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Neonatal and Children’s Immune System and COVID-19: Biased Immune Tolerance versus Resistance Strategy

Shokrollah Elahi

The recent outbreak of COVID-19 has emerged as a major global health concern. Although susceptible to infection, recent evidence indicates mostly asymptomatic or mild presentation of the disease in infants, children, and adolescents. Similar observations were made for acute respiratory infections caused by other coronaviruses (severe acute respiratory syndrome and Middle East respiratory syndrome). These observations suggest that the immune system behaves differently in children than adults. Recent developments in the field demonstrated fundamental differences in the neonatal immune system as compared with adults, whereby infants respond to microorganisms through biased immune tolerance rather than resistance strategies. Similarly, more frequent/recent vaccinations in children and younger populations may result in trained immunity. Therefore, the physiological abundance of certain immunosuppressive cells, a tightly regulated immune system, and/or exposure to attenuated vaccines may enhance trained immunity to limit excessive immune reaction to COVID-19 in the young. The Journal of Immunology, 2020, 205: 1990–1997.

It has been reported that newborns and infants are highly susceptible to infections (1). This has been attributed to an underdeveloped or immature immune system (2, 3). However, this notion has recently been challenged and replaced by the presence of “active immunosuppression” in early life (4, 5). This concept contradicts the traditional notion that the immune system aims to identify and neutralize pathogens and instead suggests that the immune system enables the host to tolerate the presence of nonpathogenic and pathogenic microorganisms, which is a distinct and smart defense strategy (6). Although the offensive mechanism(s) to eliminate the pathogen may work in some circumstances, it is not always the best defense strategy as it can be enormously costly for the host (7). The natural selection in most circumstances favors coexistence and tolerance that are not offensive because this evolutionary mechanism can prevent collateral damage and preserve resources in the host. The concept of tolerance is not only restricted to infection and can also be applied to other diseases, such as protective mechanisms to reduce further tissue destruction in autoimmune diseases (8).

The natural host defense against infection aims to either eliminate the pathogen or prevent/reduce damage to the host (9). Thus, a host defense can be divided into two main categories: 1) the clearance or resistance mechanism and 2) the tolerance mechanism. The resistance strategy protects the host by eliminating the pathogens and/or neutralizing their toxic and harmful products. This strategy is associated with the induction of innate and adaptive immunity. Although this strategy is essential to reduce the pathogen burden, it sustains a significant cost to the host fitness (8). Collateral tissue damage or immunopathology can be the negative consequence of host defense against infection (10). Of course, the magnitude and duration of resistance mechanism can determine the size of immunopathology. The optimal immune response requires a balance between the pathogen clearance and the immunopathology (11). However, such balance is not always possible; thus, to reduce the fitness cost, an alternative approach, tolerance mechanism, is crucial. Even though such a mechanism does not necessarily influence pathogen burden, it can reduce the collateral damage caused by the infection or the immune system against the pathogen (8). The best example is the lack of association between the pathogen burden and the disease severity in bacterial infection (12, 13). Thus, tolerance reduces the susceptibility of the host to tissue damage without directly influencing the pathogen burden. Recent evidence indicates that infants are highly prone to host-mediated immunopathology in the absence of a tolerance mechanism (14). For example, <5–10% of neonatal sepsis cases are culture proven and the rest are based on symptoms and clinical signs, which can be related to an excessive immune response under certain circumstances (15). It is thus not unpredictable that a tolerance mechanism has evolved for allowing the establishment of diverse commensal

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Abbreviations used in this article: ACE2, angiotensin-converting enzyme 2; CEC, CD71+ erythroid cell; HBV, hepatitis B virus; HCV, hepatitis C virus; hRSV, human respiratory syncytial virus; MDS, myeloid-derived suppressor cell; MERS, Middle East respiratory syndrome; MMR, measles, mumps, and rubella; SARS, severe acute respiratory syndrome; Treg, regulatory T cell.

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microbial communities in newborns/infants (4). Also, a tolerogenic approach is vital to prevent excess immune reaction to pathogens. Otherwise, a resistance mechanism strategy could cause increased morbidity and mortality in this most vulnerable population (16).

Disease tolerance to viral infections in infants and children

Decreased rather than increased immune response can be associated with lesser immunopathology and protection against certain pathogens in early life. The benefits of such attenuated immune effectors are well described for viral infections such as hepatitis B virus (HBV) and HIV in which the immune regulatory mechanisms (e.g., active immunosuppression) during early life attenuate excessive and potentially harmful immune responses. For example, in infants and children, HBV infection rarely results in acute hepatitis, whereas this is common in adults (17). In addition, vertical HBV infection often leads to chronic disease in infants, which might be associated with immunotolerance (17). This is also the case for hepatitis C virus (HCV) as clearance of the virus without treatment is more common in infants than adults (18). This transient HCV viremia and spontaneous viral clearance in children (19) might be related to the lack of a robust innate immune response, as shown by unchanged proinflammatory cytokines (20). These observations were further confirmed by a relative suppression of T cell activation in HCV-exposed children. These observations suggest that a balanced pro- and anti-inflammatory response in HCV-exposed children might account for a spontaneous clearance of the virus (21). The same has been found in CMV, EBV, and varicella-zoster virus, which are other highly abundant viral infections in children (22, 23). In most cases (75–80%) of CMV, infected newborns do not express clinical manifestations and excrete the virus for several years (24). This has been attributed to the inability of the neonatal immune system to control the viral replication in some organs (25). This lack of a robust immune response against the virus might be beneficial for the young because an inflammatory response can result in immunopathology and collateral damage as reported in a neonatal mouse model (26). Similarly, in early childhood, EBV infection is asymptomatic or associated with a mild disease, whereas it often manifests as an acute infectious mononucleosis in adults because of an exaggerated immune response (27, 28). The mechanism underlying the lack of EBV symptoms in early life is not well defined; however, a lower number of new infectious virions is reported to be associated with mild and subclinical symptoms (29). Mechanistically, limited viral Ags because of fewer infectious particles results in immune surveillance avoidance and is subsequently associated with EBV persistence (29). As such, the occurrence of asymptomatic EBV in early childhood elicits limited virus-specific CD8+ T cells, whereas excessive expansion of CD8+ T cells is the cause of symptoms in adolescents (e.g., acute infectious mononucleosis) (30). These observations suggest that the general concept of disease tolerance in infants can be beneficial when it comes to CMV and EBV infections. The immunological basis for uncomplicated varicella-zoster virus in children compared with life-threatening infection in healthy adolescents and adults is not well understood but might be related to changes in effector functions of APC and T cells (31). Another example is human rhinoviruses responsible for respiratory infections (32). Despite the extremely high frequency of human rhinovirus infection in healthy young children, most cases of infection remain asymptomatic or present very mild symptoms (33). Human respiratory syncytial virus (hRSV) is the main cause of respiratory infections in infants. Although the majority of infected infants display a mild upper respiratory tract infection, this is now recognized as a significant concern in the adult population (34, 35). However, there is still the unanswered question as to why some unfortunate children suffer from severe bronchiolitis. Some risk factors such as prematurity, low birth weight, low socioeconomic status, immunodeficiency, and pre-existing conditions are reported as likely contributing factors influencing the development of a severe disease (36, 37). It has been reported that exacerbated immune response by infiltration of neutrophils, T cells, and proinflammatory cytokines can cause damage to respiratory tissue (38, 39). For example, hRSV upregulates NF-κB, resulting in the induction of IL-18, TNF-α, CCL-5, and other inflammatory factors (40). In line with this, the elevation of IL-6 and TNF-α has been associated with immunopathogenesis in hRSV-infected infants with bronchiolitis (38). In particular, disease severity appears to be correlated with IL-6/TNF-α ratio in nasopharyngeal fluids of infants with bronchiolitis (41). This implies that neutralization of TNF-α might have therapeutic implications as shown in a mouse model of respiratory syncytial virus infection (42). Although the exact underlying mechanism of bronchiolitis in hRSV remains contentious, a pronounced immune cell infiltration and proinflammatory cytokines support a role for the immune-mediated tissue damage (43). Therefore, the resulting balance of viral clearance and immunopathology could be the key factor in determining the disease outcome in respiratory syncytial virus infection. This differential disease outcome is also evident in some infected children with HIV as compared with adults. In pediatric HIV infection, disease progression in the absence of antiretroviral therapy is faster than in adults (44). However, this is not the case in all children as a subset of antiretroviral therapy–naive children remains clinically healthy with normal-for-age CD4 counts defined as pediatric non-progressors (45). Nevertheless, the mechanisms associated with nonprogression are markedly different in children versus adults. Nonprogressing adults, so-called elite controllers or long-term nonprogressors, are typically characterized by having polyfunctional CD8+ T cells restricted by certain HLA alleles (mainly HLA-B27 and HLA-B57) (46–49). Such a robust CD8+ T cell response results in the suppression of viremia beneath detection levels (normally <50 HIV RNA copies per milliliter of blood in elite controllers but <10,000 in long-term nonprogressors) that high CD4+ T cell counts are maintained (46, 47). By contrast, nonprogressing HIV-infected children are not enriched with protective HLA alleles to reduce viral load (50). Therefore, in contrast to HIV-infected adults, these children, despite having high viremia (median 26,000 copies per milliliter), will maintain a normal CD4+ T cell count (50) and low levels of immune activation (51). This phenotype of normal CD4+ T cell counts with minimal immune activation levels despite high viral load suggests that the immune activation rather than virus replication may account for the disease progression (50). This concept is well accepted in the natural host of the SIV (e.g.,
sooty mangabey and African green monkey) as low level of immune activation is observed in these animals despite having high viral load (52). These observations suggest that the attenuated immune response in this group of children enables them to avoid the collateral damage and disease progression in pathogenic infection and, in fact, protects them. Overall, mounting evidence supports the concept that neonatal immunity is not underdeveloped but instead tightly regulated and dynamic in response to pathogenic and not pathogenic (e.g., microbiome) stimuli. Such an intelligent and regulated immune system plays a crucial role in protecting growing infants for invaders while at the same time preventing excessive immune response that can be costly for the host (53). Therefore, the de-escalating/tolerance versus resistance mechanism against infections in infants is a protective and intelligent mechanism for survival, continued growth, and development when considering the infants’ limited resources.

The benefits of higher infection tolerance in infants and children

The newborn gets exposure to millions of bacteria in the birth canal through natural delivery, which is the beginning of a long journey of host–microorganisms interactions. The fetus has minimal to no exposure to foreign Ags under normal circumstances, and therefore, in the absence of tolerance mechanisms, such exposure could result in intensifying inflammation at the mucosal surfaces and skin where brisk postnatal colonization with commensal microbes occurs (54). Therefore, a state of colonization tolerance is essential for allowing the swift adaptation of commensal bacteria. This tolerance is mediated in part by the physiologically enriched erythroid precursors, coexpressing CD71 (transferrin receptor) and CD235a in humans but CD71 and TER119 in mice (54). These cells are almost absent in healthy adults unless under certain physiological (e.g., pregnancy) or pathological conditions (chronic infections and cancer) (55). CD71+ erythroid precursors (CECs) exhibit immunosuppressive properties and prevent a hyperimmune reaction to pathogens and commensal microbes in early life (4, 54). CECs by the sequestration of multiple soluble factors such as arginase-2, TGF-β, reactive oxygen species, or cell–cell interactions suppress innate and adaptive immune cells (54, 56–61). In particular, we have shown that CECs promote the induction of regulatory T cells (Tregs) (61). Also, other groups have reported the abundance of another subset of suppressor cells, myeloid-derived suppressor cells (MDSCs), in infants (62, 63). The physiological abundance of certain immunosuppressive cells supports the existence of a highly regulated immune system in early life. The physiological abundance of these regulatory cells can reduce morbidity and mortality in neonates (16). For example, it has been reported that neonates are more resistant to LPS challenge than adult mice. LPS/D-GalN induces liver injury and 100% mortality in adult mice within 12 h, whereas it spares newborns (16). Studies also report a greater bacterial load in newborns infected with different pathogens, which does not seem unpredictable at first glance, because we believe infants are more susceptible to infections than adults. As such, a higher bacterial load would appear to be normal. For instance, in the case of sepsis in adults, a bacterial load of 1–30 CFU/ml blood has commonly been reported, whereas in neonates this is a much higher 50–500 CFUs, and in one-third of infected newborns, this exceeds 1000 CFUs (12, 13). This examination becomes more interesting when 100% mortality in adult patients has been associated with >100 CFU/ml blood, whereas mortality of 73% in neonates required >1000 CFUs/ml blood (64). Such has been validated in animal models that newborns can tolerate much greater bacterial loads than adults (65). These studies suggest that newborns have a greater tolerance to bacteremia and can survive levels of bacterial load in their blood that normal adults cannot. This delay in bacterial clearance has been related to inefficient phagocytosis and impaired neutrophil recruitment in neonates (66, 67). For instance, it has been shown that neonatal monocytes/neutrophils exhibit impaired phagocytic capabilities of Escherichia coli and Staphylococcus aureus in vitro, when whole blood was used (57, 68). These examples have contributed to the theory of neonatal immaturity; however, this notion has been challenged by showing comparable phagocytosis capacity of neonatal and adult monocytes and neutrophils in the absence of CECs in vitro (57). In fact, we showed that the observed deficiency was related to the presence of CECs and active immunosuppression in neonates and was not simply a state of deficiency in phagocytosis (1, 54, 57). These data highlight the difference in the used immune mechanism(s) in response to pathogens in neonates compared with adults. Given the higher mortality rate of sepsis in neonatal mice following exogenous supplementation of proinflammatory cytokines (69), newborns likely benefit from the immunosuppression that can inhibit the risk of a rapid and harmful immune response. Children and adolescents may benefit from a similar phenomenon but by a different mechanism. For instance, more frequent and more recent live attenuated viral vaccine immunizations can promote the expansion of long-lived MDSCs in children and younger adults (70). These immature phenotype cell populations exhibit remarkable immunosuppressive properties by downregulating proinflammatory cytokine production and T cell proliferation (71). Therefore, the presence of innate immune regulatory mechanism(s) in newborns and children may protect them from the collateral damage associated with infections.

The choice of effector immune response in newborns and children

The immune system not only identifies the infecting pathogen (e.g., a bacterium versus a virus or a fungus) but also selects the immune and energetic cost of its response (72). Any infection results in symptoms that are either directly associated with the pathogen-imposed damage or with an excessive immune response. The general concept is that the regulatory mechanisms modulate the immune response, resulting in optimal immune response in terms of magnitude and duration with minimal immunopathology (5). However, under different circumstances, an excessive immune response can result in collateral damage and immunopathology. Not only the quantity but also the quality of immune response can result in different immunopathological consequences. It appears that our immune system deploys different effector responses based on the effector/cost ratio. The idea is that the low-cost response is generated first; if it fails in the clearance of infection, the effector response associated with the next lowest cost is generated on a spectrum defined by the immunopathology cost (72). Sensing of microbial pathogen-associated molecular patterns by macrophages and dendritic cells in the absence of...
immune regulation may induce higher cost effector responses in newborns. For example, the response of macrophages and dendritic cells to pathogen-associated molecular patterns in the presence of CECs generates an effector response of lower-cost, reduced microbicidal activity and immunopathology (54, 57). Therefore, the presence of immunosuppression in the newborn/infant probably calibrates based on the weighted contribution of different costs for the host. An interesting model has been proposed by Iwasaki and Medzhitov (72), illustrating immune effector responses that have different costs to host fitness. For example, constitutive secretion of secretory IgA and antimicrobial peptides (73) is a low-cost protective mechanism. When this mechanism is unable to protect the host from pathogens, the next lowest-cost immune response (e.g., tissue-resident macrophages) will be induced. Recruitment of neutrophils and other immune cells to the site of infection is the next lowest-cost immune response, followed by Th1, cytotoxic T cell response, and Th17. The immune defense against life-threatening pathogens is energetically expensive, and there is a trade-off between investment in a rapid immune response versus growth and development in the infants/children (74). Therefore, the selection of the type of effector immune response in newborns/children should be energetically less costly considering the high energy cost for growth and development (75). Therefore, these different circumstances provide reasoning for the adaptation of infection tolerance versus infection resistance in newborns/infants (Fig. 1).

Infants, children, and younger adults are spared from COVID-19

Pediatric-specific risk factors for COVID-19 are not defined, and there is no clear reason to date explaining why infants, children, and younger adults are at reduced risk of developing COVID-19 once infected with SARS-CoV-2. Newborns and infants infected with SARS-CoV-2 (COVID-19) may benefit from their biased immune tolerance phenotype. Despite thousands of reported cases of infection in China (>20,000 cases by February 6, 2020), only nine infants (0.05%) were hospitalized with COVID-19 (76). Among admitted cases, four infants had a fever, two had very mild upper respiratory symptoms, one had no symptoms, and for the last two, no information was provided (76). In another report, an infant (36 h postpartum) developed a case of neonatal COVID-19 infection from an infected mother; however, the newborn did not present any respiratory symptoms (77). Another study reported a total of 10 confirmed COVID-19 children admitted to different hospitals in China with mild clinical symptoms (78). Similarly, mild symptoms were reported for another two pediatric patients (79). Among >44,000 confirmed cases of COVID-19 in China, 0.9 and 1.2% were aged 0–10 and 10–19 y, respectively (80). Overall, children appear to exhibit milder symptoms following infection with COVID-19 compared with adults, and in most cases, they are asymptomatic (81, 82). Another study categorized the clinical symptoms of 41 admitted hospital patients in Wuhan, but none of them were infants (83). The largest nationwide pediatric study in China reported 2143 patients with respiratory symptoms similar to COVID-19; however, only 34.1% of them were laboratory-confirmed cases. Although this study reported that the disease was milder in infants than adults, it suggested that infants are also susceptible to the virus. However, the major limitation of this report is that more severe and critical cases were in the suspected group than in the laboratory-confirmed group, which suggests that these severe cases might have been caused by other respiratory pathogens but not COVID-19 (84). Similarly, in the United States, among ~150,000 confirmed cases of COVID-19 for which age was noted, children <18 y old accounted for 1.7 of cases with only three deaths (85). This report supports previous data that COVID-19 cases in children present mild disease, but those asymptomatic children can play an important role in the spread of the virus in the community (85). These observations are similar to previous outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which resulted in high mortality in adults but none in pediatrics (86, 87). Thus far, evidence is emerging that COVID-19 infects infants and children with fairly high viral titer but they do not exhibit serious manifestations of the disease, and no mortality has been reported for the pediatric age group (88). Given the number of reported infections in adults, the number of infected infants and children is miniscule. More importantly, infected infants are mainly asymptomatic or exhibit very mild symptoms (76).

A similar phenomenon has been reported with the original SARS coronavirus in mice. This study demonstrated that young mice were able to clear the virus without significant clinical symptoms, whereas all infected adult mice died (89). This suggest that the differential immune response to COVID-19 in adults versus infants may lead to a differential clinical outcome.

Based on the collected preliminary data in COVID-19 patients, cytokine storm may play a role in enhanced disease pathogenesis. For instance, elevated levels of a variety of cytokines, such as IL-1β, IL-1RA, IFN-γ, IP10, IL-7, IL-8, IL-9, IL-10, GCSF, GMCSF, MIP1A, PDGF, FGF, VEGF, TNF-α, and MCP1, were detected in plasma of patients as compared with healthy adult individuals (83). In particular, admitted patients to the intensive care unit had elevated levels of IL-2, IL-7, IL-10, IP10, MCP1, MIP1A, GCSF, and TNF-α compared with those who did not require the intensive

![FIGURE 1.](http://www.jimmunol.org/) This diagram illustrates that a resistance mechanism to a pathogen in adults leads to collateral damage, but a tolerance mechanism to a pathogen in infants reduces such damage.
The abundance of only proinflammatory cytokines IL-1 was higher in COVID-19 patients (83). This is in contrast to the Th1-mediated immune response, IL-4 and IL-10 were also present in COVID-19 infections, mild infection symptoms in infants may be related to the immunotolerance mechanisms during early life. As such, physiological abundance of CECs and MDSCs may limit excessive inflammation in response to SARS-CoV-2 infection in infants. It is worth noting that newborns, children, and younger adults (<18 y old) differ from the immunological standpoint. Therefore, different potential mechanisms may explain the drastic difference in their mortality rates following COVID-19 infection compared with adults (92). Although newborns/infants may benefit from the physiological abundance of immunosuppressive cells, these cells gradually disappear with age (4, 55). Therefore, other unknown factors may account for the milder or asymptomatic infection in older children. For example, a recent report has hypothesized that the trained nonspecific innate immunity following vaccination with live attenuated vaccines such as measles, mumps, and rubella (MMR) could protect adolescents against COVID-19 (93). Thus, live attenuated vaccines such as MMR, rotavirus, smallpox, and bacillus Calmette-Guérin may provide nonspecific protective immunity (94). Another possibility is that such nonspecific effects translate into the induction of long-lived MDSCs (70). Therefore, MDSC-mediated immunosuppression diminishes any excessive inflammatory response to pathogens that can be protective because SARS, MERS, and COVID-19 are all associated with severe pulmonary inflammation and sepsis (95). In support of their claim, the milder symptoms observed in the 955 sailors in the U.S.S. Roosevelt who tested positive for COVID-19 might be related to MMR vaccination, which is commonly given to all Navy recruits (93). The role of Tregs also needs to be taken into consideration because the age-related thymic involution can lead to a decreased output of Tregs after the age of 50 (96). This decline in Treg frequency and function may contribute to age-related increased inflammation and autoimmune diseases (97). Therefore, the presence of a regulatory mechanism mediated by different immunomodulatory cells may serve as a beneficial characteristic in the immune systems of younger populations. However, there is an urgent need to evaluate how the immune system in younger populations (as compared with older populations) responds to COVID-19. We suggest that the tightly regulated nature of the neonate’s microenvironment can prevent the observed proinflammatory cytokine storm in adults as reported in other models (4, 57, 58). Therefore, such differences may explain the mechanism underlying such milder respiratory symptoms in infants and children. However, further studies are urgently needed to test such opinions.

COVID-19 patients may benefit from immunosuppression

The uncontrolled inflammatory response can itself damage the lungs via the excessive release of proteases, reactive oxygen species, and proinflammatory cytokines (98). In addition to localized damage, cytokine storm can have detrimental effects on different organs and tissues. Elevated levels of cytokines such as TNF-α and IL-6 can promote septic shock syndrome and collateral damage (98). In agreement with this concept, several immunosuppressive strategies are recommended for the treatment of COVID-19 patients. Current evidence in patients with MERS and SARS suggests that corticosteroids did not influence the mortality rate but delayed viral clearance (99, 100). Among a cohort of 41 COVID-19 patients, systemic corticosteroids were given to some patients without a clear analysis of the outcome (83). Although the administration of systemic corticosteroids for COVID-19 patients is not supported by the World Health Organization guidelines (83), several trials are under way for the efficacy of such treatment options (98). It is worth noting that glucocorticoids (e.g., dexamethasone, prednisone) exhibit differential effects that should be taken into consideration (101). Nevertheless, a most recent randomized clinical trial has shown that dexamethasone reduced deaths by one-third in patients on ventilators and by one-fifth in those receiving oxygen without invasive ventilation (P. Horby, W. S. Lim, J. Emberson, M. Mafham, J. Bell, L. Linsell, N. Staplin, C. Brightling, A. Ustianowksi, E. Elmah, B. Prudon, C. Green, T. Felton, D. Chadwick, K. Rege, C. Fegan, L. C. Chappell, S. N. Faust, T. Jaki, K. Jeffery, A. Montgomery, K. Rowan, E. Juszczak, J. K. Baillie, R. Haynes, and M. J. Landray, manuscript posted on medRxiv). This study suggests that the immunomodulatory role of dexamethasone may prevent progression to respiratory failure and death. Besides, there is another possibility that dexamethasone (because of its immune-mediated effects) can influence hematopoiesis (102), which merits further investigations. Besides, multiple clinical trials are testing the efficacy of neutralizing IL-6, GM-CSF, TNF-α, and adjuvant therapy to absorb a broad range of cytokines (98). Overall these observations indicate a beneficial role for the immunosuppression in patients infected with SARS-CoV-2 virus.

COVID-19 entry in adults versus children

The angiotensin-converting enzyme 2 (ACE2) is expressed in many organs, such as the heart, lungs, intestine, and kidneys (103). SARS-CoV-2 binds to the ACE2 receptor for cell entry (103, 104) and not only gains initial entry through ACE2 but also downregulates ACE2 expression on cell surface such that this enzyme cannot exert its protective role in organs (105). Downregulation of ACE2 in the respiratory tract is linked to neutrophil infiltration that may result in angiotensin II accumulation and lung injury (106, 107). Similarly, ACE2 expression was found to be associated with enhanced susceptibility to SARS-CoV infection (108). Although this association has been reported in vitro, the correlation of ACE2 expression and susceptibility to SARS-CoV-2 remains unknown (109). Retrospective studies on confirmed cases of COVID-19 found that children are spared from the disease (110). Although the mechanism(s) underlying these observations is unknown,
a differential expression of ACE2 in infants and children compared with adults has been suggested (111). However, there is no clear evidence showing the impact of age on ACE2 expression in the lungs except a recent study that has reported that there was no difference in the activity of ACE2 in bronchoalveolar lavage fluids of neonates, children, and adults with acute respiratory distress syndrome (112). Another supportive evidence for the differential ACE2 expression in young versus old is the decline of androgens and estrogens by age. Both these hormones upregulate ACE2 expression; thus, their reduced production by age can result in the downregulation of ACE2 expression (113). The activation of the renin-angiotensin system and the downregulation of ACE2 are reported to be involved in lung injury following SARS-CoV infection (105). Animal studies indicate that the reduced ACE2 activity or the loss of ACE2 results in neutrophil recruitment, enhanced vascular permeability, and exaggerated pulmonary edema, but in turn, supplementation of exogenous ACE2 reverses this inflammatory response (114). Interestingly, it has been reported that SARS-CoV infection downregulates ACE2 in lung tissues of mice, accompanied by lung injury (105). Considering the similarities of SARS-CoV and SARS-CoV-2, there is a possibility that SARS-CoV-2 also downregulates the ACE2 expression, resulting in pathology and lung injury (109). The role of ACE2 appears to be complex; on the one hand, it may increase the risk of SARS-CoV-2 infection as the viral entry to the cell, but on the other hand, it can reduce lung injury following the infection. Although differential tissue expression of ACE2 in children versus adults needs to be determined, higher levels of plasma ACE2 in children have already been reported (115). Therefore, further studies are required to investigate the expression level of ACE2 in children versus adults to determine its potential role in COVID-19 infection.

Conclusions
Emerging evidence indicates that although infants, children, and adolescents are susceptible to infection with COVID-19, only a few have serious symptoms. Most infected infants are asymptomatic but can act as a source of viral transmission. The mechanism(s) underlying circumvention from severe form of the disease in the young (and, in particular, infants and children) is unclear. Based on recent developments in the neonatal immunology field (1, 4, 5, 54, 75), the choice of immune response against COVID-19 in children and adolescents versus adults may serve as an explanation for the observed differential clinical outcomes. Infants may benefit from the physiological abundance of immunoregulatory cells and having a tightly regulated immune system. There is compelling evidence for the innate immune hyperactivation in driving the acute disease in SARS-CoV-2-infected adults. However, the differential immune components in the young may prevent excessive and potentially damaging immune responses to COVID-19 infection. Controlling the inflammatory response to the virus may be as crucial as targeting the virus, as the unrestrained proinflammatory response in some adults can itself result in immune cell infiltration, which triggers a cytokine storm that mediates lung inflammation and injury. Of course, this is just one potential mechanism as other mechanisms are likely involved. Another potential mechanism might be the expression level of COVID-19 receptors in the lungs and other organs/tissues of adults versus infants and children. Thus, the expression pattern of ACE2 and SARS-CoV-2 coreceptor (the transmembrane protease serine 2 [TMPRSS2]) (104) in adults versus children needs to be examined. It is possible to speculate that the differential expression of ACE2 and/or TMPRSS2 in children versus adults could explain different infection outcomes. A full picture of the crucial host immune factors that contribute to the development of severe disease in some patients and milder disease in infants and children remains poorly understood. We speculate that the unique immune compartment in children and the underlying health conditions in adults may partially explain the mild or asymptomatic disease observed in this group of children (Fig. 2). Finally, the nonspecific trained innate immunity may provide another explanation for the milder disease in adolescents. Therefore, further studies of the host immune response to SARS-CoV-2 are warranted, including a detailed investigation of the determinants of healthy versus dysfunctional immune response to address our hypothesis and better understand the immune correlates of protection in the younger population compared with adults.

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