REVIEW ARTICLE

Severe pediatric COVID-19: a review from the clinical and immunopathophysiological perspectives

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Abstract

Background Coronavirus disease 2019 (COVID-19) tends to have mild presentations in children. However, severe and critical cases do arise in the pediatric population with debilitating systemic impacts and can be fatal at times, meriting further attention from clinicians. Meanwhile, the intricate interactions between the pathogen virulence factors and host defense mechanisms are believed to play indispensable roles in severe COVID-19 pathophysiology but remain incompletely understood.

Data sources A comprehensive literature review was conducted for pertinent publications by reviewers independently using the PubMed, Embase, and Wanfang databases. Searched keywords included "COVID-19 in children", "severe pediatric COVID-19", and "critical illness in children with COVID-19".

Results Risks of developing severe COVID-19 in children escalate with increasing numbers of co-morbidities and an unvaccinated status. Acute respiratory distress stress and necrotizing pneumonia are prominent pulmonary manifestations, while various forms of cardiovascular and neurological involvement may also be seen. Multiple immunological processes are implicated in the host response to COVID-19 including the type I interferon and inflammasome pathways, whose dysregulation in severe and critical diseases translates into adverse clinical manifestations. Multisystem inflammatory syndrome in children (MIS-C), a potentially life-threatening immune-mediated condition chronologically associated with COVID-19 exposure, denotes another scientific and clinical conundrum that exemplifies the complexity of pediatric immunity. Despite the considerable dissimilarities between the pediatric and adult immune systems, clinical trials dedicated to children are lacking and current management recommendations are largely adapted from adult guidelines.

Conclusions Severe pediatric COVID-19 can affect multiple organ systems. The dysregulated immune pathways in severe COVID-19 shape the disease course, epitomize the vast functional diversity of the pediatric immune system and highlight the immunophenotypical differences between children and adults. Consequently, further research may be warranted to adequately address them in pediatric-specific clinical practice guidelines.

Keywords Immunopathophysiology · MIS-C · Pediatric critical care · Severe pediatric COVID-19

Introduction

Contrary to most recognized respiratory pathogens, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen of COVID-19, typically leads to milder disease in pediatric cases than in adult patients[1, 2], but young children, particularly infants, may still be prone to contract the virus[3, 4], and a small number may develop severe or even critical illnesses [5, 6]. Children with severe COVID-19 may develop serious complications such as acute respiratory distress syndrome, myocarditis,

acute renal failure, cardiogenic or septic shock, and multiorgan failure, and mortality can occur in extreme cases [7]. A nationwide surveillance study conducted in the United States during the peak of the pandemic recorded a COVID-19-related hospitalization rate of 48.2 per 100,000 population for children under 18 years of age from October 2020 to September 2021, of whom 26.4% required ICU admission, 6.2% required invasive mechanical ventilation, and 0.7% died while hospitalized [8]. The epidemiology of pediatric COVID-19 has also evolved substantially since the advent of successful vaccines, with new cases aggregating mostly in unvaccinated children or subgroups of children who are ineligible for immunization [9]. The picture is further

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complicated by the emergence of multisystem inflammatory syndrome in children (MIS-C), a distinctive post-infectious entity that accounted for a significant proportion of pediatric ICU admissions linked to COVID-19, and highlights the profound involvement of host immune response in the pathogenesis of severe pediatric COVID-19 and the associated conditions [10–13]. This review, therefore, aims to provide a holistic dissection of the diseases of interest with focuses on both the clinical and immunological standpoints.

Clinical approaches to severe pediatric COVID-19

Risk factors for developing severe COVID-19 in children and red flags for deterioration

The symptomology of clinically evident acute COVID-19 in children is similar to that in adults, which mostly involves the respiratory tract, with the most common presenting complaints being fever, coughs, coryzal symptoms including nasal congestion and rhinorrhea, and dyspnea, which may be accompanied by headaches, myalgia, generalized malaise, and possibly gastrointestinal symptoms such as nausea, vomiting, decreased oral intake, and diarrhea [14–16]. Identification and close monitoring of children at risk of severe COVID-19 represent a concrete first step in clinical assessment. The risk factors with the highest relative risks for severe COVID-19 in children are chronic lung diseases, obesity, diabetes, cardiovascular disease, neurological comorbidities including seizure disorders, and prematurity (among children below 2 years of age) [1, 17, 18], many of which are linked to endothelial impairment and a pro-inflammatory state [19], and odds of critical care admission and mortality increase in a step-wise manner with increased number of comorbidities [20].

Meanwhile, it is important to clarify the vaccination status in light of the well-rounded protective effects it offers against disease transmission, progression, and complications. For instance, a recent meta-analysis of 51 studies revealed that 2 doses of mRNA vaccines are 75.3% and 78% effective against COVID-19-associated hospitalizations and MIS-C, respectively, in children between the age of 5 and 11 years [21]. However, waning protection with the emergence of novel variants (e.g., Omicron)[22] and elapsed time since the last administered dose [23], especially for those aged 5–11 years as opposed to older children or adolescents [24, 25], need to be taken into consideration. It is worth noting that immunocompromised children, even if appropriately vaccinated as per the modified schedule, are still deemed at high risk of progression to severe COVID-19 due to lower response rates to vaccinations and vulnerability to SARS-CoV-2 pathogenicity [26].

Any clinical, biochemical, and radiological signs indicating deterioration, especially in at-risk children, should be promptly acknowledged and actioned upon, which include (1) increased respiratory rate; (2) poor responsiveness, drowsiness, and convulsions; (3) lymphopenia and/or thrombocytopenia; (4) hypo/hyperglycemia and/or hyperlactatemia; (5) markedly elevated inflammatory markers such as procalcitonin, C-reactive protein, and ferritin; (6) significant transaminitis and creatine kinase elevation; (7) pronounced abnormalities in coagulation function parameters; and (8) changes in head imaging such as cerebral edema or significant progression of pulmonary lesions on chest imaging [27].

Clinical characteristics of severe and critical pediatric COVID-19

Case definition

The case definition for severe pediatric COVID-19 may have slight variations across studies and guidelines, but it typically requires (1) a form of diagnostic certainty with a positive RT-PCR result for SARS-CoV-2 nucleic acids as the gold standard; (2) hospitalization as a result of COVID-19 related symptoms, thereby excluding cases managed in the outpatient setting; and (3) ICU admission, invasive mechanical ventilation, or circulatory support as the key indicators of disease severity, albeit inevitably limited by disparities in intervention thresholds between different centers and patient subgroups [1, 20]. Besides, deviations in respiratory and oxygenation indices have been used to delineate severe disease, including a blood oxygen saturation level (SpO_2) of < 94% on room air under atmospheric pressure at sea level [27, 28] and significant elevations in age-adjusted respiratory rate [27], while conditions suggestive of other organ system dysfunctions are also proxy measures [10, 29].

Respiratory

The rate of viral pneumonia is determined to be 24% among children hospitalized with a COVID-19 diagnosis by a multi-center study in the US [30]. Necrotizing pneumonia (NP) is a disastrous complication of severe pediatric COVID-19, which stemmed from aggressive bacterial superinfections causing lung tissue liquefaction and cavitation, with the most common causative organisms being *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Mycoplasma pneumoniae* [31]. Specifically, Akuamoah-Boateng et al. reported the case of a 13-year-old boy with COVID-19 and convincing laboratory and radiologic features of NP presumably caused by *Prevotella oris*, which was not detected by the blood cultures prior to antimicrobial administration but returned

positive on PCR of the surgical drainage sample of concurrent subdural empyemas [32]; and Brisca et al. reported a case of NP in a 4-month-old infant with of COVID-19 and concurrent central venous catheter-associated methicillin-susceptible *Staphylococcus aureus* bacteremia [33]. NP in both cases eventually resolved with appropriate level of respiratory support and multimodal pharmacotherapy.

Physicians should also be kept aware of COVID-19-related croup [34] that has shown increased incidences with Omicron variants [35, 36], manifests as vocal hoarseness, stridor, wheezing, or lung rales [34, 37, 38], and in critical cases may require endotracheal intubation and cardiopulmonary resuscitation, although COVID-19-associated croup is treated similarly to other viral causes of croup and respiratory distress is generally uncommon [39].

Additionally, a scrutinization of the Overcoming COVID-19 registry data has shown that acute respiratory distress syndrome (ARDS) was seen in approximately 10% of hospitalized children with severe acute COVID-19 and MIS-C [10], compared to 33% in admitted adults [40]. Despite lower incidences compared to adults, COVID-19-related pediatric ARDS required mechanical ventilation in most cases [41, 42], and the strategy of low tidal volume and limiting plateau pressure for lung protection has been routinely implemented [41, 43–45]. ARDS was also found to be independently associated with lower probability of discharge from PICU and hospital in a multivariable analysis of time to discharge [41], which reflects its protracted disease course and risk of lethality.

Cardiovascular

Cardiogenic shock [46], pericarditis [47], and myocardial injury [48–50] have all been reported in acute SARS-CoV-2 infection in children, and evidence of persistent cardiac injury could be detected 3–6 months on cardiac magnetic resonance imaging after severe pediatric COVID-19 [51]. However, a large proportion of COVID-19-related cardiovascular involvement in pediatric patients may be driven by indirect, non-cardiac insults, especially MIS-C [52]. 93% of the 283 children with MIS-C in a multicenter European study had myocardial injury, as reflected by elevated troponin levels [53], while reduced ejection fraction can be seen in approximately 30% of MIS-C patients [10, 53]. Even though SARS-CoV-2 RNA was detected with myocarditis on post-mortem cardiac biopsy of an 11-year-old child who died of MIS-C, suggesting direct viral invasion could be the inciting and perpetrating event in this particular case [54], a systemic inflammatory response is likely the principal driving force for myocarditis in most MIS-C cases

[53, 55], which is known for its multiorgan manifestations (Fig. 1) and will be discussed in further details in connection with an evaluation of its elusive pathogenesis.

Neurologic

Non-specific neurologic symptoms are relatively common in children with COVID-19, whereas serious neurologic manifestations are much more infrequent, with an estimated prevalence of 3.8% among pediatric patients admitted to hospital with COVID-19 [56]. A significant proportion of them may be broadly categorized as neuro-immune disorders, among which numerous cases of acute disseminated encephalomyelitis [57–61], a demyelinating disease affecting the central nervous system, as well as Guillain–Barré syndrome [62, 63] have been reported. On the other hand, direct viral invasion of the central nervous system (CNS) by SARS-CoV-2 is rare but has been described [64], and disruption of the blood–brain barrier and host immunity secondary to COVID-19 may predispose patients to lethal CNS co-infections, including opportunistic ones by *Mycobacterium Tuberculosis* [61]. Furthermore, cytokine storm and systematic inflammation may be the driving force of life-threatening neurologic conditions seen in severe pediatric COVID-19 such as acute necrotizing encephalopathy, a para-infectious condition most commonly precipitated by viruses of the *Orthomyxoviridae* family that is characterized by multifocal symmetrical lesions, especially in bilateral thalami [65, 66], and acute fulminant cerebral edema, which can happen in previously healthy children, causing brain herniation and death within 24–48 hours of foretelling seizures [67, 68]. Moreover, a well-conducted US study utilizing surveillance data showed that 47% of the pediatric patients hospitalized with COVID-19-related illnesses who developed life-threatening neurologic conditions met the diagnostic criteria for MIS-C [11].

Pathogenic and immunologic determinants of disease severity

SARS-CoV-2 cellular binding and entry

Like SARS-CoV, SARS-CoV-2 utilizes its spike (S) glycoprotein to facilitate entry into target cells via interaction with the angiotensin converting enzyme II (ACE2). The S1 subunit of the S protein binds to ACE2, which activates an accompanying host protease, most commonly transmembrane serine protease 2 (TMPRSS2), releasing the S2 subunit from the S1-S2 complex [69–72]. The S2 subunit then enables fusion of the viral envelope with the cellular membrane and consequently endocytosis of the
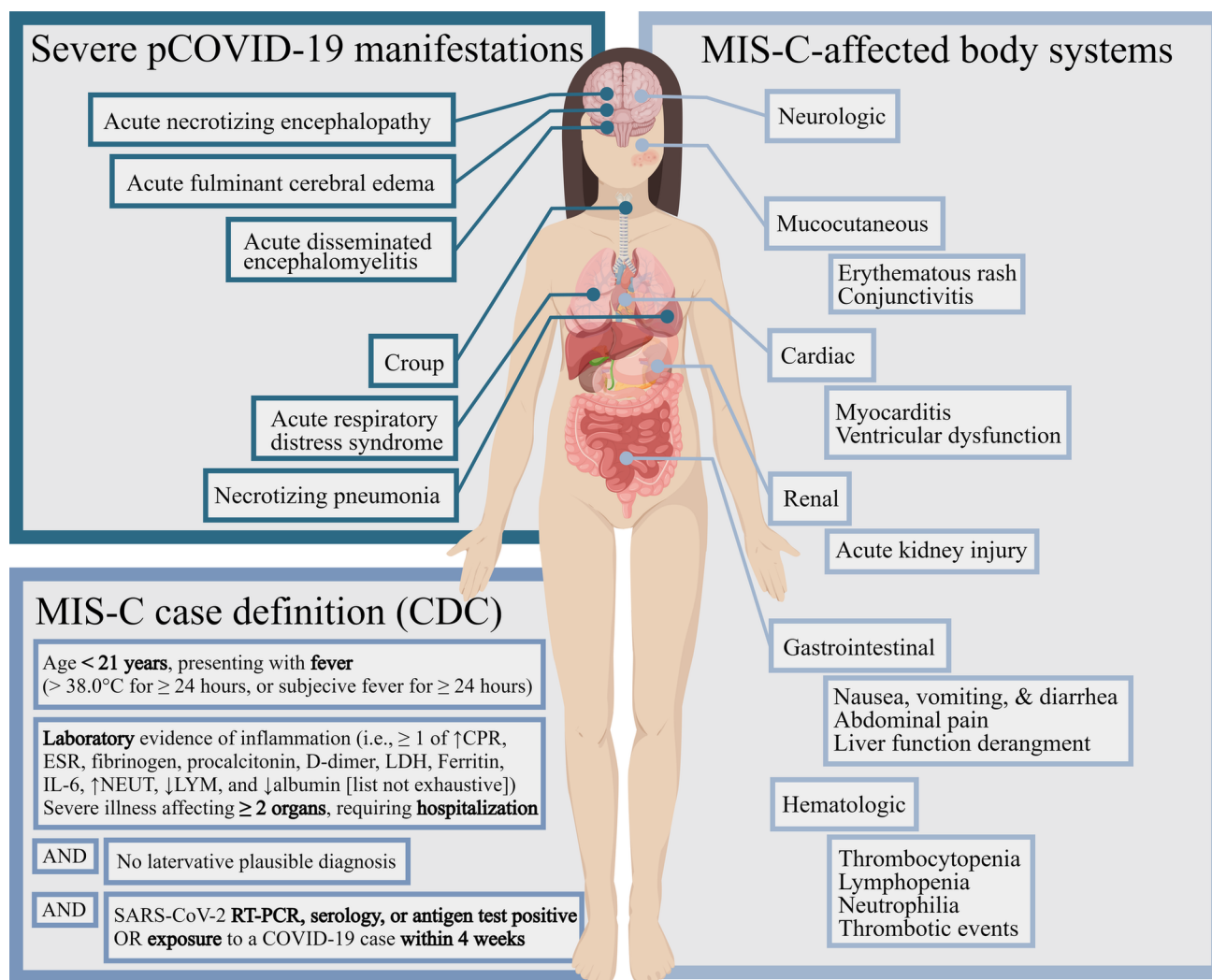
Fig. 1 Potentially life-threatening manifestations of severe pediatric COVID-19 and organ systems implicated in MIS-C. The MIS-C diagnostic criteria are adapted from the Centers of Disease Control and Prevention of the United States. *pCOVID-19* pediatric COVID-19, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *LDH* lactate dehydrogenase, *IL-6* interleukin 6, *NEUT* neutrophils, *LYM* lymphocytes, *RT-PCR* reverse transcription polymerase chain reaction

viral components [73] (Fig. 2). SARS-CoV-2 cellular tropism is therefore largely determined by co-expression of ACE2 and TMPRSS2, which is present in cells from multiple tissue origins, including nasal secretory and ciliated cells [74], alveolar epithelial type II cells (AT2s) [75], enterocytes of the small and large intestines [76, 77], proximal tubular cells of the kidney [78], cardiomyocytes [79], and vascular endothelial cells [78, 80–82], suggesting clinical manifestations in the respective organ systems may be at least partially attributed to direct cellular invasion and damage. Though still debated, many have argued that relatively lower expression and distinct distribution pattern of these entry factors in infants and children may confer protection against severe disease [83–86].

Innate immunity as the first line of defense that arbitrates the course of disease

SARS-CoV-2 is encountered by a cascade of innate immune responses in vivo, which are crucial determinants of disease course in children [87–90]. Apart from ACE2 binding, the S protein, along with other viral constituents, may act as pathogen-associated molecular patterns (PAMPs) to activate pattern recognition receptors (PRRs), which drives the production of an array of cytokines that govern responses following the viral infection. Specifically, SARS-CoV-2 proteins, single-stranded genomic RNA, and double-stranded RNA (dsRNA) replication intermediates are sensed by various subtypes of toll-like receptor (TLRs) [91–94], and cytosolic RNA by
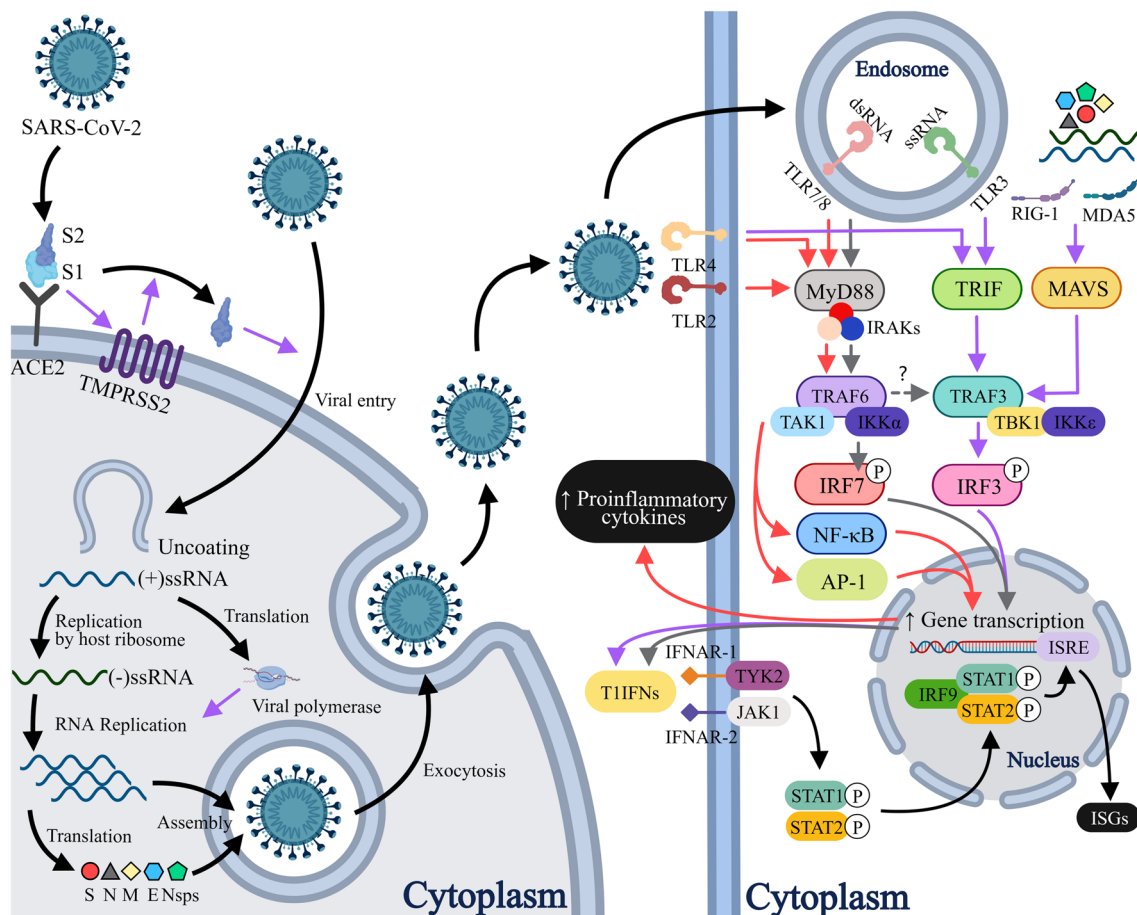
Fig. 2 ACE-2-TMPRSS2-mediated SARS-CoV-2 cell entry and type 1 interferon pathway. SARS-CoV-2-associated molecules are recognized by a wide range of PRRs located in different compartments, including TLR2, 4 and 6 on the plasma membrane, TLR3, 7 and 8 in endosomes, and RIG-1 and MDA-5 in the cytoplasm, each with its respective ligands. Ligand binding causes TLRs to dimerize and instigate the downstream signaling pathways in an MyD88-dependent or TRIF-dependent manner. Activation of TLR2, 4, 7, and 8 recruits the canonical adaptor protein MyD88, which sequentially mobilizes the IRAK complex, TRAF6, and TAK1. TAK1 is then capable of initiating the IKK-NFκB and the MAPK-AP1 pathways, stimulating production of various proinflammatory cytokines. In addition, activation of TLR7 or TLR8 also triggers IRAK, TRAF6, TRAF3, and IKKα-dependent phosphorylation and thus activation of IRF7. Contrarily, TRAF3 may be activated by TRIF recruitment following TLR3 and TLR4 activation, or MAVS recruitment secondary to RIG-1 or MDA5 activation. TRAF3 in turn gives rise to TBK1 and IKKε activation that potentiates IRF3. Both IRF3 and IRF7 act as transcription factors that promote T1IFN gene expression. T1IFNs bind to the heterodimeric IFNAR1/IFNAR2 receptor complex, which triggers the receptor-associated kinases TYK2 and JAK1 to phosphorylate STAT1 and STAT2 proteins. The phosphorylated STAT1 and STAT2 combine with IRF9 to form the ISGF3, which binds to IRSE in the nucleus to upregulate transcription of ISGs, exerting multitudinous antiviral effects. *PPRs* pattern recognition receptors, *ACE2* angiotensin-converting enzyme 2, *TMPRSS2* transmembrane serine protease 2, *(+)/(−)ssRNA* positive-/negative-sense single-stranded ribonucleic acid, *S* spike protein, *N* nucleocapsid protein, *M* membrane protein, *E* envelop protein, *Nsps* non-structural proteins, *dsRNA* double-stranded ribonucleic acid, *TLR* toll-like receptor, *RIG-1* retinoic acid-inducible gene I, *MDA5* melanoma differentiation-associated protein 5, *MyD88* myeloid differentiation primary response factor 88, *IRAKs* interleukin-1 receptor-associated kinases, *TRIF* toll-interleukin-1 receptor-domain-containing adaptor-inducing interferon-β, *MAVS* mitochondrial antiviral signaling protein, *TRAF* tumor necrosis factor receptor-associated factor, *TAK1* transforming growth factor-β activated kinase 1, *IKK* inhibitor of nuclear factor-κB (IκB) kinase, *TBK1* TANK-binding kinase 1, *IRF* interferon regulatory factor, *NF-κB* nuclear factor kappa B, *MAPK* mitogen-activated protein kinase, *AP-1* activator protein 1, *T1IFNs* type 1 interferons, *IFNAR* interferon-alpha receptor, *TYK2* tyrosine kinase 2, *JAK1* Janus kinase, *STAT* signal transducer and activator of transcription, *ISGF3* interferon-stimulated gene factor 3, *ISRE* interferon-sensitive response element

the retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) such as RIG-I and melanoma differentiation-associated gene 5 (MDA-5) [95], which ultimately evoke potent interferon (IFN) responses.

Induction of type I IFNs and, to a lesser extent, type III IFNs constitutes the backbone of innate immunity against SARS-CoV-2, which exerts its far-reaching effects via the JAK/STAT signaling pathway to ultimately mobilize

hundreds of IFN-stimulated genes (ISGs) with a myriad of direct and indirect (i.e., via recruitment of immune cells) anti-viral functions [96, 97] (Fig. 2). Age-associated features such as more robust mucosal IFN response [89, 98], more preformed cytosolic PRRs in cells populating the upper airways [99] and more efficient RIG-1 signaling [100] in the pediatric population are believed to correlate with milder presentation of COVID-19, whereas severe disease could result from blunted type 1 IFN responses [101, 102] as a consequence of in-born defects in type 1 IFN-mediated immunity [103–107], presence of IFN-neutralizing autoantibodies [108–110], and a multitude of inhibitory factors employed by SARS-CoV-2 such as its structural and non-structural proteins and the way it replicates inside enclosed membranes to evade host immune detection [96, 111–113].

Strikingly, around 10% of children hospitalized for COVID-19 pneumonia were found to have complete recessive deficiencies in one of the four type 1 IFN immunity-related molecules [107]. Inappropriate type I/III IFN responses failing to facilitate viral clearance at the point of initial contact, most commonly the upper airway, can precipitate paradoxical hyper-inflammation with delayed but sustained release of type I IFNs down the stream and may be accompanied by unchecked upregulation of pro-inflammatory cytokines that, in turn, mediate the deleterious pulmonary and systemic inflammation seen in severe and critical illnesses [73, 88, 96, 98, 102, 111, 114, 115]. Consequently, the therapeutic values of exogenous IFN formulations for COVID-19 are subject to the timing of administration. Available clinical trials found no added benefits of IFN beta-1a in hospitalized adults [116, 117], while outpatients were protected from emergency department visits and hospital admissions with a dose of pegylated interferon lambda administered within 7 days of symptom onset [118]. Relevant pediatric data are scarce.

Raging hyper-inflammation signifies severe COVID-19

Dysregulated host inflammatory response gains pathogenic dominance over the viral burden itself with COVID-19 disease progression, as evidenced by otherwise no clear correlation between viral load and disease severity, including in the pediatric population [119–121]. In severe/critical COVID-19, complex and intertwined concurrent immunopathological proceedings (Fig. 3) ensue as a result of viral dissemination under the circumstances of waning innate immunity. AT2s, which are made susceptible due to the aforementioned dual ACE2/TMPRSS2 positivity, and other cells succumbing to viral invasion release PAMPs as well as danger-associated molecular patterns (DAMPs), which are hallmarks of cellular stress that elicit various forms of programmed cell death (RCD) [122, 123]. Inflammasomes

are micrometer-level multiprotein signaling complexes that form in the cytoplasm via combining particular nucleotide-binding and oligomerization domain(NOD)-like receptors, a subtype of PRRs, with the respective adaptor molecules, secondary to priming and activation by PAMPs and DAMPs [124]. Inappropriate activation of inflammasomes has been demonstrated to play indispensable roles in linking different compartments of immunity and orchestrating the hyper-inflammatory reaction to SARS-CoV-2, with the decisive endpoint being the caspase-mediated interleukin-1b and interleukin-18 release through cell membrane-spanning pores formed by gasdermin-D oligomerization [125–128] (Fig. 3). Markers of inflammasome activation were indeed found elevated proportionately to disease severity in the sera of critically ill COVID-19 patients [126]. Pyroptosis, a form of inflammatory caspase-dependent RCD evident in as many as 6% of the monocytes in the peripheral blood of COVID-19 patients [129], is another well-recognized eventuality in the context of porous plasma membrane [130] leading to release of large intracellular molecules such as lactate dehydrogenase, which is pathognomonic for pyroptosis and a laboratory parameter of prognostic value in clinical practice [131, 132], as well as further outpouring of inflammatory cytokines and DAMPs, such as high mobility group box 1 [133]. The self-propagating vicious cycle of hyper-inflammation and cell death is thus established and culminates in dire clinical consequences. Systemically, severe COVID-19 can elicit a cytokine profile somewhat similar to that of the cytokine storms secondary to other etiologies [134–136]. Synergism of cytokines such as TNF-α and IFN-γ [137] has been demonstrated to be capable of inducing inflammatory cell death and thus may inflict tissue damage directly to end-organs and perpetuate the vicious cycle.

Features of pediatric adaptive responses in COVID-19

The traits of cellular and humoral immunity specific to children may become apparent when challenged with SARS-CoV-2. Mobilization of T and B cell pathways synchronized with the innate defense in the upper airway in children, thereby preventing severe disease development from viral dissemination [138]. Lymphopenia is a much-feared consequence and indicator of poor prognosis consistently seen in hospitalized, ICU-admitted, and non-surviving COVID-19 patients [139–141], albeit less common in children [15], that may be partly attributed to the plethora of pro-inflammatory cytokines [88, 142, 143]. Nevertheless, adults were found to have stronger CD4+ and CD8+ T cell responses in the acute infective phase, which were proposedly a compensation for the inferior innate responses and, indeed,
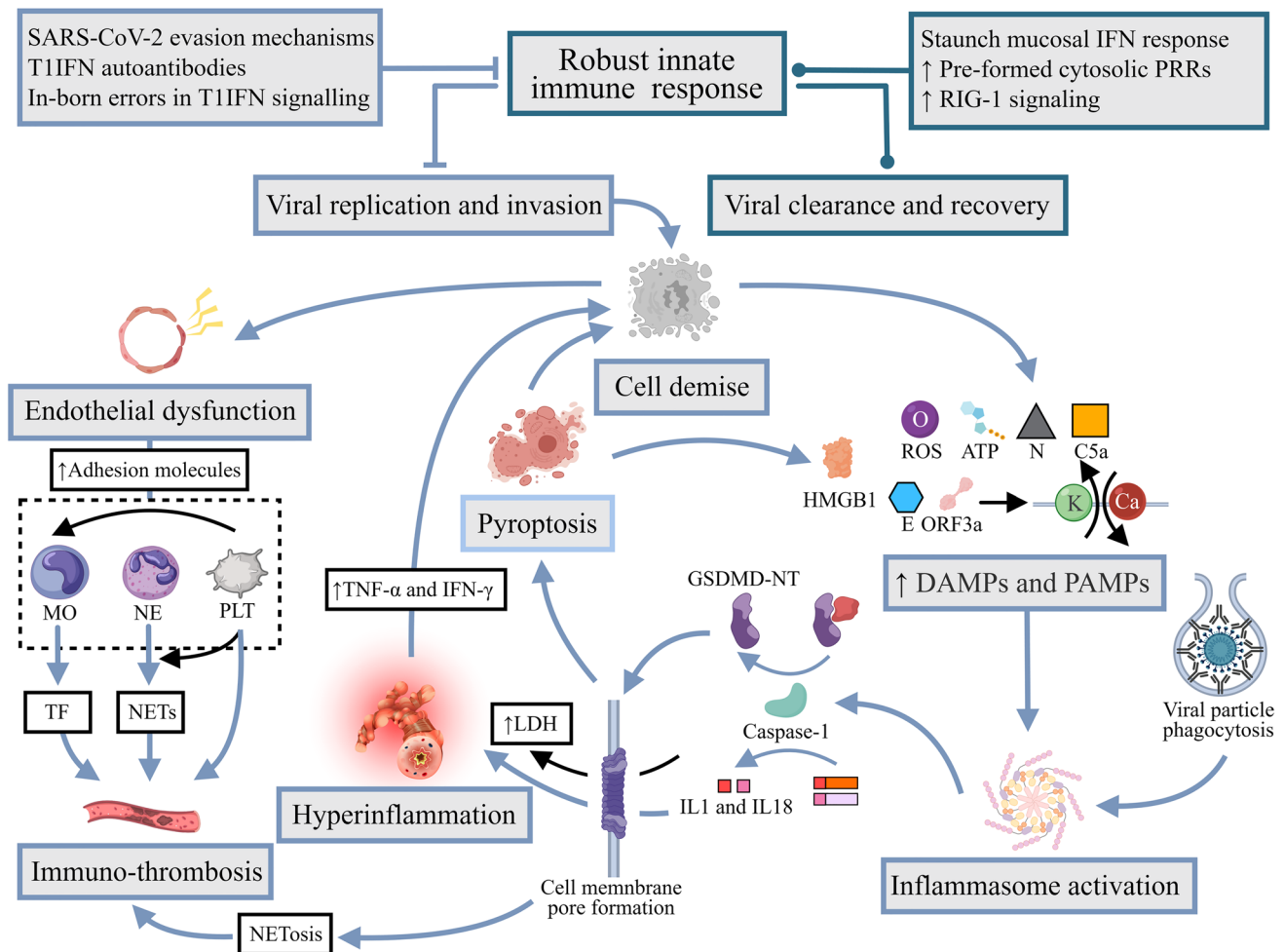
Fig. 3 Hyperinflammation and immunothrombosis in severe COVID-19. Virus-related factors like the N protein and potassium efflux and calcium influx set off by envelope and ORF3a "viroporin" proteins, and host-related factors such as extracellular ATP, complement C5a, ROS, and phagocytosis of antibody-opsonized viral particles into otherwise ACE2⁻ monocytes have all been proposed to trigger assembly of inflammasomes, most notably NLRP3, in myeloid-derived immune cells and pulmonary cells. Inflammasome activation recruits the caspase-1 canonically, which proteolytically potentiates pro-IL-1β and/or pro-IL-18 and concomitantly cleaves GSDMD into NT and CT fragments. GSDMD-NT oligomerization and translocation to plasma membrane create pores through which activated IL-1β and IL-18 can directly enter the extracellular space, mediating hyperinflammation, and simultaneously trigger pyroptosis, leading to LDH and HMGB1 release, among other pro-inflammatory DAMPs. Meanwhile, endothelial dysfunction in the hyperinflammatory milieu initiates immunothrombosis. Adhesion molecules are markers of activated endothelial cells over-expressed in COVID-19 that exhibit strong anchoring effects on monocytes and neutrophils, the former of which reciprocate with active TFs that directly institute the extrinsic coagulation pathway. Conversely, neutrophils may be prompted by direct SARS-CoV-2 entry, SAR-CoV-2-induced ROS generation, complement activation, and/or a self-sustaining loop of IL-8 production to undergo NETosis, defined by the release of large extracellular web-like structures termed NETs, which may also be triggered by the inflammasome/GSDMD pathway in COVID-19. NETs consist of decondensed chromatin embellished with histones and proteins that act as a scaffold for erythrocyte and platelet settling and fibrin deposition, while its constituents exert a range of pro-thrombotic effects with varying mechanisms. Furthermore, circulating platelets adopt a hyperactive state in the context of SARS-CoV-2 infection. Platelets recruited in response to NETs and other stimuli such as vWF on the activated endothelial cells in turn amplify NETosis via secretion of chemokines such as PF4, and may induce further expression of TF by monocytes and complementarily augment monocytic secretion of inflammatory cytokines. *N protein* nucleocapsid protein, *ORF3a* open reading frame 3a, *ATP* adenosine triphosphate, *ROS* reactive oxygen species, *NLRP3* NOD-like receptor containing pyrin domain 3, *IL-1β* interleukin-1β, *IL-18* interleukin-18, *GSDMD* gasdermin-D, *NT* N-terminal, *CT* C-terminal, *LDH* lactate dehydrogenase, *HMGB1* high mobility group box 1, *DAMPs* damage-associated molecular patterns, *TF* transcription factor, *IL-8* interleukin-8, *NETs* neutrophil extracellular traps, *vWF* von Willebrand Factor, *PF4* platelet factor 4

did not lead to favorable outcomes [98, 144, 145]. By the same token, some studies have shown that SARS-CoV-2 invokes a less vigorous antibody response in children that was restricted to S protein-specific IgG production, as opposed to anti-S IgM, IgG, and IgA as well as antibody formation against other viral proteins in adults [146–148]. Otherwise, there have been mixed results regarding the neutralizing activity of SARS-CoV-2-specific immunoglobulins derived from children [144, 149, 150], although they are generally longer lasting than their adult counterparts, offering protection from re-infection for months and beyond [147, 149, 151, 152].

Devastating cross-talk of the inflammatory and coagulation pathways

In the lungs, the highly inflammatory alveolar microenvironment is the harbinger of alveolar epithelial injury and dysfunction, supported by transcriptomic evidence of AT2 and AT1 exhaustion and demise in fatal COVID-19 [153–155]. The resultant denudation of the alveolar basement membrane and exposure of the underlying endothelial cells to the detrimental cocktail of hypoxia, viral content, apoptotic and necrotic debris, immune cells, cytokines, and chemokines trigger their activation, transformation to a leaky state due to cytoskeleton and intercellular junction alterations [156], and potentially direct cell death that, in combination with the increased epithelial permeability, precipitates leukocyte extravasation and accumulation of the proteinaceous edema characteristic of ARDS [73, 157].

In the meantime, loss of the usual quiescent endothelial cell phenotype under the influence of cytokine overdrive ignites the sophisticated and incompletely understood interplay between the immune and hemostatic mediators in an attempt to limit the spread of the pathogen that ultimately leads to the micro- and macro-thrombus formation frequently observed in severe/critical COVID-19 [158–161], as alveolar capillary microthrombi are found to be close to 10 times as prevalent in patients who died of COVID as in those who died of ARDS following H1N1 influenza [162]. The injurious positive feedback loop of immunothrombosis, which may notably involve NETosis [163, 164] (Fig. 3), eventually gives rise to the formation of the pathognomonic alveolar hyaline membranes in ARDS [157, 165]. The fibrin-rich exudates may significantly compromise the alveolar-capillary interface for gas exchange, resulting in the profound refractory hypoxemia seen in respiratory failure secondary to severe/critical COVID-19 [73, 165].

Similarly, there are evidently increased incidences of pulmonary emboli [166, 167], thrombosis, and angiopathy of the microvasculature that may contribute to multi-organ failure [168, 169], and extrapulmonary arterial and venous thromboembolic phenomena in adults [170, 171], and to a lesser degree, in children and adolescents with COVID-19, where nine (2.1%) of the 426 hospitalized pediatric patients with symptoms developed thrombotic events across seven children's hospitals in the US [172]. Therefore, thrombo-inflammatory markers such as D-dimer are the most common abnormal laboratory findings in adult and pediatric COVID-19 [173], and may be predictive of disease course [174, 175].

MIS-C, a riddle unresolved

Since the emergence of SARS-CoV-2, surges in MIS-C cases appear to aggregate 3–6 weeks following peak incidences of COVID-19 cases in a heavily affected locale and whose symptomology bears resemblance to but is distinct from Kawasaki disease (KD), toxic shock syndrome (TSS), and macrophage activation syndrome (MAS) [176–178] (Fig. 1). MIS-C may share clinical features of KD including sustained high fevers, conjunctivitis, diffuse non-vesicular erythematous rash, and dry and cracked lips, but clearly diverges from KD in that it (1) is more frequently reported in older children of non-Asian descent with an average age of 9 years, no apparent gender bias, and an overall mortality rate of 2%, and increased age may be associated with risks of ICU admissions [12, 13], which are required for up to 65%–70% of all cases[179–181]; (2) has a markedly high rate of gastrointestinal (GI) tract (80%) and neurological involvement [11, 182], and cardiac manifestations as discussed but less likelihood of developing severe or persistent coronary artery aneurysms [10, 53, 55, 183, 184]; and (3) is notably associated with ferritinemia in severe disease and thrombocytopenia [185, 186].

Although there are commonalities of shock, multiorgan failure, endothelial damage and coagulopathy, neutrophilia, lymphocytopenia, elevated inflammatory markers between severe/critical pediatric COVID-19 and MIS-C, the latter is less likely to have primary respiratory implications and mostly arise in otherwise healthy children and adolescents devoid of major pre-existing co-morbidities who have already seroconverted with IgG predominance at time of MIS-C diagnosis and mild to no symptoms on initial infection or exposure [187]. MIS-C also carries distinguishing cytokine signatures including enrichment of the type II interferon (IFN-γ) and the downstream effector molecules [115, 188–192] that may explain its homogeneous features with MAS. Admittedly, the immunological landscape of MIS-C appears rather complex and only partially defined, and there has not been a unifying pathophysiological blueprint to account for the manifold stigmata of MIS-C, but much progress has been

made in delineating the nuances in immunophenotypes that may shed light on their similarities and differences to other systemic inflammatory syndromes.

Given the overlaps between MIS-C with TSS, which has bacterial superantigens as the unequivocal trigger [193], and detection of SARS-CoV-2 in various organs on autopsy of patients who died of MIS-C [194], it is reasonable to hypothesize that SARS-CoV-2 proteins may possess superantigenic properties that set off the hyper-inflammatory response in MIS-C, where computational analysis has indeed identified a sequence motif exclusive to SARS-CoV-2 S protein capable of T cell activation that shows striking structural similarity to a segment of the staphylococcal enterotoxin B, the culprit responsible for TSS [195, 196]. The definitive reservoir of superantigens in MIS-C, however, has not yet been found, given the varied nasopharyngeal RT-PCR positivity status in MIS-C cases [197]. In accordance with the prominent gastrointestinal complaints in MIS-C, persistence of SARS-CoV-2 in the GI tract [198, 199] and subsequently the compromise to the intestinal barrier integrity have been posited as a potential route of antigenic entry and dissemination, as evidenced by elevation of enterocyte damage [200] and intestinal permeability [201] and inflammation [202] makers in MIS-C children, although studies have yielded conflicting results on whether antigenemia is present in most cases of MIS-C [115, 201, 203]. Moreover, numerous groups have unanimously demonstrated a phenomenon typical of superantigenic stimulation where, similar to TSS, MIS-C is characterized by extensive polyclonal proliferation of a specific T cell receptor (TCR) β-chain variable domain subset, namely TRBV11-2 in MIS-C [115, 200, 201, 204–207], and de-escalation of the expansion appears to coincide with abatement in inflammatory cytokine levels and clinical improvement with therapy, especially after glucocorticoid administration [115, 205], further supporting the potential roles of TRBV11-2-expressing T cells in pathogenesis. On the contrary, many studies have detected autoantibodies against endothelial, cardiac, gastrointestinal, and immune antigens [207–210] in MIS-C as the alternative pathogenic mediators that may provoke damage to the respective organ systems, although intravenous immunoglobulin therapies may be a confounding factor [115, 211].

In addition, several genetic predispositions have been identified for MIS-C including the specific combination of HLA class I alleles A02, B35, C04 that is associated with TRBV11-2 expansion [115, 204], albeit not supported by findings of many groups [200, 205, 206] possibly due to differing ethnic compositions of the study populations, as well as flaws in down-regulators of inflammation such as an autosomal recessive defect in the OAS-Rnase L pathway, which normally disposes of the cytosolic dsRNA that can stimulate production of pro-inflammatory cytokines [212], and nonsynonymous mutations in XIAP, CYBB and SOCS1 genes [213]. Ongoing immune profiling efforts are underway to advance mechanistic understanding of this perplexing disease entity, as with many other inflammatory conditions, through which more universally applicable insights may also be generated into the broader immune system as a whole.

Management, prognosis, and long-term sequelae

Fortunately, COVID-19 in the vast majority of children is self-limiting and would not qualify for treatment other than supportive care and symptomatic management until spontaneous resolution, and although pediatric clinical trial data are lacking, the number needed to treat for therapeutic benefits is considered to be higher in children than in adults [214].

Several pharmacological agents are available to reduce the risk of progression to severe disease in vulnerable outpatients, should the potential benefits be deemed to outweigh the risks. Paxlovid, a combination medication of nirmatrelvir and ritonavir available in oral formulations that can be conveniently taken in the outpatient setting, has been demonstrated in the cornerstone phase III trial involving 1219 adults at-risk for severe disease to have an astonishing 89% risk reduction in COVD-19-related hospitalizations or deaths if administered within 3 days of symptom onset [215]. Paxlovid appears still highly effective in the time of Omicron preeminence [216], but has only been authorized by the US Food and Drug Administration (FDA) for use in children aged 12 years or older and weighing 40 kg or greater, and is limited by its extensive interactions with other medications due to ritonavir being a potent CYP3A inhibitor [217]. Alternatively, remdesivir represents the sole FDA-authorized agent for prevention of disease progression in the community setting for at-risk and mildly to moderately symptomatic children with at least 28 days of age and a weight of at least 3 kg, with the logistical caveat of requiring intravenous dosage delivery on 3 consecutive days [218]. In contrast, clinical decisions regarding inpatient management of severe COVID-19-related diseases in children are not infrequently extrapolated from adult guidelines and made on a case-by-case basis given the scarcity of large-scale randomized controlled trials in the pediatric population from which evidence-based recommendations can be derived [16, 219, 220].

Despite the generally favorable outcomes even in the critically ill children [221], the full picture of the long-term impacts of COVID-19 on pediatric health may not be readily apparent at this stage given the recency of the pandemic. The term long COVID, sometimes also referred to as post-acute sequelae of COVID-19, has been coined as the diagnosis of exclusion to encompass the constellation of complaints after the acute stage of COVID-19 has

settled [222]. One or more persistent symptoms are reported in 16.2% of children for 3 months or greater post-infection as estimated by a recently published meta-analysis [223]. Some of the most commonly reported symptoms range from persistent sore throat, fever, dyspnea, anosmia/ageusia, muscle weakness, and coughs to various vague and largely non-localizing neuropsychiatric troubles, including fatigue, mood and sleep disturbances, and mental dysfunction [223–226], seemingly so heterogeneous that categorizations in clinical phenotypes of diverse pathogenesis for subgroup analysis may be advisable [227]. Children with less than 5 years of age, underlying comorbidities, or admission to ICU during the acute phase of disease are found to be especially susceptible [228], but symptomatic or asymptomatic non-hospitalized patients are not precluded from developing the condition [223]. Of note, among the several pathophysiological hypotheses that have been put forward for long COVID are viral persistence [229], autoimmunity [230], endothelial dysfunction with microcirculation thrombosis [231, 232], and immune dysregulation with potential reactivation of latent viral infections such as Epstein-Barr virus and herpesviruses given the shared features with myalgic encephalomyelitis/chronic fatigue syndrome and dysautonomia including orthostatic intolerance and profound fatigue [233–235]. The rather limited understanding of long COVID at this point in time has prompted well-coordinated systematic research undertakings such as the RECOVER initiative to comprehensively delineate the disease, which notably has a branch of effort dedicated to children and young people [236].

Expert opinion and conclusions

Various measures can be implemented at different stages to minimize adverse outcomes associated with severe COVID-19 in children. Vaccination proves to be effective in reducing severe disease development and should be administered as per protocol, if not contraindicated.

Red flags for deterioration should be recognized and attended to without delay, especially in children with predisposing comorbidities. Management of severe disease should generally observe a holistic approach to account for the multi-system manifestations, where emphases are placed on airway and respiratory status optimization, hemodynamic support, modulation of the detrimental hyperinflammatory response, addressing the comorbid conditions and superinfections if any, and preservation of organ functions.

The contrasting susceptibilities and responses to SARS-CoV-2 and the variations in the disease course are, to a great extent, an attestation of the monumental differences in the ways pediatric and adult immune systems are

programmed to resist a highly immunogenic viral threat. In conjunction with protective antibodies with longer lifespans and lower expression of SARS-CoV-2 entry factors, a swiftly induced T1IFN response of the optimal magnitude at the mucosal surface and upper airway serves as a powerful protective barrier for children against viral spread, consequently mitigating the risk of severe COVID-19, which may see indiscriminate firing of various proinflammatory apparatuses such as inflammasomes and NETs. Further research on severe pediatric COVID-19 and relevant conditions such as MIS-C and long COVID remains of scientific and clinical significance, as it offers a novel viewpoint for deciphering the age-specific characteristics of immunity. With ongoing intermittent outbreaks, clinicians must remain vigilant of the telltale signs of deterioration, especially in those children at risk, and rationalize the use of therapeutic measures for the best outcome, although more pediatric-specific clinical trials are required before recommendations with high level of evidence can be made, as unsuspecting application of findings in adult studies to pediatric patients is a fundamentally unscientific practice that disregards the unique qualities of pediatric immunity and physiology. Additionally, rapidly evolving SARS-CoV-2 strains and the immunological memory that has formed along the way will only make it more difficult to interpret earlier studies. In more general terms, the collective knowledge gained from the COVID-19 pandemic serves as a methodological construct for better understanding of and responding to similar communicable diseases with heavy pediatric disease burdens, such as influenza and mycoplasma pneumonia, as well as existing and emerging pathogens with pandemic potential.

Declarations

be received from any party related directly or indirectly to the subject of this article. The authors declared no conflicts of interest.

Ethical approval This study did not involve the participation of human or animal subjects, and, therefore, was exempt from formal assessment by the ethics committee for clinical research of our center.

References

1. Woodruff RC, Campbell AP, Taylor CA, Chai SJ, Kawasaki B, Meek J, et al. Risk factors for severe COVID-19 in children. Pediatrics. 2022;149:e2021053418.
2. Kompaniyets L, Bull-Otterson L, Boehmer TK, Baca S, Alvarez P, Hong K, et al. Post-COVID-19 symptoms and conditions among children and adolescents—United States, March 1, 2020-January 31, 2022. MMWR Morb Mortal Wkly Rep. 2022;71:993–9.
3. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145:e20200702.
4. Bhuiyan MU, Stiboy E, Hassan MZ, Chan M, Islam MS, Haider N, et al. Epidemiology of COVID-19 infection in young children under five years: A systematic review and meta-analysis. Vaccine. 2021;39:667–77.
5. Otto WR, Geoghegan S, Posch LC, Bell LM, Coffin SE, Sammons JS, et al. The epidemiology of severe acute respiratory syndrome coronavirus 2 in a pediatric healthcare network in the United States. J Pediatric Infect Dis Soc. 2020;9:523–9.
6. Pierce CA, Herold KC, Herold BC, Chou J, Randolph A, Kane B, et al. COVID-19 and children. Science. 2022;377:1144–9.
7. Blatz AM, Randolph AG. Severe COVID-19 and multisystem inflammatory syndrome in children in children and adolescents. Crit Care Clin. 2022;38:571–86.
8. Delahoy MJ, Ujamaa D, Taylor CA, Cummings C, Anglin O, Holstein R, et al. Comparison of influenza and coronavirus disease 2019-associated hospitalizations among children younger than 18 years old in the United States: FluSurv-NET (October-April 2017–2021) and COVID-NET (October 2020-September 2021). Clin Infect Dis. 2023;76:e450–9.
9. Hamid S, Woodworth K, Pham H, Milucky J, Chai SJ, Kawasaki B, et al. COVID-19-Associated Hospitalizations Among U.S. Infants Aged <6 Months - COVID-NET, 13 States, June 2021-August 2022. MMWR Morb Mortal Wkly Rep. 2022;71:14422–8.
10. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA. 2021;325:1074–87.
11. LaRovere KL, Riggs BJ, Poussaint TY, Young CC, Newhams MM, Maamari M, et al. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol. 2021;78:536–47.
12. Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health. 2021;5:323–31.
13. Merckx J, Cooke S, El Tal T, Bitnun A, Morris SK, Yeh EA, et al. Predictors of severe illness in children with multisystem inflammatory syndrome after SARS-CoV-2 infection: a multi-centre cohort study. CMAJ. 2022;194:E513–23.
14. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr. 2020;16:223–31.
15. Cui X, Zhao Z, Zhang T, Guo W, Guo W, Zheng J, et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). J Med Virol. 2021;93:1057–69.
16. Irfan O, Muttalib F, Tang K, Jiang L, Lassi ZS, Bhutta Z. Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis. Arch Dis Child. 2021;106:440–8.
17. Choi JH, Choi SH, Yun KW. Risk factors for severe COVID-19 in children: a systematic review and meta-analysis. J Korean Med Sci. 2022;37: e35.
18. Antoon JW, Grijalva CG, Thurm C, Richardson T, Spaulding AB, Teufel RJ 2nd, et al. Factors associated with COVID-19 disease severity in US children and adolescents. J Hosp Med. 2021;16:603–10.
19. Druzak S, Iffrig E, Roberts BR, Zhang T, Fibben KS, Sakurai Y, et al. Multiplatform analyses reveal distinct drivers of systemic pathogenesis in adult versus pediatric severe acute COVID-19. Nat Commun. 2023;14:1638.
20. Harwood R, Yan H, Talawila Da Camara N, Smith C, Ward J, Tudur-Smith C, et al. Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: A systematic review and individual patient meta-analysis. EClinicalMedicine. 2022;44:101287.
21. Piechotta V, Siemens W, Thielemann I, Toews M, Koch J, Vygen-Bonnet S, et al. Safety and effectiveness of vaccines against COVID-19 in children aged 5–11 years: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2023;7:379–91.
22. Cohen-Stavi CJ, Magen O, Barda N, Yaron S, Peretz A, Netzer D, et al. BNT162b2 vaccine effectiveness against omicron in children 5 to 11 years of age. N Engl J Med. 2022;387:227–36.
23. Powell AA, Kirsebom F, Stowe J, McOwat K, Saliba V, Ramsay ME, et al. Effectiveness of BNT162b2 against COVID-19 in adolescents. Lancet Infect Dis. 2022;22:581–3.
24. Fowlkes AL, Yoon SK, Lutrick K, Gwynn L, Burns J, Grant L, et al. Effectiveness of 2-Dose BNT162b2 (Pfizer BioNTech) mRNA vaccine in preventing SARS-CoV-2 infection among children aged 5–11 years and adolescents aged 12–15 years—PROTECT Cohort, July 2021-February 2022. MMWR Morb Mortal Wkly Rep. 2022;71:422–8.
25. Dorabawila V, Hoefer D, Bauer UE, Bassett MT, Lutterloh E, Rosenberg ES. Effectiveness of the BNT162b2 vaccine among children 5–11 and 12–17 years in New York after the Emergence of the Omicron Variant. medRxiv. 2022:2022.02.25.22271454.
26. National Institutes of Health. Special Considerations in People Who Are Immunocompromised. [Available from: https://www.covid19treatmentguidelines.nih.gov/special-populations/immunocompromised/.
27. General Office of the National Health Commission, General Division of the State Administration of Traditional Chinese

Medicine. Diagnosis and Treatment Plans for SARS-CoV-2 (Tentative 10th Edition). 2023. Available from: https://www.gov.cn/zhengce/zhengceku/2023-01/06/5735343/files/5844ce04246b431dbd322d8ba10afb48.pdf. Accessed 29 June, 2023.

28. National Institutes of Health. Clinical Spectrum of SARS-CoV-2 Infection. COVID-19 Treatment Guidelines. Updated March 6, 2023. Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. Accessed 29 June 2023.

29. Fisler G, Izard SM, Shah S, Lewis D, Kainth MK, Hagmann SHF, et al. Characteristics and risk factors associated with critical illness in pediatric COVID-19. Ann Intensive Care. 2020;10:171.

30. Fuller CC, Cosgrove A, Shinde M, Rosen E, Haffenreffer K, Hague C, et al. Treatment and care received by children hospitalized with COVID-19 in a large hospital network in the United States, February 2020 to September 2021. PLoS ONE. 2023;18:e0288284.

31. Chen Y, Li L, Wang C, Zhang Y, Zhou Y. Necrotizing pneumonia in children: early recognition and management. J Clin Med. 2023;12:2256.

32. Akuamoah Boateng G, Ristagno EH, Levy E, Kahoud R, Thacker PG, Setter DO, et al. A complicated presentation of pediatric COVID-19 with necrotizing pneumonia and pulmonary artery pseudoaneurysms. Pediatr Pulmonol. 2021;56:4042–4.

33. Brisca G, Buratti S, Basso L, Miano M, Salvati P, Castagnola E, Moscatelli A. Necrotizing pneumonia and severe COVID-19 in an infant with catheter-related bloodstream infection by methicillin-sensitive *Staphylococcus aureus*. Pediatr Int. 2023;65: e15401.

34. Brewster RC, Parsons C, Laird-Gion J, Hilker S, Irwin M, Sommerschield A, et al. COVID-19-associated croup in children. Pediatrics. 2022;149:e2022056492.

35. Iijima H, Kubota M, Ogimi C. Clinical characteristics of pediatric patients with COVID-19 between Omicron era vs. pre-Omicron era. J Infect Chemother. 2022;28:1501–5.

36. Choi YY, Kim YS, Lee SY, Sim J, Choe YJ, Han MS. Croup as a manifestation of SARS-CoV-2 omicron variant infection in young children. J Korean Med Sci. 2022;37:e140.

37. Kamali Aghdam M, Shabani Mirzaee H, Eftekhari K. Croup is one of the clinical manifestations of novel coronavirus in children. Case Rep Pulmonol. 2021;2021:8877182.

38. Cassedy EA, Kim S, Silver AH. An unexpected cause of croup in a pediatric patient. Clin Pediatr. 2021;60:574–6.

39. Park S, You J, Lee J, Park E. Two case reports of life-threatening croup caused by the sARS-CoV-2 omicron BA.2 variant in pediatric patients. J Korean Med Sci. 2022;37: e192.

40. Tzotzos SJ, Fischer B, Fischer H, Zeitlinger M. Incidence of ARDS and outcomes in hospitalized patients with COVID-19: a global literature survey. Crit Care. 2020;24:516.

41. Derespina KR, Kaushik S, Plichta A, Conway EE Jr, Bercow A, Choi J, et al. Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York City. J Pediatr. 2020;226:55-63.e2.

42. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò Carducci FI, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020;4:653–61.

43. Chao JY, Derespina KR, Herold BC, Goldman DL, Aldrich M, Weingarten J, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 at a Tertiary Care Medical Center in New York City. J Pediatr. 2020;223:14-9.e2.

44. Khemani RG, Smith LS, Zimmerman JJ, Erickson S. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16:S23-40.

45. Sarkar M, Das B, Mahapatra MK, Roychowdhoury S, Das S, Konar MC. A retrospective analysis of clinical manifestations, management and outcome of acute respiratory distress syndrome associated with coronavirus disease-2019 infection in children. Indian J Crit Care Med. 2022;26:331–8.

46. Garau G, Joachim S, Duliere GL, Melissopoulou M, Boccar S, Fraipont V, et al. Sudden cardiogenic shock mimicking fulminant myocarditis in a surviving teenager affected by severe acute respiratory syndrome coronavirus 2 infection. ESC Heart Fail. 2021;8:766–73.

47. Raymond TT, Das A, Manzuri S, Ehrett S, Guleserian K, Brenes J. Pediatric COVID-19 and pericarditis presenting with acute pericardial tamponade. World J Pediatr Congenit Heart Surg. 2020;11:802–4.

48. Trogen B, Gonzalez FJ, Shust GF. COVID-19-associated myocarditis in an adolescent. Pediatr Infect Dis J. 2020;39:e204–5.

49. Gnecchi M, Moretti F, Bassi EM, Leonardi S, Totaro R, Perotti L, et al. Myocarditis in a 16-year-old boy positive for SARS-CoV-2. Lancet. 2020;395:e116.

50. Kesici S, Aykan HH, Orhan D, Bayrakci B. Fulminant COVID-19-related myocarditis in an infant. Eur Heart J. 2020;41:3021.

51. Chochkova-Bukova LA, Funken D, Bukova M, Genova KZ, Ali S, Stoencheva S, et al. Cardiac MRI with late gadolinium enhancement shows cardiac involvement 3–6 months after severe acute COVID-19 similar to or worse than PIMS. Front Cardiovasc Med. 2023;10:1115389.

52. Jone PN, John A, Oster ME, Allen K, Tremoulet AH, Saarel EV, et al. SARS-CoV-2 infection and associated cardiovascular manifestations and complications in children and young adults: a scientific statement from the American Heart Association. Circulation. 2022;145:e1037–52.

53. Valverde I, Singh Y, Sanchez-de-Toledo J, Theocharis P, Chikermane A, Di Filippo S, et al. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 Infection in Europe. Circulation. 2021;143:21–32.

54. Dolhnikoff M, Ferreira Ferranti J, de Almeida Monteiro RA, Duarte-Neto AN, Soares Gomes-Gouvêa M, Viu Degaspare N, et al. SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome. Lancet Child Adolesc Health. 2020;4:790–4.

55. Grimaud M, Starck J, Levy M, Marais C, Chareyre J, Khraiche D, et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care. 2020;10:69.

56. Ray STJ, Abdel-Mannan O, Sa M, Fuller C, Wood GK, Pysden K, et al. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study. Lancet Child Adolesc Health. 2021;5:631–41.

57. Siracusa L, Cascio A, Giordano S, Medaglia AA, Restivo GA, Pirrone I, et al. Neurological complications in pediatric patients with SARS-CoV-2 infection: a systematic review of the literature. Ital J Pediatr. 2021;47:123.

58. de Miranda Henriques-Souza AM, de Melo A, de Aguiar Coelho Silva Madeiro B, Freitas LF, Sampaio Rocha-Filho PA, Gonçalves FG. Acute disseminated encephalomyelitis in a COVID-19 pediatric patient. Neuroradiology. 2021;63:141–5.

59. Akçay N, Bektaş G, Menentoğlu ME, Oğur M, Sofuoğlu A, Palabiyik FB, Şevketoğlu E. COVID-19-associated acute disseminated encephalomyelitis-like disease in 2 children. Pediatr Infect Dis J. 2021;40:e445–50.

60. McLendon LA, Rao CK, Da Hora CC, Islamovic F, Galan FN. Post–COVID-19 Acute disseminated encephalomyelitis in a 17-month-old. Pediatrics. 2021;147:e2020049678.

61. Lindan CE, Mankad K, Ram D, Kociolek LK, Silvera VM, Boddaert N, et al. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. The Lancet Child & Adolescent Health. 2021;5:167–77.

62. Curtis M, Bhumbra S, Felker MV, Jordan BL, Kim J, Weber M, Friedman ML. Guillain-Barré syndrome in a child with COVID-19 infection. Pediatrics. 2021;147:e2020015115.

63. Orak SA, Kubur Ç, Atasever AK, Polat M. Two case reports and a literature review of typical GBS and rare GBS variants associated with COVID-19. Arch Pediatr. 2023;30:236–9.

64. Gomes I, Karmirian K, Oliveira JT, Pedrosa CdSG, Mendes MA, Rosman FC, et al. SARS-CoV-2 infection of the central nervous system in a 14-month-old child: a case report of a complete autopsy. Lancet Reg Health Am. 2021;2:100046.

65. Lin X, Wang Y, Li X, Abdalla M, Zhang F, Dong C, et al. Acute necrotizing encephalopathy in children with COVID-19: a retrospective study of 12 cases. Front Neurol. 2023;14:1184864.

66. Wu D, Zheng Y, Li Y, Peng M, Lin H, Wang K. Exploring the molecular and clinical spectrum of COVID-19-related acute necrotizing encephalopathy in three pediatric cases. J Hum Genet. 2023;68:769–75.

67. Lin J-J, Tu Y-F, Chen S-J, Kuo Y-T, Jeng M-J, Hsin-Ju Ko M, Chiu C-H. Fatal fulminant cerebral edema in six children with SARS-CoV-2 omicron BA.2 infection in Taiwan. J Pediatric Infect Dis Society. 2022;12:99–103.

68. Botre A, Otiv M, Parekar A. Acute fulminant cerebral edema presenting as refractory status epilepticus in a SARS-CoV-2 PCR-positive child without pulmonary involvement. Indian J Pediatr. 2023;90:529.

69. Hoffmann M, Kleine-Weber H, Pöhlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol Cell. 2020;78:779-84.e5.

70. Markus Hoffmann HKW, Schroeder S, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:1–10.

71. Benton DJ, Wrobel AG, Xu P, Roustan C, Martin SR, Rosenthal PB, et al. Receptor binding and priming of the spike protein of SARS-CoV-2 for membrane fusion. Nature. 2020;588:327–30.

72. Peacock TP, Goldhill DH, Zhou J, Baillon L, Frise R, Swann OC, et al. The furin cleavage site in the SARS-CoV-2 spike protein is required for transmission in ferrets. Nat Microbiol. 2021;6:899–909.

73. Lamers MM, Haagmans BL. SARS-CoV-2 pathogenesis. Nat Rev Microbiol. 2022;20:270–84.

74. Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med. 2020;26:681–7.

75. Huang J, Hume AJ, Abo KM, Werder RB, Villacorta-Martin C, Alysandratos KD, et al. SARS-CoV-2 infection of pluripotent stem cell-derived human lung alveolar type 2 cells elicits a rapid epithelial-intrinsic inflammatory response. Cell Stem Cell. 2020;27:962-73.e7.

76. Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z, et al. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. Gut. 2020;69:1010–8.

77. Zang R, Castro MFG, McCune BT, Zeng Q, Rothlauf PW, Sonnek NM, et al. TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. Sci Immunol. 2020;5:eabc3582.

78. Jansen J, Reimer KC, Nagai JS, Varghese FS, Overheul GJ, de Beer M, et al. SARS-CoV-2 infects the human kidney and drives fibrosis in kidney organoids. Cell Stem Cell. 2022;29:217-31.e8.

79. Yang J, Chen T, Zhou Y. Mediators of SARS-CoV-2 entry are preferentially enriched in cardiomyocytes. Hereditas. 2021;158:4.

80. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. The Lancet. 2020;395:1417–8.

81. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell. 2020;181:905-13.e7.

82. Kumar A, Narayan RK, Kumari C, Faiq MA, Kulandhasamy M, Kant K, Pareek V. SARS-CoV-2 cell entry receptor ACE2 mediated endothelial dysfunction leads to vascular thrombosis in COVID-19 patients. Med Hypotheses. 2020;145:110320.

83. Zhang Z, Guo L, Huang L, Zhang C, Luo R, Zeng L, et al. Distinct disease severity between children and older adults with coronavirus disease 2019 (COVID-19): impacts of ace2 expression, distribution, and lung progenitor cells. Clin Infect Dis. 2021;73:e4154–65.

84. Silva MG, Falcoff NL, Corradi GR, Di Camillo N, Seguel RF, Tabaj GC, et al. Effect of age on human ACE2 and ACE2-expressing alveolar type II cells levels. Pediatr Res. 2023;93:948–52.

85. Muus C, Luecken MD, Eraslan G, Sikkema L, Waghray A, Heimberg G, et al. Single-cell meta-analysis of SARS-CoV-2 entry genes across tissues and demographics. Nat Med. 2021;27:546–59.

86. Schuler BA, Habermann AC, Plosa EJ, Taylor CJ, Jetter C, Negretti NM, et al. Age-determined expression of priming protease TMPRSS2 and localization of SARS-CoV-2 in lung epithelium. J Clin Invest. 2021;131:e140766.

87. Chou J, Thomas PG, Randolph AG. Immunology of SARS-CoV-2 infection in children. Nat Immunol. 2022;23:177–85.

88. Diamond MS, Kanneganti TD. Innate immunity: the first line of defense against SARS-CoV-2. Nat Immunol. 2022;23:165–76.

89. Pierce CA, Sy S, Galen B, Goldstein DY, Orner E, Keller MJ, et al. Natural mucosal barriers and COVID-19 in children. JCI Insight. 2021;6:e148694.

90. Rotulo GA, Palma P. Understanding COVID-19 in children: immune determinants and post-infection conditions. Pediatr Res. 2023;94:434–42.

91. Zheng M, Karki R, Williams EP, Yang D, Fitzpatrick E, Vogel P, et al. TLR2 senses the SARS-CoV-2 envelope protein to produce inflammatory cytokines. Nat Immunol. 2021;22:829–38.

92. Aboudounya MM, Heads RJ. COVID-19 and toll-like receptor 4 (TLR4): SARS-CoV-2 may bind and activate TLR4 to increase ACE2 expression, facilitating entry and causing hyperinflammation. Mediators Inflamm. 2021;2021:8874339.

93. Bortolotti D, Gentili V, Rizzo S, Schiuma G, Beltrami S, Strazzabosco G, et al. TLR3 and TLR7 RNA sensor activation during SARS-CoV-2 infection. Microorganisms. 2021;9:1820.

94. Zhao Y, Kuang M, Li J, Zhu L, Jia Z, Guo X, et al. SARS-CoV-2 spike protein interacts with and activates TLR41. Cell Res. 2021;31:818–20.

95. Thorne LG, Reuschl A-K, Zuliani-Alvarez L, Whelan MVX, Turner J, Noursadeghi M, et al. SARS-CoV-2 sensing by RIG-I and MDA5 links epithelial infection to macrophage inflammation. EMBO J. 2021;40:e107826.

96. Kim Y-M, Shin E-C. Type I and III interferon responses in SARS-CoV-2 infection. Exp Mol Med. 2021;53:750–60.

97. Lazear HM, Schoggins JW, Diamond MS. Shared and Distinct Functions of Type I and Type III Interferons. Immunity. 2019;50:907–23.

98. Yoshida M, Worlock KB, Huang N, Lindeboom RGH, Butler CR, Kumasaka N, et al. Local and systemic responses to SARS-CoV-2 infection in children and adults. Nature. 2022;602:321–7.

99. Loske J, Röhmel J, Lukassen S, Stricker S, Magalhães VG, Liebig J, et al. Pre-activated antiviral innate immunity in the upper airways controls early SARS-CoV-2 infection in children. Nat Biotechnol. 2022;40:319–24.

100. Molony RD, Nguyen JT, Kong Y, Montgomery RR, Shaw AC, Iwasaki A. Aging impairs both primary and secondary RIG-I signaling for interferon induction in human monocytes. Sci Signal. 2017;10:eaan2392.

101. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science. 2020;369:718–24.

102. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Møller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell. 2020;181:1036-45.e9.

103. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science. 2020;370:eabd4570.

104. Asano T, Boisson B, Onodi F, Matuozzo D, Moncada-Velez M, Maglorius Renkilaraj MRL, et al. X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19. Sci Immunol. 2021;6:eabl4348.

105. Abolhassani H, Landegren N, Bastard P, Materna M, Modaresi M, Du L, et al. Inherited IFNAR1 deficiency in a child with both critical COVID-19 pneumonia and multisystem inflammatory syndrome. J Clin Immunol. 2022;42:471–83.

106. van der Made CI, Simons A, Schuurs-Hoeijmakers J, van den Heuvel G, Mantere T, Kersten S, et al. Presence of genetic variants among young men with severe COVID-19. JAMA. 2020;324:663–73.

107. Zhang Q, Matuozzo D, Le Pen J, Lee D, Moens L, Asano T, et al. Recessive inborn errors of type I IFN immunity in children with COVID-19 pneumonia. J Exp Med. 2022;219:e20220131.

108. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science. 2020;370:eabd4585.

109. Bastard P, Gervais A, Le Voyer T, Rosain J, Philippot Q, Manry J, et al. Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. Sci Immunol. 2021;6:eabl4340.

110. Lemarquis A, Campbell T, Aranda-Guillén M, Hennings V, Brodin P, Kämpe O, et al. Severe COVID-19 in an APS1 patient with interferon autoantibodies treated with plasmapheresis. J Allergy Clin Immunol. 2021;148:96–8.

111. Lei X, Dong X, Ma R, Wang W, Xiao X, Tian Z, et al. Activation and evasion of type I interferon responses by SARS-CoV-2. Nat Commun. 2020;11:3810.

112. Wang W, Zhou Z, Xiao X, Tian Z, Dong X, Wang C, et al. SARS-CoV-2 nsp12 attenuates type I interferon production by inhibiting IRF3 nuclear translocation. Cell Mol Immunol. 2021;18:945–53.

113. Han L, Zhuang MW, Deng J, Zheng Y, Zhang J, Nan ML, et al. SARS-CoV-2 ORF9b antagonizes type I and III interferons by targeting multiple components of the RIG-I/MDA-5-MAVS, TLR3-TRIF, and cGAS-STING signaling pathways. J Med Virol. 2021;93:5376–89.

114. Ravichandran S, Tang J, Grubbs G, Lee Y, Pourhashemi S, Hussaini L, et al. SARS-CoV-2 immune repertoire in MIS-C and pediatric COVID-19. Nat Immunol. 2021;22:1452–64.

115. Sacco K, Castagnoli R, Vakkilainen S, Liu C, Delmonte OM, Oguz C, et al. Immunopathological signatures in multisystem inflammatory syndrome in children and pediatric COVID-19. Nat Med. 2022;28:1050–62.

116. Kalil AC, Mehta AK, Patterson TF, Erdmann N, Gomez CA, Jain MK, et al. Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021;9:1365–76.

117. Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed antiviral drugs for Covid-19—interim WHO solidarity trial results. N Engl J Med. 2021;384:497–511.

118. Reis G, Moreira Silva EAS, Medeiros Silva DC, Thabane L, Campos VHS, Ferreira TS, et al. Early treatment with pegylated interferon lambda for Covid-19. N Engl J Med. 2023;388:518–28.

119. Yonker LM, Boucau J, Regan J, Choudhary MC, Burns MD, Young N, et al. Virologic Features of Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Children. J Infect Dis. 2021;224:1821–9.

120. Kam KQ, Yung CF, Cui L, Tzer Pin Lin R, Mak TM, Maiwald M, Well Infant With Coronavirus Disease A, et al. With High Viral Load. Clin Infect Dis. 2019;2020:847–9.

121. Wu M, Chen Y, Xia H, Wang C, Tan CY, Cai X, et al. Transcriptional and proteomic insights into the host response in fatal COVID-19 cases. Proc Natl Acad Sci U S A. 2020;117:28336–43.

122. Land WG. Role of DAMPs in respiratory virus-induced acute respiratory distress syndrome—with a preliminary reference to SARS-CoV-2 pneumonia. Genes Immun. 2021;22:141–60.

123. Naqvi I, Giroux N, Olson L, Morrison SA, Llanga T, Akinade TO, et al. DAMPs/PAMPs induce monocytic TLR activation and tolerance in COVID-19 patients; nucleic acid binding scavengers can counteract such TLR agonists. Biomaterials. 2022;283:121393.

124. Guo H, Callaway JB, Ting JPY. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nat Med. 2015;21:677–87.

125. Vora SM, Lieberman J, Wu H. Inflammasome activation at the crux of severe COVID-19. Nat Rev Immunol. 2021;21:694–703.

126. Rodrigues TS, de Sá KSG, Ishimoto AY, Becerra A, Oliveira S, Almeida L, et al. Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients. J Exp Med. 2020;218:e20201707.

127. Wang M, Yu F, Chang W, Zhang Y, Zhang L, Li P. Inflammasomes: a rising star on the horizon of COVID-19 pathophysiology. Front Immunol. 2023;14:1185233.

128. Sefik E, Qu R, Junqueira C, Kaffe E, Mirza H, Zhao J, et al. Inflammasome activation in infected macrophages drives COVID-19 pathology. Nature. 2022;606:585–93.

129. Junqueira C, Crespo Â, Ranjbar S, de Lacerda LB, Lewandrowski M, Ingber J, et al. FcγR-mediated SARS-CoV-2 infection of monocytes activates inflammation. Nature. 2022;606:576–84.

130. Liu X, Zhang Z, Ruan J, Pan Y, Magupalli VG, Wu H, Lieberman J. Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. Nature. 2016;535:153–8.

131. Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, Lippi G. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: a pooled analysis. Am J Emerg Med. 2020;38:1722–6.

132. Kojima K, Yoon H, Okishio K, Tsuyuguchi K. Increased lactate dehydrogenase reflects the progression of COVID-19 pneumonia on chest computed tomography and predicts subsequent severe disease. Sci Rep. 2023;13:1012.

133. Newton K, Dixit VM, Kayagaki N. Dying cells fan the flames of inflammation. Science. 2021;374:1076–80.

134. Yang L, Xie X, Tu Z, Fu J, Xu D, Zhou Y. The signal pathways and treatment of cytokine storm in COVID-19. Signal Transduct Target Ther. 2021;6:255.

135. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med. 2020;8:1233–44.

136. Lucas C, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature. 2020;584:463–9.

137. Karki R, Sharma BR, Tuladhar S, Williams EP, Zalduondo L, Samir P, et al. Synergism of TNF-α and IFN-γ triggers inflammatory cell death, tissue damage, and mortality in SARS-CoV-2 infection and cytokine shock syndromes. Cell. 2021;184:149-68. e17.

138. Mick E, Tsitsiklis A, Spottiswoode N, Caldera S, Serpa PH, Detweiler AM, et al. Upper airway gene expression shows a more robust adaptive immune response to SARS-CoV-2 in children. Nat Commun. 2022;13:3937.

139. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.

140. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan. China Jama. 2020;323:1061–9.

141. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. J Infect. 2020;80:656–65.

142. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang Y-Q, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020;5:33.

143. Jafarzadeh A, Jafarzadeh S, Nozari P, Mokhtari P, Nemati M. Lymphopenia an important immunological abnormality in patients with COVID-19: possible mechanisms. Scand J Immunol. 2021;93: e12967.

144. Pierce CA, Preston-Hurlburt P, Dai Y, Aschner CB, Cheshenko N, Galen B, et al. Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. Sci Transl Med. 2020;12:eabd5487.

145. Cohen CA, Li APY, Hachim A, Hui DSC, Kwan MYW, Tsang OTY, et al. SARS-CoV-2 specific T cell responses are lower in children and increase with age and time after infection. Nat Commun. 2021;12:4678.

146. Weisberg SP, Connors TJ, Zhu Y, Baldwin MR, Lin WH, Wontakal S, et al. Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. Nat Immunol. 2021;22:25–31.

147. Dowell AC, Butler MS, Jinks E, Tut G, Lancaster T, Sylla P, et al. Children develop robust and sustained cross-reactive spike-specific immune responses to SARS-CoV-2 infection. Nat Immunol. 2022;23:40–9.

148. Rowntree LC, Nguyen THO, Kedzierski L, Neeland MR, Petersen J, Crawford JC, et al. SARS-CoV-2-specific T cell memory with common TCRαβ motifs is established in unvaccinated children who seroconvert after infection. Immunity. 2022;55:1299-315.e4.

149. Renk H, Dulovic A, Seidel A, Becker M, Fabricius D, Zernickel M, et al. Robust and durable serological response following pediatric SARS-CoV-2 infection. Nat Commun. 2022;13:128.

150. Karron RA, Garcia Quesada M, Schappell EA, Schmidt SD, Deloria Knoll M, Hetrich MK, et al. Binding and neutralizing antibody responses to SARS-CoV-2 in very young children exceed those in adults. JCI Insight. 2022;7:e157963.

151. Garrido C, Hurst JH, Lorang CG, Aquino JN, Rodriguez J, Pfeiffer TS, et al. Asymptomatic or mild symptomatic SARS-CoV-2 infection elicits durable neutralizing antibody responses in children and adolescents. JCI Insight. 2021;6:e150909.

152. Stoddard CI, Sung K, Yaffe ZA, Weight H, Beaudoin-Bussières G, Galloway J, et al. Elevated binding and functional antibody responses to SARS-CoV-2 in infants versus mothers. Nat Commun. 2023;14:4864.

153. Melms JC, Biermann J, Huang H, Wang Y, Nair A, Tagore S, et al. A molecular single-cell lung atlas of lethal COVID-19. Nature. 2021;595:114–9.

154. Delorey TM, Ziegler CGK, Heimberg G, Normand R, Yang Y, Segerstolpe Å, et al. COVID-19 tissue atlases reveal SARS-CoV-2 pathology and cellular targets. Nature. 2021;595:107–13.

155. Wang S, Yao X, Ma S, Ping Y, Fan Y, Sun S, et al. A single-cell transcriptomic landscape of the lungs of patients with COVID-19. Nat Cell Biol. 2021;23:1314–28.

156. Herrero R, Sanchez G, Lorente JA. New insights into the mechanisms of pulmonary edema in acute lung injury. Ann Transl Med. 2017;6:32.

157. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, et al. Acute respiratory distress syndrome. Nat Rev Dis Primers. 2019;5:18.

158. Bonaventura A, Vecchié A, Dagna L, Martinod K, Dixon DL, Van Tassell BW, et al. Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. Nat Rev Immunol. 2021;21:319–29.

159. Urata R, Ikeda K, Yamazaki E, Ueno D, Katayama A, Shin-Ya M, et al. Senescent endothelial cells are predisposed to SARS-CoV-2 infection and subsequent endothelial dysfunction. Sci Rep. 2022;12:11855.

160. Nicolai L, Leunig A, Brambs S, Kaiser R, Joppich M, Hoffknecht ML, et al. Vascular neutrophilic inflammation and immunothrombosis distinguish severe COVID-19 from influenza pneumonia. J Thromb Haemost. 2021;19:574–81.

161. Bussani R, Schneider E, Zentilin L, Collesi C, Ali H, Braga L, et al. Persistence of viral RNA, pneumocyte syncytia and thrombosis are hallmarks of advanced COVID-19 pathology. EBioMedicine. 2020;61:103104.

162. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383:120–8.

163. Silva CMS, Wanderley CWS, Veras FP, Gonçalves AV, Lima MHF, Toller-Kawahisa JE, et al. Gasdermin-D activation by SARS-CoV-2 triggers NET and mediate COVID-19 immunopathology. Crit Care. 2022;26:206.

164. Potere N, Garrad E, Kanthi Y, Di Nisio M, Kaplanski G, Bonaventura A, et al. NLRP3 inflammasome and interleukin-1 contributions to COVID-19-associated coagulopathy and immunothrombosis. Cardiovasc Res. 2023;119:2046–60.

165. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis. 2020;20:1135–40.

166. Miró Ò, Jiménez S, Mebazaa A, Freund Y, Burillo-Putze G, Martín A, et al. Pulmonary embolism in patients with COVID-19: incidence, risk factors, clinical characteristics, and outcome. Eur Heart J. 2021;42:3127–42.

167. Ameri P, Inciardi RM, Di Pasquale M, Agostoni P, Bellasi A, Camporotondo R, et al. Pulmonary embolism in patients with COVID-19: characteristics and outcomes in the Cardio-COVID Italy multicenter study. Clin Res Cardiol. 2021;110:1020–8.

168. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, Deigendesch N, et al. Postmortem examination of COVID-19 patients

reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology. 2020;77:198–209.

169. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med. 2020;8:681–6.

170. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46:1089–98.

171. Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, et al. Deep vein thrombosis in hospitalized patients with COVID-19 in Wuhan, China: prevalence, risk factors, and outcome. Circulation. 2020;142:114–28.

172. Whitworth H, Sartain SE, Kumar R, Armstrong K, Ballester L, Betensky M, et al. Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C. Blood. 2021;138:190–8.

173. Mansourian M, Ghandi Y, Habibi D, Mehrabi S. COVID-19 infection in children: a systematic review and meta-analysis of clinical features and laboratory findings. Arch Pediatr. 2021;28:242–8.

174. Shi Q, Wang Z, Liu J, Wang X, Zhou Q, Li Q, et al. Risk factors for poor prognosis in children and adolescents with COVID-19: a systematic review and meta-analysis. EClinicalMedicine. 2021;41:101155.

175. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.

176. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395:1607–8.

177. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395:1771–8.

178. Toraih EA, Hussein MH, Elshazli RM, Kline A, Munshi R, Sultana N, et al. Multisystem inflammatory syndrome in pediatric COVID-19 patients: a meta-analysis. World J Pediatr. 2021;17:141–51.

179. Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J, Gupta A. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. Paediatr Respir Rev. 2021;38:51–7.

180. Santos MO, Gonçalves LC, Silva PAN, Moreira ALE, Ito CRM, Peixoto FAO, et al. Multisystem inflammatory syndrome (MIS-C): a systematic review and meta-analysis of clinical characteristics, treatment, and outcomes. J Pediatr (Rio J). 2022;98:338–49.

181. Encinosa W, Moon K, Figueroa J, Elias Y. Complications, adverse drug events, high costs, and disparities in multisystem inflammatory syndrome in children vs COVID-19. JAMA Netw Open. 2023;6:e2244975.

182. LaRovere KL, Poussaint TY, Young CC, Newhams MM, Kucukak S, Irby K, et al. Changes in distribution of severe neurologic involvement in US pediatric inpatients with COVID-19 or multisystem inflammatory syndrome in children in 2021 vs 2020. JAMA Neurol. 2023;80:91–8.

183. Chang JC, Matsubara D, Morgan RW, Diorio C, Nadaraj S, Teachey DT, et al. Skewed cytokine responses rather than the magnitude of the cytokine storm may drive cardiac dysfunction in multisystem inflammatory syndrome in children. J Am Heart Assoc. 2021;10: e021428.

184. Felsenstein S, Duong P, Lane S, Jones C, Pain CE, Hedrich CM. Cardiac pathology and outcomes vary between Kawasaki disease and PIMS-TS. Clin Immunol. 2021;229: 108780.

185. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis. 2020;79:999–1006.

186. Licciardi F, Pruccoli G, Denina M, Parodi E, Taglietto M, Rosati S, Montin D. SARS-CoV-2-induced kawasaki-like hyperinflammatory syndrome: a novel COVID phenotype in children. Pediatrics. 2020;146:e20201711.

187. Sharma C, Ganigara M, Galeotti C, Burns J, Berganza FM, Hayes DA, et al. Multisystem inflammatory syndrome in children and Kawasaki disease: a critical comparison. Nat Rev Rheumatol. 2021;17:731–48.

188. Carter MJ, Fish M, Jennings A, Doores KJ, Wellman P, Seow J, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Nat Med. 2020;26:1701–7.

189. Diorio C, Shraim R, Vella LA, Giles JR, Baxter AE, Oldridge DA, et al. Proteomic profiling of MIS-C patients indicates heterogeneity relating to interferon gamma dysregulation and vascular endothelial dysfunction. Nat Commun. 2021;12:7222.

190. Esteve-Sole A, Anton J, Pino-Ramirez RM, Sanchez-Manubens J, Fumadó V, Fortuny C, et al. Similarities and differences between the immunopathogenesis of COVID-19–related pediatric multisystem inflammatory syndrome and Kawasaki disease. J Clin Investig. 2021;131:e144554.

191. Huang JJ, Gaines SB, Amezcua ML, Lubell TR, Dayan PS, Dale M, et al. Upregulation of type 1 conventional dendritic cells implicates antigen cross-presentation in multisystem inflammatory syndrome. J Allergy Clin Immunol. 2022;149:912–22.

192. Kumar D, Rostad CA, Jaggi P, Villacis Nunez DS, Prince C, Lu A, et al. Distinguishing immune activation and inflammatory signatures of multisystem inflammatory syndrome in children (MIS-C) versus hemophagocytic lymphohistiocytosis (HLH). J Allergy Clin Immunol. 2022;149:1592-606.e16.

193. McCormick JK, Yarwood JM, Schlievert PM. Toxic shock syndrome and bacterial superantigens: an update. Annu Rev Microbiol. 2001;55:77–104.

194. Duarte-Neto AN, Caldini EG, Gomes-Gouvêa MS, Kanamura CT, de Almeida Monteiro RA, Ferranti JF, et al. An autopsy study of the spectrum of severe COVID-19 in children: From SARS to different phenotypes of MIS-C. eClinicalMedicine. 2021;35:100850.

195. Noval Rivas M, Porritt RA, Cheng MH, Bahar I, Arditi M. Multisystem inflammatory syndrome in children and long COVID: the SARS-CoV-2 viral superantigen hypothesis. Front Immunol. 2022;13:941009.

196. Cheng MH, Zhang S, Porritt RA, Noval Rivas M, Paschold L, Willscher E, et al. Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation. Proc Natl Acad Sci U S A. 2020;117:25254–62.

197. Feleszko W, Okarska-Napierała M, Buddingh EP, Bloomfield M, Sediva A, Bautista-Rodriguez C, et al. Pathogenesis, immunology, and immune-targeted management of the multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome (PIMS): EAACI Position Paper. Pediatr Allergy Immunol. 2023;34:e13900.

198. Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med. 2020;26:502–5.

199. Mayordomo-Colunga J, Vivanco-Allende A, López-Alonso I, López-Martínez C, Fernández-Vega I, Gil-Peña H, Rey C. SARS-CoV-2 spike protein in intestinal cells of a patient with coronavirus disease 2019 multisystem inflammatory syndrome. J Pediatr. 2022;243:214-8.e5.

200. Hoste L, Roels L, Naesens L, Bosteels V, Vanhee S, Dupont S, et al. TIM3+TRBV11–2 T cells and IFNγ signature in patrolling monocytes and CD16+ NK cells delineate MIS-C. J Exp Med. 2021;219:e20211381.

201. Yonker LM, Gilboa T, Ogata AF, Senussi Y, Lazarovits R, Boribong BP, et al. Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier. J Clin Invest. 2021;131:e149633.

202. Rey-Jurado E, Espinosa Y, Astudillo C, Jimena Cortés L, Hormazabal J, Noguera LP, et al. Deep immunophenotyping reveals biomarkers of multisystemic inflammatory syndrome in children in a Latin American cohort. J Allergy Clin Immunol. 2022;150:1074-85.e11.

203. Sigal GB, Novak T, Mathew A, Chou J, Zhang Y, Manjula N, et al. Measurement of severe acute respiratory syndrome coronavirus 2 antigens in plasma of pediatric patients with acute coronavirus disease 2019 or multisystem inflammatory syndrome in children using an ultrasensitive and quantitative immunoassay. Clin Infect Dis. 2022;75:1351–8.

204. Porritt RA, Paschold L, Rivas MN, Cheng MH, Yonker LM, Chandnani H, et al. HLA class I–associated expansion of TRBV11–2 T cells in multisystem inflammatory syndrome in children. J Clin Investig. 2021;131:e146614.

205. Moreews M, Le Gouge K, Khaldi-Plassart S, Pescarmona R, Mathieu A-L, Malcus C, et al. Polyclonal expansion of TCR Vβ 21.3+ CD4+ and CD8+ T cells is a hallmark of multisystem inflammatory syndrome in children. Sci Immunol. 2021;6:eabh1516.

206. Lam KP, Chiñas M, Julé AM, Taylor M, Ohashi M, Benamar M, et al. SARS-CoV-2-specific T cell responses in patients with multisystem inflammatory syndrome in children. Clin Immunol. 2022;243: 109106.

207. Ramaswamy A, Brodsky NN, Sumida TS, Comi M, Asashima H, Hoehn KB, et al. Immune dysregulation and autoreactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children. Immunity. 2021;54:1083-95.e7.

208. Gruber CN, Patel RS, Trachtman R, Lepow L, Amanat F, Krammer F, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell. 2020;183:982-95.e14.

209. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell. 2020;183:968-81.e7.

210. Pfeifer J, Thurner B, Kessel C, Fadle N, Kheiroddin P, Regitz E, et al. Autoantibodies against interleukin-1 receptor antagonist in multisystem inflammatory syndrome in children: a multicentre, retrospective, cohort study. The Lancet Rheumatology. 2022;4:e329–37.

211. Burbelo PD, Castagnoli R, Shimizu C, Delmonte OM, Dobbs K, Discepolo V, et al. Autoantibodies against proteins previously associated with autoimmunity in adult and pediatric patients with COVID-19 and children With MIS-C. Front Immunol. 2022;13:841126.

212. Lee D, Le Pen J, Yatim A, Dong B, Aquino Y, Ogishi M, et al. Inborn errors of OAS-RNase L in SARS-CoV-2-related multisystem inflammatory syndrome in children. Science. 2023;379:eabo3627.

213. Chou J, Platt CD, Habiballah S, Nguyen AA, Elkins M, Weeks S, et al. Mechanisms underlying genetic susceptibility to multisystem inflammatory syndrome in children (MIS-C). J Allergy Clin Immunol. 2021;148:732-8.e1.

214. National Institutes of Health. Clinical Management of Children Summary. Accessed July 26, 2023. https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-children/clinical-management-of-children-summary/.

215. Mahase E. Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. BMJ. 2021;375: n2713.

216. Najjar-Debbiny R, Gronich N, Weber G, Khoury J, Amar M, Stein N, et al. Effectiveness of paxlovid in reducing severe coronavirus disease 2019 and mortality in high-risk patients. Clin Infect Dis. 2022;76:e342–9.

217. The U.S. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for PAXLOVID^TM. 2021. Accessed July 26, 2023. https://www.fda.gov/media/155050/download.

218. Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. N Engl J Med. 2021;386:305–15.

219. Harahsheh AS, Portman MA, Khoury M, Elias MD, Lee S, Lin J, McCrindle BW. Management of multisystem inflammatory syndrome in children: decision-making regarding a new condition in the absence of clinical trial data. Can J Cardiol. 2023;39:803–14.

220. National Institutes of Health. Therapeutic Management of Hospitalized Children With COVID-19. COVID-19 Treatment Guidelines. Updated July 21, 2023. Accessed July 28, 2023. https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-children/hospitalized-children-therapeutic-management/.

221. González-Dambrauskas S, Vásquez-Hoyos P, Camporesi A, Díaz-Rubio F, Piñeres-Olave BE, Fernández-Sarmiento J, et al. Pediatric critical care and COVID-19. Pediatrics. 2020;146:e20201766.

222. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023;21:133–46.

223. Jiang L, Li X, Nie J, Tang K, Bhutta ZA. A systematic review of persistent clinical features after SARS-CoV-2 in the pediatric population. Pediatrics. 2023;152:e2022060351.

224. Matteudi T, Luciani L, Fabre A, Minodier P, Boucekine M, Bosdure E, et al. Clinical characteristics of paediatric COVID-19 patients followed for up to 13 months. Acta Paediatr. 2021;110:3331–3.

225. Kikkenborg Berg S, Palm P, Nygaard U, Bundgaard H, Petersen MNS, Rosenkilde S, et al. Long COVID symptoms in SARS-CoV-2-positive children aged 0–14 years and matched controls in Denmark (LongCOVIDKidsDK): a national, cross-sectional study. Lancet Child Adolesc Health. 2022;6:614–23.

226. Lopez-Leon S, Wegman-Ostrosky T, Ayuzo del Valle NC, Perelman C, Sepulveda R, Rebolledo PA, et al. Long-COVID in children and adolescents: a systematic review and meta-analyses. Sci Rep. 2022;12:9950.

227. Gentilotti E, Górska A, Tami A, Gusinow R, Mirandola M, Rodríguez Baño J, et al. Clinical phenotypes and quality of life to define post-COVID-19 syndrome: a cluster analysis of the multinational, prospective ORCHESTRA cohort. EClinicalMedicine. 2023;62:102107.

228. Rao S, Lee GM, Razzaghi H, Lorman V, Mejias A, Pajor NM, et al. Clinical features and burden of postacute sequelae of SARS-CoV-2 infection in children and adolescents. JAMA Pediatr. 2022;176:1000–9.

229. Chen B, Julg B, Mohandas S, Bradfute SB. Viral persistence, reactivation, and mechanisms of long COVID. Elife. 2023;12:e86015.

230. Wallukat G, Hohberger B, Wenzel K, Fürst J, Schulze-Rothe S, Wallukat A, et al. Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. J Transl Autoimmun. 2021;4:100100.

231. Kruger A, Vlok M, Turner S, Venter C, Laubscher GJ, Kell DB, Pretorius E. Proteomics of fibrin amyloid microclots in long COVID/post-acute sequelae of COVID-19 (PASC) shows many entrapped pro-inflammatory molecules that may also contribute to a failed fibrinolytic system. Cardiovasc Diabetol. 2022;21:190.

232. Kell DB, Laubscher GJ, Pretorius E. A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications. Biochem J. 2022;479:537–59.

233. Raj SR, Arnold AC, Barboi A, Claydon VE, Limberg JK, Lucci VM, et al. Long-COVID postural tachycardia syndrome: an American Autonomic Society statement. Clin Auton Res. 2021;31:365–8.

234. Morrow AK, Malone LA, Kokorelis C, Petracek LS, Eastin EF, Lobner KL, et al. Long-term COVID 19 sequelae in adolescents: the overlap with orthostatic intolerance and ME/CFS. Curr Pediatr Rep. 2022;10:31–44.

235. Sukocheva OA, Maksoud R, Beeraka NM, Madhunapantula SV, Sinelnikov M, Nikolenko VN, et al. Analysis of post COVID-19 condition and its overlap with myalgic encephalomyelitis/chronic fatigue syndrome. J Adv Res. 2022;40:179–96.

236. Gross R, Thaweethai T, Rosenzweig EB, Chan J, Chibnik LB, Cicek MS, et al. Researching COVID to enhance recovery (RECOVER) pediatric study protocol: rationale, objectives and design. medRxiv. 2023. 2023.04.27.23289228.

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