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Immunology of SARS-CoV-2 infections in children

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Abstract

Children exhibit a broad range of clinical outcomes from SARS-CoV-2 infection, with the majority having minimal to mild symptoms. However, some succumb to a hyperinflammatory post-infectious complication, Multisystem Inflammatory Syndrome in Children, which predominantly affects previously healthy children. Studies characterizing the immunologic differences associated with these clinical outcomes have identified key pathways important for host immunity against SARS-CoV-2 and innate modulators of disease severity. Herein, we delineate the immunologic mechanisms underlying the spectrum of pediatric immune response to SARS-CoV-2 infection, with comparisons to that of adults.

Introduction

At the start of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, most children were initially spared, with very few developing moderate to severe coronavirus 2019 disease (COVID-19).[1–7] As the virus spread globally, the great majority of children <18 years of age had asymptomatic infection or mild COVID-19 and hospitalization was rare.[8–12] Those children that did develop severe COVID-19 generally had risk factors including underlying respiratory, neurologic and immune disorders.[13] This contrasts with the susceptibility of young children to other respiratory viruses, including respiratory syncytial virus (RSV), influenza, and parainfluenza where infants and young children are highly susceptible to severe disease.[14,15] In April 2020, a post-infectious syndrome known as Multisystem Inflammatory Syndrome in Children (MIS-C) emerged in patients under 21 years of age, with the majority of patients requiring intensive care for life-threatening complications. Investigating age-associated determinants of the spectrum of clinical outcomes in children and adults related to SARS-CoV-2 infection is paramount for understanding host susceptibility and outcome and could help optimize disease prevention and treatment.

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This review synthesizes key principles of developmental immunology with published evidence linking immunobiology and clinical outcomes of SARS-CoV-2 infections in children and adults. We do not address neonatal SARS-CoV-2 infection, given that the many differences between host immunity during the neonatal period and subsequent developmental stages merit a separate review. Because severe COVID-19 and MIS-C are uncommon in children, sample sizes for published studies are limited. To address this, we highlight findings that are common as well as disparate across published studies, with the goal of identifying fundamental distinctions between the pediatric and adult response to SARS-CoV-2 infections. Due to the spectrum of disease associated with SARS-CoV-2 infections, We compare the immunologic response of children and adults within distinct clinical phenotypes. These include asymptomatic SARS-CoV-2 infections, mild COVID-19, characterized by the presence of upper respiratory symptoms not requiring supportive care, and symptomatic COVID-19 prompting medical attention. Within each section, we discuss the hypotheses that have been investigated to explain why children are protected from moderate to severe COVID-19 compared to older adults.

Asymptomatic SARS-CoV-2 Infection to Mild COVID-19

Overall, studies have shown that responses to asymptomatic or mild COVID-19 are largely similar between adults and children. Three studies found that the viral loads of children with asymptomatic SARS-CoV-2 or mild disease have been found to be comparable[16] to, or slightly lower than that of those of adults with similarly mild infections.[17,18] Jia et al. showed that the cytokine profiles of children with mild COVID-19 resembles that of healthy children, reflecting a low level of inflammation.[19] Similarly, Cohen et al. found no differences in the percentages of IFN-γ $CD4^+$ or $CD8^+$ T cells against structural, accessory, and non-structural proteins in nine asymptomatic children compared to nine adults, with comparable capacities for generating multiple cytokines.[20] This occurred despite reduced levels of cross-reactive antibodies to β-coronaviruses other than SARS-CoV-2 in children compared to adults with similarly mild infections, suggesting that differences in antecedent infections do not significantly affect the T cell response in individuals with mild SARS-CoV-2 infections.[20]

In parallel with a robust cellular response to SARS-CoV-2, children are capable of mounting a robust serologic response to mild SARS-CoV-2 infections. A study comparing 25 children and adolescents to 34 adults with mild COVID-19 showed that both cohorts had similar levels of anti-spike IgG with comparable functionality, including the capacity for activating complement and phagocytic cells.[21] Two studies showed even higher neutralizing activity in anti-SARS-CoV-2 antibodies from children under 10 years of age, compared to adolescents and young adults.[22,23] The impact of disease severity on the antibody response is indicated by lower levels of convalescent antibodies to the spike and nucleocapsid proteins in children with asymptomatic or mild infections compared to those with moderate COVID-19 requiring hospitalization.[24,25] Collectively, these studies do not show major differences in the viral load or measured immune response to mild COVID-19 between children and adults, although relative few studies have investigated the immune response in individuals with asymptomatic or mild SARS-CoV-2 infections.

Moderate to severe COVID-19

In contrast to the comparable pediatric and adult immune responses during mild COVID-19, notable differences emerge in cases of patients hospitalized with COVID-19. Even though the numbers of pediatric inpatients with COVID-19 increased after spread of the Delta variant,[26] most children and adolescents hospitalized for COVID-19 required shorter hospitalizations, less respiratory support, and had less mortality compared to hospitalized adults.[27,28] In the United States, individuals older than 50 years of age account for at least 90% of all deaths.[29] When reviewing these studies, it is important to consider that differences in immune responses could be either predictive or reflective of COVID-19 disease severity. Additionally, comorbid conditions differ between adults and children, as does alcohol and tobacco use and obesity, which all influence immune outcomes. In this section, we discuss the differences in the immune systems of children and adults that have been investigated as potential drivers of age-associated clinical outcomes from COVID-19 (Fig. 1).

SARS-CoV-2 entry factors

Upon encountering respiratory mucosa, the receptor binding domain (RBD) of the SARS-CoV-2 spike protein binds to the widely expressed angiotensin-converting enzyme 2 (ACE2) receptor.[30–32] The subsequent fusion of viral and cellular membranes is facilitated by cleavage of the viral spike protein by host proteases, such as transmembrane serine protease 2 (TMPRSS2) and cathepsin L, thereby enabling cellular entry.[33,34] The expression of TMPRSS2 increases with age, and is significantly higher in the airway epithelium of healthy adults compared to that of infants.[35–38] Similarly, a meta-analysis of 31 lung single-cell RNA-sequencing studies from 228 individuals without a history of lung disease showed a positive correlation between age and the expression of ACE2 in alveolar cells.[39] However, distinctions in the expression of viral entry factors between children and adults are less clear: some, but not all, studies have evidence supporting the hypothesis that fewer ACE2 receptors in children may account for reduced viral entry into the lung.[35,40,41]

In adults with COVID-19, higher viral loads measured through naso- or oro-pharyngeal swabs have been associated with more severe disease in some, but not all studies, particularly since asymptomatic individuals may have viral loads comparable to those found in hospitalized individuals.[16,42–45] While studies have found higher viral loads in symptomatic children than asymptomatic children, viral loads have not been found to be predictive of disease severity in children either.[46,47] Furthermore, children and adults with similar disease severity have comparable viral loads.[16,17] The variability in these studies may arise from differences in collection techniques and the inability to sample the lower respiratory tract in non-intubated patients. Nonetheless, studies have not conclusively shown that differences in viral loads account for the improved clinical outcomes seen in the majority of children with COVID-19.

Interferon signaling

While the ACE2 receptor is critical for SARS-CoV-2 entry in cells, other viral components activate widely expressed pattern recognition receptors, such as Toll-like receptors (TLR)

and retinoic acid inducible gene I (RIG-I)-like receptors, to initiate the innate immune response.[48] Structural proteins, such as the SARS-CoV-2 envelope protein and spike protein, are sensed by TLR2 and TLR4, respectively. Single-stranded viral genomic RNA activates TLR7/8, while the virus's double-stranded RNA intermediates bind TLR3; cytosolic RNA is sensed by the RIG-I-like receptors.[49] Activation of TLRs and RIG-I induce a robust interferon response. As a counter-regulatory mechanism, SARS-CoV2 proteins, such as ORF9b, non-structural proteins 1 and 13, and the nucleocapsid protein inhibit the host interferon response.[49,50] Differences in interferon signaling has been investigated in children and adults with COVID-19. Adults with severe COVID-19 have lower circulating levels of Type I IFNs, which has been attributed to neutralizing antibodies to type I IFNs[51–53] as well as reduced Type I IFN secretion from plasmacytoid dendritic cells (DCs).[54,55] Pierce et al. compared the immune response in nasal secretions from 12 children and 27 adults hospitalized for moderate to severe COVID-19; the children had much milder disease than the adults, requiring no respiratory support and resulting in no mortality.[40] The children exhibited increased expression of genes downstream of Type I and II IFNs and the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome compared to the adults, but both groups had similar viral loads and levels of anti-SARS-CoV-2 IgG and IgA in nasal fluid.[40] In correlating the increased IFN and inflammasome signaling in the nasal mucosa with better clinical outcomes, this study further supports the hypothesis that children are protected from severe disease due to more robust innate immunity allowing them to overcome SARS-CoV-2. One caveat is that upper respiratory samples may not reflect the cellular composition and gene expression of cells and fluid from lower airways or peripheral blood.[56,57]

The heightened interferon response in children does not arise exclusively from intrinsic age-associated differences in this pathway. IFN responses are reduced from the time of birth until approximately two years of age; between two to five years of life, cytokine profiles shift toward that of an adult, with increased expression of Type I IFNs, reduced IL-6 and IL-23, and increased IL-12 and IL-10.[58,59] A reduction in the IFN response is seen again in adults over the age of 65 years, in part due to age-associated reductions in Interferon Regulatory Factor 8 (IRF), a transcription factor downstream of RIG-I signaling, and proteolysis of tumor receptor-associated factor 3 (TRAF3), a signaling protein utilized by multiple TLRs.[60] Additionally, as individuals age, Type I IFN receptors in $CD4^+$ T cells are more frequently complexed with Src homology region 2 domain-containing phosphatase 1 (SHP-1), an inhibitory protein tyrosine phosphatase that restrains Type I IFN signaling.[61,62] Exogenous factors that reduce the IFN response also accumulate with age. These include chronic viral infections, such as human cytomegalovirus, known to cause exhaustion of plasmacytoid DCs and reduced IFN secretion, as well as anti-interferon autoantibodies.[51,63–65] Although the effects of reduced IFN signaling are most pronounced in individuals over the age of 65 years, these factors progressively impair the IFN response and may contribute to the increased frequency of severe COVID-19 in middle-aged and older adults.

T cell homeostasis and activation

T cell lymphopenia in the blood and airway fluid is a marker of COVID-19 severity in both children and adults.[40,57,66] In a study comparing the immune response of 65 children and young adults under the age of 24 years to 60 adults, all of whom were hospitalized for COVID-19, pediatric patients had significantly higher absolute lymphocyte counts.[27] However, adults generated increased percentages of spike-specific $CD4^+IFN\text{-}\gamma^+$ T cells compared to children and infants.[27] In another study analyzing T cell responses from 34 children and 36 adults, the overall magnitude of SARS-CoV-2-specific-$CD4^+$ and $CD8^+$ T cell responses were lower in the blood of children than adults.[20] The targets of $CD4^+$ T cells varied widely between children and adults, with those of adults targeting primarily structural proteins; in contrast, pediatric $CD4^+$ T cells had a significant proportion of targets in Open Reading Frame (ORF) 1ab, which encodes 16 non-structural proteins.[20] As some of these non-structural proteins are known to block the host interferon response,[50] these studies raise the possibility that differences in T cell targets may contribute to the age-associated decline in the IFN response to SARS-CoV-2 infection.

Given the dynamic changes affecting T cell development throughout life, multiple age-related differences in T cell number and function likely contribute to the increased frequency of severe COVID-19 in adults compared to children. Thymic output is maximal at one year of age, and declines gradually thereafter, with negligible output occurring by approximately 85 years of age.[67] The TCR repertoire is another factor that evolves throughout an individual's lifetime. Pathogen-specific memory responses expand as infants and young children encounter new infections, including the formation of tissue resident memory T cells.[68] Although studies have identified cross-reactivity between T cell recognizing the epitopes of SARS-CoV-2 and those of other human coronaviruses, no definitive correlation between clinical outcomes and T cell epitope cross-reactivity has yet emerged.[69] Aging is also associated with shifts in the transcriptional profiles of T cells. Studies of aging mice kept in specific pathogen-free environments accumulate cytotoxic and effector $CD4^+$ T cells, with increased expression of genes associated with chronic inflammation (such as S100 protein family members), the cytotoxic T cell response to viral infections (such as granzymes and the transcription factor eomesodermin), and T cell exhaustion.[70] The similarities between T cell dysfunction in aging adults and in those with severe COVID-19 suggest that the gradual onset of T cell dysfunction in adulthood may set the stage for the dysfunction T cell response associated with severe COVID-19. Although studies have delved deeply into mechanisms of T cell dysfunction in the elderly,[71,72] additional investigations are needed to delineate the threshold of T cell dysfunction associated with susceptibility to severe COVID-19.

Serologic responses during COVID-19

SARS-CoV-2 drives the expansion of plasmablasts and plasma cells during both mild and severe COVID-19, even beyond what is usually associated with influenza vaccination and infection.[73–76] Children and adults hospitalized with COVID-19 had comparable levels of plasmablasts, regardless of need for ventilatory support.[77] Increased plasmablast frequencies correlated with percentages of proliferating $CD4^+$ T cells, rather than levels of anti-spike antibodies.[77,78] Adults with acute severe COVID-19 had increased levels of neutralizing

antibodies compared to titers from convalescent adults or pediatric patients with MIS-C, the latter two of which were comparable in one study.[57]

The differences in the serologic response to COVID-19 in children and adults are concordant with known age-associated differences in B cell development (Fig. 1). The response to T-independent antigens takes approximately two years to mature, as infants produce more IgG1 than IgG2, the latter of which preferentially recognizes polysaccharide antigens.[79,80] Environmental factors also shape B cell development. Clonal expansion and somatic hypermutation begin during infancy and increase with environmental and infectious exposures.[80–82] The rate of SHM can be increased, even during infancy, through exposures to infectious pathogens.[81] However, it is also important to note that the severity of COVID-19 in adults also impacts the serologic response.[8–12] In support of this, Bartsch et al. showed that adults with severe COVID-19 have increased titers of anti-SARS-CoV-2 IgG and IgA with more functionality in activating complement and phagocytic cells compared to either adults or children with mild SARS-CoV-2 infections.[21]

Antibody repertoires also evolve with age and infectious exposures. With respect to other common coronaviruses, including 229E, NL63, OC43, and KHU1, a study of 231 children and 1168 adults found that children had increased levels of antibodies against the spike, nucleocapsid, and matrix structural proteins, while a nonstructural protein of unknown function was the most common target of antibodies in adults.[83] Age-associated differences in epitope reactivity have been identified in antibodies against other respiratory viruses as well, including RSV and influenza, suggesting that serologic immunity is achieved through targeting of different viral epitopes in children compared to adults.[84–87] These differences have been attributed, at least in part, to original antigenic sin or immunologic imprinting, in which exposures to specific pathogen epitopes skew subsequent antibody repertoires due to the reliance of adaptive immunity on existing memory cells.[87] Antigenic sin has been shown to contribute to differences in age-associated mortality with influenza virus subtypes.[88–90] With response to COVID-19, no definitive associations between prior coronavirus infections and the serologic response to SARS-CoV-2. A study of 37 adults with COVID-19 found that serologic responses to the spike protein of other betacoronaviruses were inversely proportional to IgM and IgG antibodies against the spike and nucleocapsid proteins of SARS-CoV-2.[91] Similarly, another study of 232 patients with COVID-19 identified a negative correlation between antibody responses to SARS-CoV-2 and other human coronaviruses.[92] In contrast, another study of young and older adults hospitalized for COVID-19 (10 young adults, aged 27 to 39 years old; 20 older adults spanning 69 to 82 years of age, of whom nine required ventilation) found positive correlations between antibodies to the spike protein of other human betacoronaviruses and SARS-CoV-2; serologic memory to earlier coronaviruses did not correlate with clinical outcomes.[93] Another study of 65 children and 60 adults did not find significant correlations between serologic memory to other human coronaviruses and either age or outcome.[27] The heterogeneous outcomes from these studies indicates the complexity of investigating immunologic imprinting in diverse human populations with a broad range of environmental and infectious exposures; future studies with animal models of serial viral infections may provide more definitive conclusions.

Summary of mechanisms increasing the prevalence of severe COVID-19 in adults

Collectively, these studies show that developmental differences in innate and adaptive immunity, particularly those relating to IFN signaling and T cell function, likely contribute to the increased susceptibility to severe COVID-19 in adults. In support of this, the prevalence of severe COVID-19 was higher in immunodeficient cohorts enriched in disorders of T cell development and/or function,[94–96] compared to that of the general pediatric population or cohorts of patients with a broader diversity of primary or secondary immunodeficiencies, such as antibody deficiencies, autoimmune disorders, and use of immunosuppressive medications.[6,97,98] This parallels increased mortality from COVID-19 in the elderly, another population with reduced T cell number and function.[99,100] Notably, co-morbidities associated with severe COVID-19,[101] including cardiovascular disease, diabetes, malignancies, renal failure, and neurodegenerative disease, occur more frequently in adults than children. Certain chronic diseases, such as cerebrovascular disease, obesity, and diabetes, result in a dysfunctional immune response to infections through epigenetic and metabolic reprogramming of immune activation.[102–104] Other comorbidities, such as chronic lung disease, may result in anatomic susceptibility to more severe COVID-19. When present in children and young adults, these comorbidities also increase the risk of severe COVID-19.[6,9,10,13,105]

Multisystem Inflammatory Syndrome in Children (MIS-C)

In April 2020, during the wake of viral surges occurring in Italy and the United Kingdom,[106–109] children presented with mucocutaneous features resembling Kawasaki disease (KD) and/or toxic shock syndrome. Soon after, descriptive reports by Feldstein et al. and Dufort et al., totaling almost 300 U.S. cases, confirmed that the timing was approximately 4 weeks after the peak of SARS-CoV-2 activity in a region.[110,111] This disease entity is now referred to as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)[108] or Multisystem Inflammatory Syndrome in Children (MIS-C).[112] The diagnostic criteria from the Centers for Disease Control and Prevention for MIS-C include at least 24 hours of fever and inflammation severe enough to affect at least two organ systems and require hospitalization. These symptoms must occur within four weeks of SARS-CoV-2 infection or exposure to COVID-19 in an individual younger than 21 years of age who has no alternative diagnosis for these symptoms.[112] At least 75% of children in published cohorts have positive SARS-CoV-2 antibody testing, but fewer (up to 52%) have positive respiratory testing, suggesting the post-infectious timing of MIS-C.[109–111,113] Milder symptoms of MIS-C include fevers, rashes, and gastrointestinal symptoms, but can progress to life-threatening cytopenias, coagulopathy, myocardial dysfunction, coronary aneurysms, and/or shock.[1–5] The majority of children diagnosed with MIS-C were previously healthy, but critically ill mostly due to shock and/or left ventricular dysfunction, with less severe or no respiratory involvement.[110,111] Approximately 40% of the patients met criteria for KD, a vasculitic syndrome associated with coronary artery aneurysms. In a study of over 1,000 children with MIS-C or severe COVID-19, those with MIS-C were more likely to have cardiovascular and/or mucocutaneous involvement, with higher CRP levels and a neutrophil to lymphocyte ratios.[113] Compared to children and adolescents with acute COVID-19, MIS-C is more likely to affect those between six and

12 years of age, rather than younger or older patients.[113,114] MIS-C has been reported in Europe, North and South America, the Middle East, South Africa, and South Asia.[115] Relatively fewer cases have been reported from East Asia which has a high frequency of Kawasaki disease, and it is unclear if this is due to differences in the genetic background of local populations or environmental conditions.[115,116] In the U.S., non-Hispanic Black children may be at higher risk of developing MIS-C than acute COVID-19, compared to non-Hispanic White patients.[113,114]

Analogously, multisystem inflammation in adults (MIS-A) has been reported in individuals 21 years or older.[117–123] The diagnosis of MIS-A differs from that of MIS-C in that patients with MIS-A cannot have severe respiratory disease, thereby differentiating this disease from severe COVID-19 in adults.[124] Additionally, the diagnosis of MIS-A requires hospitalization for at least one extra-pulmonary complication occurring within 12 weeks of SARS-CoV-2 infection. In a study of 839 adults hospitalized with SARS-CoV-2 infection, 11.7% were diagnosed with MIS-A.[117] Patients with MIS-A were younger than those with COVID-19, with a median age of 45.1 years for the MIS-A cohort compared to 56.5 years for COVID-19 patients.[117] No other differences in demographics or other comorbidities were found between adults with MIS-A and those with COVID-19.[117] As the immunologic features of MIS-A are largely not understood, and there is believed to be overlap with acute COVID-19 with cardiovascular involvement,[117,121] the remainder of this section will focus on the immunobiology underlying MIS-C with comparisons to COVID-19 in children and adults.

Cellular activation affecting multiple hematopoietic lineages is a consistent feature of MIS-C. High levels of inflammatory cytokines, including IFN-α, IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-17, have been identified in all studies of MIS-C,[125–131] but no single archetypal cytokine signature of MIS-C has emerged. Evidence of myeloid cell activation in patients with MIS-C include increased expression of CD64 on monocytes and neutrophils as well as the alarmin-related S100A genes, both of which are also elevated in adults with severe COVID-19.[125,132] NK cells from patients with MIS-C also exhibit evidence of increased activation, with higher expression of perforin and granzymes compared to controls.[132] Single cell RNA-seq of peripheral blood mononuclear cells from eight children with MIS-C, compared to four children with COVID-19 pneumonia and nine controls, showed that those with MIS-C and COVID-19 had similarly increased expression of genes downstream of inflammatory cytokines (Type I/II IFNs, IL-1, IL-6, and IL-17) and NF-κB activation, even though all patients with MIS-C had been treated with immunomodulatory therapies prior to study enrollment.[131] The inflammatory signature in the MIS-C cohort was restricted to monocytes and dendritic cells, highlighting the contributions of these cells to the systemic inflammation characteristic of MIS-C.[131]

Commensurate with multi-lineage immune activation, patients with MIS-C have evidence of tissue inflammation, including increased gastrointestinal permeability, schistocytes and elevated circulating levels of complement C5b9 indicative of microangiopathy, and release of troponin and natriuretic peptides indicative of cardiac inflammation.[109–111,113,126,129,130,133] Patients with MIS-C may have mucocutaneous inflammation and coronary artery aneurysms, features characteristic of Kawasaki disease.

However, studies have identified distinctions between the immunologic abnormalities associated with these diseases. Compared to patients with KD, those with MIS-C have more severe lymphopenia, neutropenia, and thrombocytopenia as well as increased expression of T cell activation markers, including HLA-DR and CD57, a marker of $CD4^+$ T cell senescence.[126,127] Circulating levels of Discoidin as well as CUB And LCCL Domain Containing 2 (DCBLD2), a protein associated with endothelial damage, are higher in patients with KD than MIS-C,[127] reflecting the more frequent coronary artery involvement in KD.[126] These differences may explain why the great majority of coronary artery aneurysms in MIS-C resolve within 30 days, which contrasts with the persistent aneurysms associated with KD.

T cells have been investigated for their role in MIS-C pathogenesis. In patients with MIS-C, lymphopenia appeared to be a general feature in the acute phase of disease.[134] One study found a strong enrichment for patrolling $CX3CR1^+CD8^+$ T cells, potentially contributing to the vascular manifestations of MIS-C.[77] $PD1^+CD39^+CD8^+$ T cells were also elevated, nominally higher than levels in adults with severe disease, indicative of prolonged activation and TCR signaling. Three separate studies, each with unique cohorts of children with MIS-C, identified pronounced skewing of the T cell receptor (TCR) Vβ repertoire,[132,135,136] with up to 24% of the sequenced clones expressing the TRBV11-2 V-region (Vβ21.3) in one study.[136] The polyclonal nature of this expansion, highlighted in two studies,[135,136] is suggestive of superantigen-driven activation. Concordant with these findings, a superantigen-like motif has been identified in the SARS-CoV-2 spike protein sequence.[137] TCR skewing has been similarly identified in adults with severe COVID-19, although the Vβ signatures identified in adults with severe COVID-19 appears to differ, thus far, from those found in patients with MIS-C.[137,138] In contrast, TRBV11-2 enrichment was not observed in subjects with mild SARS-CoV-2, KD, toxic shock syndrome, or age-matched febrile controls.[132,135,136] After resolution of the disease, the repertoire of T cells from children with MIS-C re-normalized in distribution.[132] In light of the skewed TCR repertoires evident in some patients with MIS-C, studies have investigated post-infectious sources of antigens.[130,139] Given the frequency of gastrointestinal symptoms in patients with MIS-C,[6,108–110,113] it has been hypothesized that the gastrointestinal tract may serve as a reservoir for SARS-CoV-2,[130,139,140] as the virus is known to infect gut enterocytes.[141] Compared to controls and children with COVID-19, a single-center cohort of 19 patients with MIS-C investigated by Yonker et al. had evidence of significantly increased gastrointestinal permeability and increased circulating levels of SARS-CoV-2 spike protein and the S1 subunit, the latter of which correlated with TRBV11-2 expression.[130] Additional studies with larger, multi-center MIS-C cohorts are needed to determine the generalizability of these findings.

The serologic features of MIS-C reflect the post-infectious timing of this disease. Patients with MIS-C have IgG antibodies to SARS-CoV-2 with levels and neutralizing capacity similar to those of convalescent adults, irrespective of concomitant RT-PCR positivity.[21,128] Additionally, higher levels of total and neutralizing antibodies against the spike and RBC proteins have been found in children with MIS-C compared to those with acute COVID-19.[142] These findings suggest that the nasopharyngeal load of virus reflects an antecedent, rather than acute, infection.[128,133] In addition to robust antibody responses to

SARS-CoV-2, children with MIS-C have a concomitant expansion of antibodies against other common viruses, including common coronaviruses, influenza, respiratory syncytial viruses, Epstein-Barr virus.[21] This is similar to the antibody profiles of non-hospitalized adult patients with mild to moderate COVID-19; in contrast, adults with severe COVID-19 requiring hospitalization have more limited expansion of antibodies to pathogens other than SARS-CoV-2.[21,92] The cause of differences in the breadth of the serologic response are not known, but studies have hypothesized that the attenuated immunity with aging leads to a narrower humoral response during SARS-CoV-2 infection.[92] In concordance with this, patients with MIS-C exhibit increased frequencies of proliferating $CD27^+CD38^+$ plasmablasts, which correlated with increased percentages of proliferating $CD4^+$ T cells – a feature that diminishes with age.[77,78]

Differences in age-associated morbidity and mortality to subtypes of respiratory viruses has prompted investigations of how exposure to other coronavirus infections affects susceptibility to MIS-C. A small study of three children with MIS-C identified a lack of antibodies against common human coronaviruses HKU1 and betacoronavirus 1.[127] However, subsequent studies have identified comparable or increased levels antibodies against HKU1 and other seasonal coronaviruses in children hospitalized with either MIS-C, compared to those with acute COVID-19 and healthy children, with no consistent correlation across studies in the relationship between antibodies against seasonal coronaviruses and neutralizing antibodies to SARS-CoV-2.[143,144]

The end organ inflammation characteristic of MIS-C has prompted studies to investigate the contributions of autoantibodies to the pathogenesis of MIS-C. Increased levels of circulating autoantibodies have been identified in patients with MIS-C,[127,128,132] including in samples taken prior to administration of IVIG. The spectrum of autoantibodies targets antigens enriched in endothelial cells and the gastrointestinal tract, those associated with rheumatologic disorders (systemic lupus erythematosus, Sjogren's disease, and idiopathic inflammatory myopathies), and those against widely expressed tissue antigens (MAP2K2 and members of the casein kinase family).[127,128,132] Additionally, two studies have found evidence of B cell clonal expansion in patients with MIS-C,[132,145] with the study by Porritt et al. showing that a higher frequency of immunoglobulin heavy chain genes associated with autoimmune disorders in patients with TRBV11-2 expression.[145] Notably, studies of children with MIS-C have not identified autoantibodies against IFN or interferon stimulated genes,[131,146] thus differentiating autoantibodies in children with MIS-C from those found in adults with severe COVID-19.[51,65]

Genetic risk factors associated with susceptibility to MIS-C are also distinct from those associated with severe COVID-19 in adults. Multiple studies of adults with severe COVID-19 have identified an association between severe COVID-19 and loss of function variants in TLR7, a sensor for SARS-CoV-2 single stranded RNA.[147–150] TLR7 signaling promotes IFN signaling, the secretion of IL-6, IL-1β, and IL-23, and the generation of Th17 T cells in response to viral infections.[151,152] Thus, reduced function of TLR7, which is located on the X chromosome, is one mechanism contributing to the increased prevalence of severe COVID-19 in men compared to women.[153–155] In contrast to these risk variants for COVID-19, variants impairing negative regulators of inflammation have

been found in patients with MIS-C.[156,157] These include *SOCS1* (encoding Suppressor of Cytokine Signaling 1), *XIAP* (encoding X-linked Inhibitor of Apoptosis), and *CYBB* (encoding cytochrome b-245, beta subunit).[157] Even seven months after recovery, patients with these genetic risk variants exhibited transcriptional evidence of increased interferon and inflammatory signaling, thus constituting a counterpoint to the reduced IFN signature associated with severe COVID-19 in adults. Extending beyond monogenic risk factors, studies have identified HLA class I alleles as factors potentially increasing a child's risk of MIS-C. In the study by Porritt *et al.*, which had a predominance of Hispanic patients from the U.S., four of seven patients with MIS-C had TRBV11-2 expansion and all four also shared the HLA class I alleles A02, B35, and C04,[135] In contrast, this was not found in the sub-cohort of HLA genotyped patients presented by Moreews *et al.*, which was comprised predominantly of children from Afro-Caribbean backgrounds.[136] Thus, larger cohort studies will be necessary to quantify the association between HLA genotype on the susceptibility to MIS-C.

In summary, studies have shown that the post-infectious timing and broad hyperactivity of both innate and adaptive immunity distinguish MIS-C from severe COVID-19 in children and adults,[77,133] as well as KD and macrophage activation syndrome.[126,128] Many questions remain regarding genetic and environmental risk factors, since MIS-C most often occurs in previously healthy school-aged children who have been exposed to a diversity of infectious pathogens in group care and school settings. Triggers for MIS-C onset remain unknown, and it is challenging to distinguish driver pathways in MIS-C from those activated as a result of disease progression. Overall, immunity in older children and adolescents is an understudied area and MIS-C may provide the impetus for future studies of the immune response in these pediatric age groups.

Limitations of research generated during a pandemic

Many limitations of the studies presented here arise from challenges inherent in a pandemic. Worldwide, clinicians faced unpredictable barriers in providing medical care due to supply chain shortages and viral surges,[158] rendering it even more difficult for investigators to obtain biospecimens. This was further compounded by the fact that many parents of children hospitalized with COVID-19 are ill themselves, and unable to provide consent for their child to participate in research, and critically ill COVID-19 adults are unable to consent. There was no precedent for use of deferred consent in a pandemic, which could have helped with obtaining early samples in adults and children.[159]

The enrollment of children in research studies has additional complexities, including limitations on blood volume, and smaller sample sizes due to the lower prevalence of SARS-CoV-2-associated complications in pediatric populations compared to adult cohorts.[160] The relative rarity of intubation required for children with COVID-19 limited the amount of pediatric bronchial lavage samples available, prompting the use of nasopharyngeal samples as surrogates. The viral load, immune cell composition, and gene expression profiles of nasal and airway samples are distinct and not interchangeable.[56] Differences in the inflammatory response observed in cells obtained from bronchial samples compared to peripheral blood suggest that high-resolution immune studies of circulating and tissue-

resident cells would enable a more complete understanding of COVID-19 or MIS-C pathogenesis.[161]

Studies showing the real-world effectiveness of intravenous immunoglobulin and glucocorticoids for the treatment of MIS-C prompted rapid initiation of treatment in children with MIS-C,[113,162,163] and thus, most studies utilized samples from pre-treated children. The immunomodulatory treatments given to patients with MIS-C affects the transcriptional signature of immune cells, as seen in longitudinal studies of MIS-C.[77,125,127] Finally, differences in processing methodologies among research studies, including types of anti-coagulants used, timing of sample processing and freezing, affect measurements of circulating cytokines, a parameter investigated in most studies of SARS-CoV-2.[164] Historically, these types of limitations have been overcome by utilizing animal models of disease to confirm the findings from patient studies. However, due to interspecies differences in the susceptibility and response to SARS-CoV-2 infection, there are no animal models that recapitulate the two most severe manifestations of SARS-CoV-2 infection in humans, acute respiratory distress syndrome or MIS-C.[165]

Concluding remarks

Collectively, these studies show that the immune response of children and adults to mild SARS-CoV-2 infection are similar, but diverge upon development of severe disease (Fig. 2). Adults with severe COVID-19 may have loss of immune synchrony: T cell lymphopenia, reduced circulating T follicular helper cells, and impaired IFN-mediated signaling juxtaposed with high frequencies of activated SARS-CoV-2-specific T cells, robust humoral responses, and myeloid cell activation. In contrast, patients with MIS-C exhibit multilineage immune cell activation beyond that of pediatric or adult COVID-19, as evidenced by greater IFN and inflammasome signaling, widespread T cell activation, and activation of a broad humoral response reactive to common viruses as well as SARS-CoV-2. These differences in the immunologic profiles point to many unanswered questions.

The association of severe COVID-19 in children and adults with pre-existing medical conditions underscores the contributions of these comorbidities to disease severity. However, the impact of these comorbidities on immune synchrony are incompletely understood. Studies of pediatric populations in multiple countries have shown that SARS-CoV-2 infections across the developmental spectrum encompassing the neonatal period through adolescence are mostly asymptomatic or mild, despite developmental differences in immunity, variations in genetic background, and diversity of living environments. This suggests that developmental immaturity in host immunity is not, in and of itself, a risk factor for severe COVID-19 or MIS-C. Although studies have started to identify demographic and genetic risk factors for MIS-C, the constellation of factors that lead to MIS-C remains largely undefined. Diagnosis of MIS-C will become more challenging as more of the pediatric population becomes SARS-CoV-2 antibody positive through prior infection or vaccination. The spread of viral variants among unvaccinated pediatric populations may also change the spectrum of disease in children. The solutions to these questions will emerge as scientists and clinicians continue to develop multi-center studies with larger cohorts alongside new tools for investigating SARS-CoV-2 pathogenesis.

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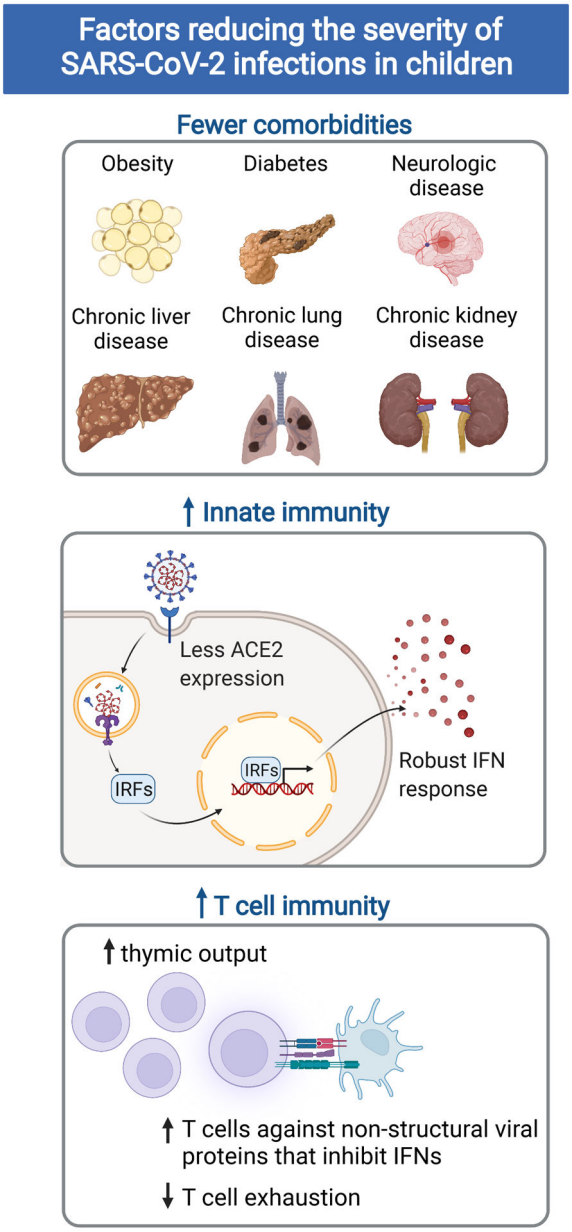

Figure 1.
Summary of factors reducing the severity of SARS-CoV-2 infections in children

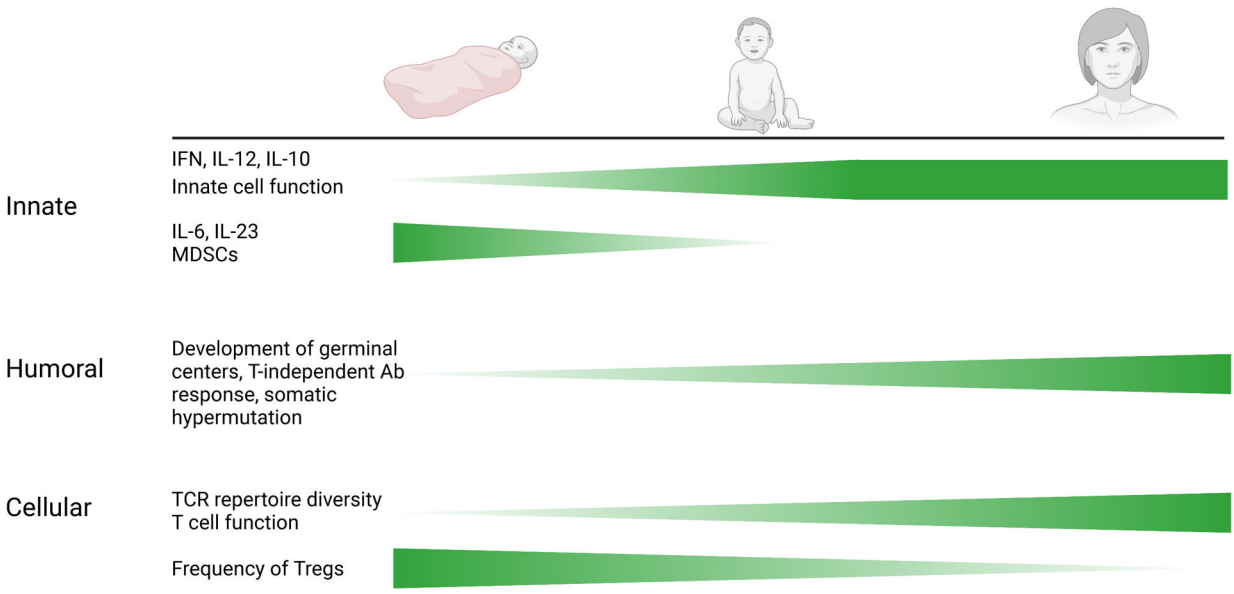

Figure 2.

Key developmental differences in pediatric and adult immune mechanisms against viral infections.

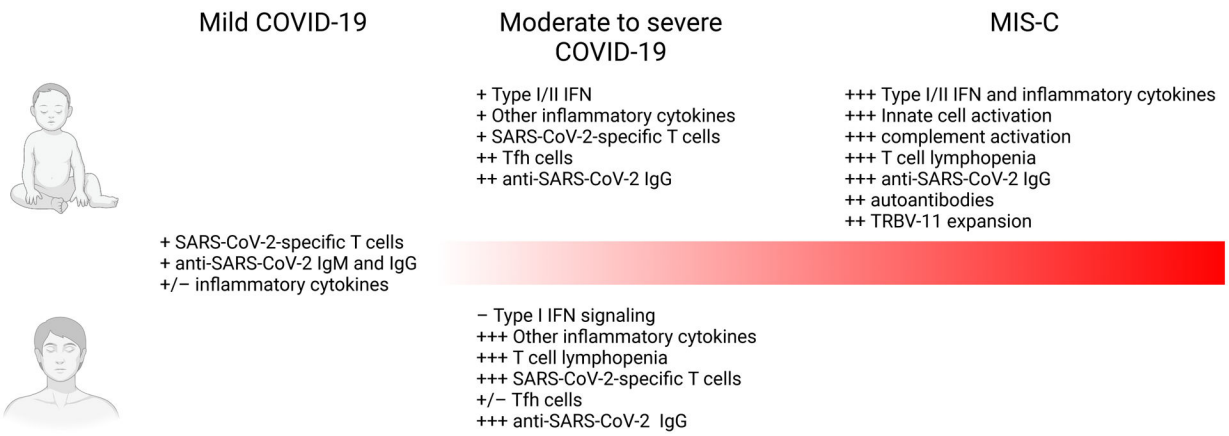

Figure 3.

Comparison of differences in the immune response to SARS-CoV-2 in children and adults, across the spectrum of disease severity.