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Clinical Commentary Review

Age-Related Differences in Immunological Responses to SARS-CoV-2

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There is a striking age-related disparity in the prevalence and severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced coronavirus disease 2019 infections, which might be explained by age-dependent immunological mechanisms. These include age-related physiological differences in immunological responses, cross-neutralizing antibodies, and differences in levels and binding affinity of angiotensin-converting enzyme 2, the SARS-CoV-2 target receptor; antibody-dependent enhancement in adults manifesting with an overexuberant systemic inflammation in response to infection; and the increased likelihood of comorbidities in adults and the elderly. Emerging immunological phenomena such as Pediatric Multi-System Inflammatory Disorder Temporally associated with SARS-CoV-2 or Multisystem Inflammatory Syndrome in Children are now being observed, though the underlying mechanisms are still unclear. Understanding the mechanisms through which pediatric patients are protected from severe novel coronaviruses infections will provide critical clues to the pathophysiology of coronavirus disease 2019 infection and inform future therapeutic and prophylactic interventions. Asymptomatic carriage in children may have major public health implications, which will have an impact on social and health care policies on screening and isolation practices, school reopening, and safe distancing requirements in the community. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:3251-8)

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BACKGROUND

Severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), is the newest human coronavirus (HCoV) that first emerged in December 2019 and has now spread to more than 215 countries, with more than 13.2 million people infected and approximately 575,663 deaths.[1] The spectrum of infection ranges from asymptomatic or mild upper respiratory tract symptoms to severe pneumonia and acute respiratory distress syndrome.[2] Marked disparities in disease prevalence and severity have been observed between pediatric and adult populations. In this review, we summarize the age-dependent differences in COVID-19 phenotypes, and postulate immunological mechanisms that may explain these observations.

CLINICAL PRESENTATION OF COVID-19 IN PEDIATRIC AND ELDERLY POPULATIONS

Although insufficient data exist on the incidence of SARS-CoV-2 infection in children versus adults, particularly in asymptomatic individuals, COVID-19 rates are clearly different between these groups. Most patients with COVID-19 are aged 30 to 79 years (87%), and the highest fatality rate (14.8%) has been reported in those older than 80 years. A systematic review of all COVID-19 literature published between January 1, 2020, and March 18, 2020, found that children accounted for just 1% to 5% of all COVID-19 cases.[3]

A clinically mild disease phenotype has been a consistent finding in pediatric COVID-19 infection. In the largest study of pediatric patients, the prevalence of severe pediatric cases (as defined by the presence of hypoxemia <92%) was 5.9%, a third of that in adults (18.5%).[4] Case reports indicate that infected pediatric patients may demonstrate minimal symptoms and the prevalence of asymptomatic infections may be up to 15.8%.[5] Few pediatric patients with COVID-19 have required intensive care or mechanical ventilation.[5] In contrast, the elderly have a much higher risk of severe disease, intensive care and mechanical ventilation requirements, and fatality.[6] Case-fatality rates in Italy and China show an increasing trend with advancing age—from 3.5% to 3.6% (age 60-69 years), 8.0% to 12.8% (age 70-79 years) to 14.8% to 20.2% (age 80 years and above).[7]

Several explanations for the relatively low rate and severity of disease in children have been postulated. Low community exposure alone would not explain this because children are commonly exposed to large community gatherings such as school

Abbreviations used

ACE- Angiotensin-converting enzyme
ACE-2- Angiotensin-converting enzyme 2
Ang- Angiotensin
ADE- Antibody-dependent enhancement
CoV- Coronavirus
COVID-19- Coronavirus disease 2019
HCoV- Human coronavirus
KD- Kawasaki disease
MIS-C- Multisystem Inflammatory Syndrome in Children
PMIS-TS- Pediatric Multi-System Inflammatory Disorder Temporally associated with SARS-CoV-2
S protein- Spike protein
SARS- Severe acute respiratory syndrome
SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2

and childcare. Inherent biological differences in immune responses between age groups that influence susceptibility to infection and/or progression to disease and clinical manifestations and the higher prevalence of comorbidities in older adults may potentially better explain the discrepant clinical observations. Figure 1 illustrates possible mechanisms contributing to the differences in infection rates and disease severity between children, adults, and the elderly.

POSTULATED MECHANISMS FOR THE AGE-DEPENDENT DIFFERENCES IN IMMUNOLOGICAL RESPONSES TO COVID-19

Cross-protective neutralizing anticoronavirus antibodies

An intriguing possibility for the reduced susceptibility of children may be cross-protection from previous exposure to endemic coronaviruses (CoVs) implicated in the common cold. It is hypothesized that seroconversion to HCoV-NL63 and HCoV-OC43 (non−SARS-HCoVs) may produce antibodies to spike protein (S protein) of CoVs that have some degree of neutralizing and cross-protective activity against infection to another HCoV from the same group.[8] Thus, it is possible that high and sustained seroconversion toward the common non−SARS-HCoVs, which has been demonstrated in the pediatric population, may confer protection against SARS-CoV-2 as well.

Seropositivity to HCoVs also increases gradually with age until early adulthood,[9] but subsequently wanes with increasing age.[10] Other studies have demonstrated high seroprevalence to NL63 and 229E in young children. Dijkman et al[11] found that 75% and 65% of the children aged 2.5 to 3.5 years were HCoV-NL63 and HCoV-229E seropositive, respectively. A study of seasonal CoV infection in healthy children in the community found that OC43 and NL63 were the most frequently implicated HCoVs.[8] Hovi et al[12] also showed that antibody titers to HCoV-OC43 increased rapidly up to age 14 years before tapering off and decreasing after age 60 years. Because this protective cross-neutralizing effect may be attenuated with the waning of neutralizing antibody titers with age, this may possibly manifest as higher infection rates and more severe disease presentation in adulthood.

Antibody-dependent enhancement in adults

An effective humoral response to infection is influenced by the quality and magnitude of the antibody response, with high-affinity antibodies specific to the virus important in achieving viral neutralization.[13,14] SARS-CoV-2 infection is initiated by the binding of surface S proteins on viruses to angiotensin-converting enzyme 2 (ACE-2) receptors present on various host cell types.[15,16] This results in the production of SARS-CoV-2−specific IgM and IgG antibodies.

However, cross-reactive antibodies from other similar virus serotypes may have varying neutralizing abilities on SARS-CoV-2, depending on antibody titers, isotypes, and specificity/affinity for the ACE-2 receptor.

Antibody-dependent enhancement (ADE) occurs when antibodies produced to one virus serotype interacts with a second serotype (cross-reactive) without neutralizing it fully, resulting in enhanced virulence and downstream inflammatory responses.[17] The Fc receptor on monocytes/macrophages and granulocytes has been implicated as the primary receptor to which virus-antibody complexes bind.[18] One of the postulated mechanisms behind ADE in CoV infections involves a circulating neutralizing antibody from a previous infection with a closely related virus binding to a CoV's virion spike, forming an antibody-Fc receptor complex that mimics a viral receptor, triggering a conformational change in the spike, which enhances viral entry into various cells, and an ensuing exuberant inflammatory response.[19]

Antibody concentrations appear to modulate the immune response to SARS-CoV infection. *In vitro* assays for SARS in human cell lines showed that exposure to antisera diluted 10- to 100-fold demonstrated greater viral neutralization, whereas antisera diluted 1000- to 2000-fold facilitated infection and increased cell apoptosis.[20] This is similar to reports from dengue infections where viral neutralization was observed in the presence of high antibody concentrations, which saturated available virion-binding sites, contrasting with low antibody concentrations, which resulted in partial receptor binding facilitating viral enhancement effects, mediated by interactions between the virion-bound antibody and target cells' Fc receptors.[21] These anti−S-IgG and FcR interactions then trigger robust inflammatory responses akin to a cytokine storm, manifesting with acute respiratory distress syndrome and respiratory failure.[16] Higher titers of cross-neutralizing antibodies were linked to lower odds of reinfection, whereas lower subneutralizing levels were linked to ADE.[22] It is thus possible that higher cross-reactive antibody titers in children may be protective, whereas low antibody titers in adults may facilitate ADE.

Differences in antibody isotype, specificity, and affinity also influence the host response toward neutralization or ADE.[13] In murine studies of viral vector vaccines encoding the SARS-CoV S protein and nucleocapsid protein, respectively, nucleocapsid protein−immunized mice showed significant upregulation of proinflammatory processes and lung disease.[23] In contrast, antibodies to different epitopes of the S protein demonstrated differential immune responses, such as protective responses generated by antibodies to the receptor-binding domain or the HR2 domain, and ADE by antibodies specific to other S epitopes.[24]

In addition, older adults and elderly may exhibit greater afucosylation of IgG.[25] Patients with dengue hemorrhagic fever or dengue shock syndrome caused by ADE were found to produce

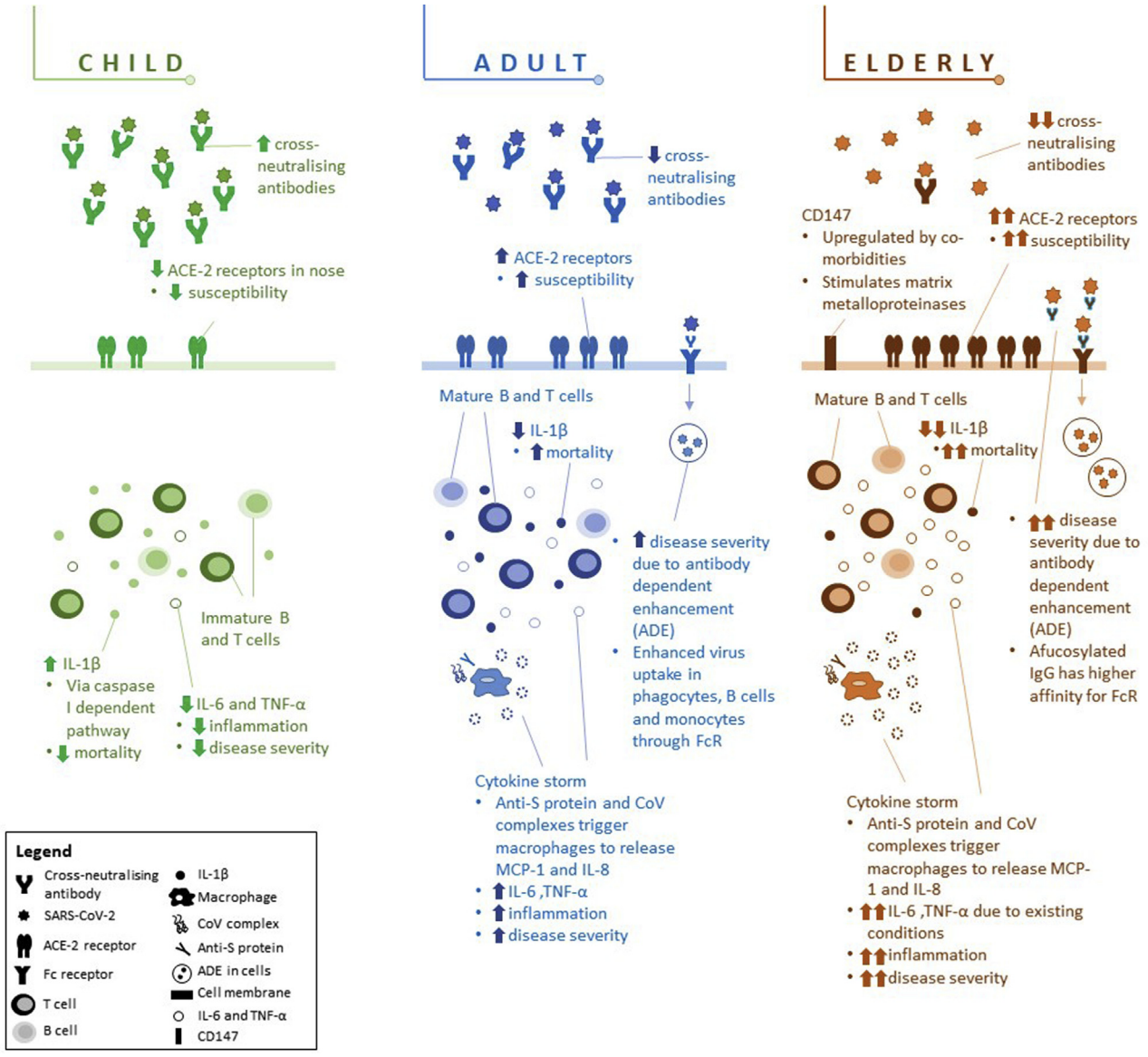

FIGURE 1. Differences in physiological responses of children, adults, and elderly to SARS-CoV-2. Children generally experience infrequent, mild, and self-limiting infections, which may be due to (a) higher levels of cross-neutralizing antibodies, (b) lower levels of ACE-2 receptors in nasal epithelium, which lowers susceptibility to infection, (c) immature B and Tcells and higher regulatory T-cell response, and (d) lower IL-6 and TNF-α production, limiting inflammatory response. Moreover, adults may experience ADE where the S protein enhances entry into cells via Fc receptors, resulting in cytokine storms, which cause severe lung injury. Elderly may be even more susceptible to ADE because they have more afucosylated IgG, which has a higher affinity with Fc receptors. Existing comorbidities in elderly also result in upregulation of CD147, increasing viral entry as well as exacerbation of proinflammatory responses, which increase mortality risk.

greater quantities of afucosylated IgG with stronger affinity to Fc receptors.[26] A preprint by Larsen et al[27] also highlighted that patients with severe COVID-19 expressed heightened afucosylated IgG responses. The higher likelihood of increased afucosylated IgG in adults and elderly may account for the higher incidence of ADE and aggravated symptoms.

Finally, ADE may also arise *de novo* as a pathogenic process unrelated to cross-reactive antibodies. The "multiple hit" model of neutralization proposes that viral neutralization corresponds to the number of antibodies coating the virion, which is influenced by the affinity and concentration of antibodies.[28]

Physiological differences in immunological responses in children versus adults and elderly

Immature immune system in children compared with adults. Children generally develop milder forms of viral disease, which may be due to their relatively immature immune systems.[29] Children exhibit predominantly T_H2, T_H17, and low T_H1, IFN type 1 immune responses,[30] as well as lower levels of memory T and B cells due to reduced lifetime exposure to foreign antigens.[30,31] Regulatory T cells, more abundant in children, exert stronger immune regulatory effects than those in

adults, which may protect them against severe disease manifestations.[32]

Children also appear to exhibit limited proinflammatory responses. A study in 8 pediatric patients with SARS showed that selective activation of the caspase I—dependent pathway in infected macrophages resulted in a large increase in circulating IL-1β levels but only marginal increases in other proinflammatory cytokines such as IL-6 and IL-12.[33] In clinical studies, it has been observed that most children with COVID-19 also do not have increased inflammatory markers such as procalcitonin, C-reactive protein, and IL-6.[34]

In contrast, adults manifest with heightened T_H1-inflammatory responses are associated with increased disease severity. SARS-infected adults demonstrated elevated IL-1β, IL-6, and IL-12 levels with activation of the nuclear factor kappa B pathway.[35,36] The overproduction of proinflammatory cytokines (cytokine storm) has been shown to result in severe inflammatory lung damage in adult SARS fatalities.[37]

Although definitive immunophenotyping of pediatric and adult immune responses to SARS-CoV-2 is yet to be published, the SARS experience suggests that similar mechanisms may be applicable in SARS-CoV-2 infections due to their high viral sequence homology. A preprint by Rodriguez et al[38] on longitudinal immune profiling of adult patients with COVID-19 showed that proinflammatory IL-6 and IFN-γ levels correlated with severity of COVID-19.

The role of immunosenescence and inflammaging. Aging is associated with 2 profound biological changes in the immune system: Immunosenescence is a gradual decline in the host ability to mount robust immune responses to pathogens, while inflammaging is a chronic increase in low-grade inflammation arising from an overactive yet ineffective alert system.[39,40] Immunosenescence has been shown to impair innate and humoral immunity, whereby immune cells exhibit functional impairment such as reduced migratory, phagocytic, and proliferative capacity resulting in poorer responses and antibody generation along with ineffective clearance of the foreign antigen.[41,42] Toll-like receptors (TLRs), T-cell receptor expression and diversity, as well as downstream cytokine responses have also been shown to decline with age.[43,44] These changes may thus increase disease susceptibility and hamper the mounting of an effective immune response against SARS-CoV-2 in the elderly. The interplay between immunosenescence and inflammaging has been hypothesized to be responsible for the phenomenon of COVID-19 "cytokine storm" in the elderly.[45] In the aged immune system, an initial ineffective innate immune response leads to poor viral clearance and greater viral replication.[46,47] High levels of infected cells drive increased inflammatory cytokine signaling,[48] resulting in sustained dysregulated immune activation, which triggers the cytokine storm.

Balance in renin-angiotensin system pathways. The renin-angiotensin system plays a crucial role in regulating host cardiovascular and renal physiology.[49] Two of the key enzymes in the renin-angiotensin system are the angiotensin-converting enzyme (ACE) and ACE-2. ACE converts angiotensin (Ang) I to Ang II, and also binds to angiotensin receptor subtype 1a AT1aR, which is responsible for driving lung injury through production of proinflammatory cytokines.[50,51]

However, ACE-2 counteracts ACE activity by converting Ang II to Ang (1-7).[52] Consequently, ACE-2 is protective against severe acute lung injury, as depicted in murine models.[53] ACE-2 is also shown to reduce hyperoxic lung injury in mice by inhibiting the proinflammatory nuclear factor kappa B pathway and promoting the Nrf2 pathway, which increases production of antioxidants HO-1 and NQO1.[54]

In COVID-19, binding of SARS-CoV and SARS-CoV-2 virus to cell surface ACE-2 receptors allows viral entry and downregulates ACE-2 expression.[55] This results in reduced protection against lung injury and upregulation of the proinflammatory Ang II pathway, manifesting as increased disease severity.[56] Likewise, increased serum Ang II levels correlating to viral load and lung injury have been observed in individuals with COVID-19.[55] Children (<10 years) were found to have lower ACE-2 expression (2.4 mean $\log_2$, counts per million) in the nasal epithelium, one of the main points of entry of SARS-CoV-2. A marked increase with mean $\log_2$ counts per million of 2.77 and 3.02 were seen in older children and young adults, respectively, which may explain the lower incidence of COVID-19 in the younger age group.[57] Evidence from murine models also showed increased expression of ACE-2 in olfactory epithelium with age[58]; hence, the elderly may be more susceptible to infection.

Impact of comorbidities on immunological responses to COVID-19

Epidemiological studies show that the presence of comorbidities is a risk factor for COVID-19 infection and severe disease. A meta-analysis of 6 studies found that 17.1% of patients with COVID-19 were hypertensive, 16.4% had cardiac/cerebrovascular disease, and 9.7% were diabetic.[59] In this study, patients requiring intensive care were also 2 to 3 times more likely to be hypertensive (28.8% vs 14.1% in non—intensive care unit cases; relative risk, 2.03; 95% CI, 1.54-2.68), have cardio/cerebrovascular disease (16.7% vs 6.2%; relative risk, 3.30; 95% CI, 2.03-5.36), or have diabetes (11.7% vs 4.0%; relative risk, 2.21; 95% CI, 0.88-5.57).

Cardiovascular disease. Several mechanisms have been proposed for the increased cardiac morbidity in COVID-19: (1) direct viral-induced myocardial damage, (2) indirect myocardial injury through viral-mediated cytokine storm,[60] and (3) upregulation of ACE-2 receptors by drugs.

Direct viral-induced myocardial damage. SARS-CoV—infected mice demonstrated an ACE-2—dependent myocardial infection, with downregulated ACE-2 protein expression, which mediates increased pulmonary vascular permeability resulting in pulmonary edema and respiratory failure.[61] Autopsy samples from deceased patients with SARS also showed detectable viral RNA, marked macrophage infiltration, and myocardial damage in myocardial samples,[61] demonstrating the ability of SARS-CoV to mediate myocardial inflammation and damage (myocarditis), which is likely responsible for the high cardiovascular morbidity, particularly in patients with preexisting cardiovascular disease.

Indirect cardiac injury due to cytokine storm. Severe pneumonia or acute respiratory distress syndrome induces a significant inflammatory response termed a cytokine storm, producing high levels of proinflammatory cytokines, which in turn induce myocyte damage and impairment of myocardial

function,[62] as well as exacerbate systemic hypoperfusion, myocardial and multiorgan ischemia, and ventilation-perfusion mismatch. Autopsy specimens from SARS-infected patients demonstrated high levels of MCP-1TGF-β1, TNF-α, IL-1β, and IL-6, along with dense infiltration of T cells, monocytes/macrophages, and lymphocytes in pulmonary interstitial tissues, and significant apoptosis of pneumocytes, demonstrating the viral cytopathic effect and immunologically mediated cell damage, which may be due to a combination of cytokine storm and ADE effects.[63]

Upregulation of ACE-2 receptors by drugs. ACE-2 expression can be upregulated by drugs such as ACE inhibitors or Ang II type I receptor blockers.[64] ACE inhibitors block ACE receptors from converting Ang I to Ang II, whereas ACE inhibitors or Ang II type I receptor blockers prevent Ang II from binding to Ang II type 1 receptors.[65] Human intestinal cells expressed higher levels of ACE-2 after treatment with ACE inhibitors *in vitro*.[66]

Diabetes mellitus. Murine diabetes mellitus models have demonstrated increased ACE-2 expression in the lung, kidney, heart, and pancreas.[67] Novel genetic epidemiology tools such as phenome-wide Mendelian randomization study have enabled investigation of association between genetic variants and disease phenotypes.[68] Phenome-wide Mendelian randomization study demonstrated a tentative causal association between diabetes-related traits and ACE-2 expression in the lung.[69] Type 2 diabetes mellitus is characterized by increased proinflammatory T_H1 and T_H17 cells and decrease in anti-inflammatory regulatory T cells,[70] accentuating the systemic inflammatory responses in the COVID-19—associated cytokine storm, which leads to more severe end-organ damage and increased morbidity in patients with diabetes mellitus.[71]

In addition to ACE-2, CD147 has been identified as a second receptor for SARS-CoV-2.[72] CD147 and matrix metalloproteinase expression levels are often upregulated in inflammatory diseases, suggesting that the increased mortality in patients with other comorbidities may be due to the high expression of CD147 and matrix metalloproteinase, hence increasing susceptibility to infection.[73,74]

Pediatric multisystem inflammatory disorder. Recent reports of a new postinfectious pediatric multisystem inflammatory disorder have emerged from regions recovering from severe COVID-19 outbreaks. This entity has been described as PMIS-TS (Pediatric Multi-System Inflammatory Disorder Temporally associated with SARS-CoV-2) or MIS-C (Multisystem Inflammatory Syndrome in Children).[71,75-77] The first published series of cases from London, United Kingdom, described 8 children with a hyperinflammatory syndrome akin to Kawasaki disease (KD) shock syndrome. These children presented with fever, rash, conjunctivitis, peripheral edema, and evidence of coronary artery inflammation similar to that of KD, a well-known pediatric autoinflammatory systemic vasculitis thought to be viral-triggered. A second case series from Italy compared clinical, laboratory, and immunological characteristics of 10 children with PIMS-TS to a retrospective cohort of 19 patients with KD. In contrast to the retrospective cohort, patients were generally older (mean age, 7.5 years vs 3.0 years), more likely to present with incomplete KD, and had prominent gastrointestinal and meningeal symptoms, with significant lymphopenia and thrombocytopenia. There was a higher incidence of severe disease manifesting with hypotension and hypoperfusion, abnormal echocardiography, elevated cardiac enzymes, and increased adjunctive steroid requirements.[78] The 2 largest series of MIS-C to date reported clinical data on 91 cases from New York, and 186 cases from 26 other states.[79,80] Although features of KD were found in one-third of the cohort, only 60% fulfilled criteria for typical or atypical KD, with younger children (below 12 years old) being more likely to present with KD. The course of illness was severe, with 80% requiring intensive care unit admissions, 50% with hypotension requiring inotropic support, and a mortality rate of 0.1% to 2%. Cardiac dysfunction, coagulopathy, gastrointestinal symptoms, and significantly raised inflammatory markers were prominent features consistent with a systemic hyperinflammatory state. Most of the patients received immunomodulatory treatment with intravenous immunoglobulin, and glucocorticoids, IL-6 inhibitors (toculizumab and siltuximab), and IL-1Ra inhibitor (anakinra) were used in a subset of patients.

The pathogenesis and immune mechanisms underlying PMIS-TS/MIS-C are still poorly understood. The prevalent hypothesis involves an abnormal immune response to SARS-CoV-2 in genetically susceptible populations. There is a strikingly higher incidence of typical KD in East Asian populations compared with Western populations (239.6 vs 20.8 and 14.7 per 100,000 children <5 years in Japan, the United States, and Italy, respectively),[81,82] suggesting that genetic predisposition is an important factor in the pathogenesis of KD. The case series from the United States and the United Kingdom found a higher proportion of PMIS-TS/MIS-C in black and Hispanic children than in the general population, although this may also reflect the higher incidence of COVID-19 in these communities.[79,80] Certain endemic HCoVs (in particular HCoV-229E) have previously been implicated as triggers of KD in Japanese children.[83] A novel CoV, New Haven HCoV, was also speculated to be a trigger for KS in a cohort of children from the United States.[84] This association was not found in a larger restrospective study from Japan, which found an RNA sequence of HCoV-NH in 5% of controls, but none in children with KD.[85]

Interestingly, no confirmed cases of PMIS-TS have been reported in Asia so far, although many of these countries have experienced similar large COVID-19 outbreaks, and earlier in the pandemic due to proximity to China. This could be due to under recognition, an increased genetic susceptibility to PMIS-TS/MIS-C in non-Asian populations, and/or differing viral strains in different countries, with a predominant viral strain in Europe and the United States responsible for this geographically limited immune phenomenon.

Further study is urgently required to delineate the clinical, laboratory, and immunological features of PMIS and long-term sequelae, establish causative links to COVID-19 infection, and investigate the genetic, epigenetic, and immunological mechanisms underlying PMIS-TS. Despite valid concerns about the emergence of post-infectious PMIS as a cause of significant morbidity in a small group of children, overall morbidity from COVID-19 in children remains markedly low in comparison to the adult population.[3]

CONCLUSIONS AND SOCIAL IMPLICATIONS FOR POLICYMAKERS

The pediatric population appears to be spared the brunt of COVID-19 morbidity. The disparity between the pediatric and adult populations might be explained by inherent biological differences in immunological responses to CoV infections and the presence of comorbidities in older adults. Understanding the immunological differences between the young and the old could potentially lay the groundwork for future therapeutics such as convalescent plasma infusions,[86] mAbs,[87] or vaccine development.[88]

In addition, the unique features of pediatric COVID-19 may have an impact on clinical decision making and health care policy frameworks addressing the growing threat of COVID-19. Most pediatric COVID-19 cases are detected only in family cluster screening, displaying very mild or no symptoms at all[89] and demonstrating prolonged viral shedding in their nasopharynx and stools for up to 2 to 4 weeks after infection.[90] In addition, the detection of a high prevalence of asymptomatic/presymptomatic carriage in children would strongly support screening and quarantine of whole family clusters upon a positive diagnosis in an adult to reduce the risk of perpetuating community spread.

The evidence on seroprevalence and changes in antibodies with age suggest that natural immunity to SARS-CoV-2 may be relatively short lived. Antibody titers in survivors of SARS, the most closely related virus to SARS-CoV-2, have been shown to decline after a few years.[91,92] It is also possible that subsequent SARS-CoV-2 infections could be more severe than the initial infection. Moreover, because vaccine-induced immunity is typically less potent and less enduring than naturally acquired immunity, it might be postulated that vaccinated individuals may be susceptible to more severe COVID-19 sooner than those who acquire immunity through natural infection. Although this is beyond the scope of the current review, it has potentially far-reaching implications for vaccine development, which is currently touted as the solution to the current global crisis.

Large-scale seroepidemiological studies will be required to definitively characterize trends of transmissibility, infection, asymptomatic carriage, and longevity of immunity across separate age groups. Future research should also focus on identifying predictors of clinical phenotypes, prognosis, and outcomes across the different age groups and aim to elucidate protective immunological mechanisms in patients with mild clinical phenotypes, to guide therapeutics and vaccine development. Health policies governing containment efforts such as social distancing, school and workplace closures as well as plans for economic restoration should also be made in careful consideration of the biological differences in clinical manifestations, viral carriage, and transmissibility in pediatric versus adult populations.

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