critical prognostic marker for microvascular thrombosis, endothelial injury, and organ dysfunction.
Multiplex Respiratory PCR Panel	Molecular diagnostic assay utilizing nucleic acid amplification to identify viral genomes.	Detects specific viral etiologies and uncovers high-risk viral-viral or viral-bacterial co-infections.	Gold-standard diagnostic tool for rapid, precise etiological identification and targeted infection control.

Discussion

The systematic synthesis of recent scientific evidence clearly demonstrates that children with comorbid conditions are predisposed to severe, complicated courses of viral respiratory infections due to a combination of anatomical, metabolic, and immunological vulnerabilities. The standard paradigm that pediatric viral infections are universally benign is challenged when applied to cohorts with chronic illnesses. In these patients, pre-existing conditions compromise structural and cellular defenses, rendering them unable to effectively limit viral replication or cope with the physiological stress of a severe respiratory infection.

A central finding of this review is the relationship between the host immune response and clinical severity. While healthy children typically mount a localized,

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self-limiting immune response, children with comorbidities frequently exhibit a dysregulated system. Pre-existing chronic conditions—such as the systemic inflammation seen in obesity or the metabolic stress of diabetes—effectively "prime" the immune system. When a viral pathogen is introduced, this primed state can lead to a delayed initial interferon response, followed by an overcompensated, systemic release of pro-inflammatory cytokines ((IL-1}\beta$, (IL-6), (TNF}-\alpha$). This hyperinflammatory state can cause significant tissue damage, leading to alveolar epithelial destruction, microvascular thrombosis, and rapid clinical deterioration into acute respiratory failure or multi-organ dysfunction.

Comparing different viral pathogens reveals distinct clinical and immunological profiles across comorbid cohorts. (RSV) continues to pose a severe risk to infants with bronchopulmonary dysplasia or congenital heart defects, frequently causing severe lower airway obstruction and bronchiolitis. Influenza remains a major driver of secondary bacterial superinfections, particularly in children with chronic asthma or neuromuscular disorders. Meanwhile, (SARS-CoV-2) continues to present unique challenges, specifically the risk of severe interstitial pneumonia and the development of post-infectious hyperinflammatory syndromes like (MIS-C) in children with metabolic or neurological conditions.

These distinct profiles underscore the need for early risk stratification, utilizing comprehensive multiplex (PCR) testing and serial biomarker assessments (such as (CRP), (PCT), ferritin, and D-dimer) to identify high-risk patients before severe symptoms develop. Ultimately, mitigating these risks requires moving away from uniform treatment protocols toward individualized, proactive management strategies that combine early antiviral intervention, optimized supportive care, and strict adherence to comprehensive immunization schedules.

Conclusion

Based on a comprehensive review of the scientific literature from 2021 to 2026, the following key conclusions are established:

1. Pre-existing comorbid conditions—most notably bronchial asthma, chronic lung diseases, obesity, type 1 diabetes mellitus, congenital cardiovascular defects, and neurological disorders—are major independent risk factors that significantly increase the severity, ICU admission rates, and complication rates of viral respiratory infections in the pediatric population.

2. The immunopathogenesis of severe disease in comorbid children is characterized by a dysregulated hyperinflammatory response. This state is marked by an impaired primary interferon defense and an excessive, systemic release of pro-inflammatory cytokines ((IL-1}\beta$, (IL-6), (TNF}-\alpha$), which drives

extensive tissue damage and multi-organ dysfunction rather than effective viral clearance.

3. Serial evaluation of specific laboratory biomarkers—including absolute lymphocyte counts, (CRP), procalcitonin, ferritin, and D-dimer—combined with rapid molecular multiplex (PCR) testing, is crucial for early risk stratification and the timely identification of secondary bacterial superinfections or systemic hyperinflammatory complications.

4. Effective management of this vulnerable population requires moving away from reactive treatment protocols toward proactive, individualized care. This approach must integrate early, targeted antiviral therapies, calibrated supportive care, and strict monitoring of the child's underlying chronic conditions.

5. Comprehensive prevention strategies remain the most effective means of reducing the disease burden. This requires high immunization coverage, including annual influenza vaccines and updated (COVID-19) boosters for high-risk children and their immediate close contacts, alongside targeted monoclonal antibody prophylaxis against (RSV) for eligible infants.

6. Future research in pediatric infectious diseases should focus on elucidating the precise molecular pathways that connect specific metabolic and genetic comorbidities to immune dysregulation. Additionally, multi-center clinical trials are needed to evaluate the efficacy and safety of early, targeted immunomodulatory therapies for children experiencing severe, virus-induced hyperinflammatory states.

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