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Understanding the age divide in COVID-19: Why are children overwhelmingly spared?

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Abstract

The rapid emergence and subsequent global dissemination of SARS-CoV-2 Disease (COVID-19) has resulted in over 4 million cases worldwide. The disease has a marked predilection for adults, and children are relatively spared. Understanding the age-based differences in pathophysiological pathways and processes relevant to the onset and progression of disease both in the clinical course and in experimental disease models may hold the key to the identification of therapeutic targets. The differences in the clinical course are highlighted by the lack of progression of the SARS-CoV-2 infection beyond mild symptoms in a majority of children, while in adults, the disease progresses to acute lung injury and an ARDS-like phenotype with high mortality. The pathophysiological mechanisms leading to decreased lung injury in children may involve the decreased expression of the mediators necessary for viral entry into the respiratory epithelium and differences in the immune system responses in children. Specifically, decreased expression of proteins, including angiotensin converting enzyme 2 (*ACE2)* and Transmembrane Serine Protease 2 (*TMPRSS2)* in the airway epithelium in children may prevent viral entry. The immune system differences may include a relative preponderance of CD4+T-cells, decreased neutrophil infiltration, decreased production of pro-inflammatory cytokines, and increased production of immunomodulatory cytokines in children compared to adults. Notably, the developing lung in children may have a greater capacity to recover and repair after viral infection. Understanding the relative contribution of the above processes to the protective phenotype in the developing lung can guide the trial of the appropriate therapies in adults.

Introduction:

SARS-CoV-2 is a newly identified member of the β-coronavirus family that emerged from Wuhan (Hubei Province China) in December 2019 (13). The rapid emergence and subsequent global dissemination of this novel Coronavirus (SARS-CoV-2) Disease in 2019 (COVID-19) has resulted in over 4.7 million cases worldwide (https://coronavirus.jhu.edu/map.html; accessed 5/18/2020). Moreover, there have been more than 300,000 deaths, which calculates to an overall mortality rate of ~6.7%. Domestically in the US, we have experienced over 1.4 million cases and over 89,000 deaths, for mortality of ~6.0% (https://coronavirus.jhu.edu/us-map; accessed 5/18/2020). Although COVID-19 is mild in the majority of cases, a subset of patients rapidly develops acute respiratory distress syndrome (ARDS), a clinical presentation of acute lung injury (ALI), that leads to respiratory failure requiring mechanical ventilation (10).

Differences in Clinical Presentation in Adults vs. Children

One of the most intriguing observations is the significantly reduced prevalence, severity, and mortality among pediatric patients (3). Early reports from China and Italy noted low case numbers among children <18yo. (12) (21) These trends remained the same in the US, and even more compelling data emerged. Among the first 149,082 US cases (through 4/2/2020), only 2,572 (~1.7%) were infants, children, and adolescents <18yo (children <18yo make up 22% of the US population) (4). A systematic review of literature showed that children accounted for 1-5% of diagnosed cases (23). Further, children were less likely to have symptoms and a lower rate of hospitalization. Strikingly, only three pediatric deaths were identified by the Centers for Disease Control at that time. These profoundly decreased rates of symptomatic infection, hospitalization, and death are well beyond statistical significance, require further examination, and may hold the key to identifying therapeutic targets.

In 2015 alone, 291.8 million episodes of lower respiratory tract infection (LRI) occurred worldwide, of which more than 1/3 occurred among children <5yo (11). An estimated 704,000 deaths occurred among children <5yo. Approximately 6.6% of these pediatric deaths (more than 46,000) were attributed to respiratory syncytial virus (RSV) or influenza. While these viruses cause significant morbidity and mortality, other coronavirus outbreaks have led to a curiously similar pattern as SARS-CoV-2 (3) (**Figure 1**).

Adults exposed to SARS-CoV-2 who are beginning to develop COVID-19 usually display fever, cough, or shortness of breath (93%) (4). Cough is the most common presenting symptom, occurring 80% of the time, whereas fever and shortness of breath occur among 71% and 43% of affected adults, respectively. Finally, myalgia (61%) and headache (58%) are also symptoms found in over half of infected adults. Furthermore, when it comes to adults, advanced age, obesity, male sex, and the presence of diabetes appears to confer an independent risk for mortality when compared to healthy adults. Of note, what is most striking is that COVID-19 is not just a pulmonary disease but one with a pulmo-hematological-endothelial-inflammatory consequence, unlike any other viral pneumonia that has been reported thus far. COVID-19 patients with elevated d-dimer, ferritin, lower lymphocyte count, elevated neutrophil to lymphocyte ratio probably have a pro-inflammatory microenvironment, which in turn portends a worse prognosis when compared to those that do not.

Pediatric patients respond to SARS-CoV-2 exposure differently. Neonates, children, and adolescents <18 with SARS-CoV-2 are less likely to have any symptoms (4). Among children, fever is the most common presenting symptom, occurring 56% of the time, whereas cough and shortness of breath occur in only 54% and 13%, respectively. Myalgia (23%) and headache (28%) are relatively infrequent symptoms in children. In neonates and infants, the disease may have a non-specific presentation with fever and lethargy (16)(27). Among forty children admitted in North American pediatric intensive care units with COVID-19, an overwhelming majority (83%) had preexisting underlying medical conditions (32). These statistics may even overstate the frequencies, given that many children may have such mild symptoms that few seek medical care. Recently, a multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19) has been reported in children, leading to a CDC advisory. This Kawasaki disease-like syndrome presents with persistent fever and symptoms including hypotension, multiorgan involvement, and elevated inflammatory markers (29). Intriguingly, respiratory involvement was not seen in all cases (36). This syndrome is still rare amongst children with a reported incidence of no more than one in 100 SARS-CoV-2 exposed children.

To further understand the difference between the children and adults, we focused on the following mechanisms that have been reported or postulated to date. 1. Differences in mediators necessary for viral entry, and 2. Immune system mediated response.

Differences in Mediators Necessary for Viral Entry:

SARS-CoV-2 enters host cells following the binding of the viral spike (S) protein to angiotensin-converting enzyme 2 (ACE2) and priming of the S protein by host proteases such as TMPRSS2 (14). ACE2 also converts angiotensin-2 to angiotensin (1-7)_ (8) and protects the lung from injury by keeping angiotensin-2 levels in check. Binding of SARS-CoV-2 to ACE2 can result in inhibition of the enzyme and even its internalization, tilting the balance from the generation of angiotensin (1-7), which are protective towards angiotensin 2 that is known to have detrimental effects (30). A pre-print study with snRNA-seq data from the lung across the age-span shows an increase in the proportion of alveolar epithelial cells expressing *ACE2* and *TMPRSS2* in adults compared to young lungs. This may suggest reduced viral entry and replication in the lung epithelial cells in children compared to adults (37). Another preprint study with an integrated analysis of single-cell atlas to elucidate the cell-specific expression of viral entry mediators found that *ACE2* and *TMPRSS2* expression in airway epithelial and alveolar type 2 (AT2) cells increases with age with very low expression in infants and young children (25). Recent GSEA analysis revealed that high expression of ACE2 was also related to the activation of neutrophils, NK cells, Th17 cells, Th2 cells, Th1 cells, dendritic cells, TNFα secreting cells leading to a severe inflammatory response (20). However, a clinical study in ARDS patients showed that expression levels of ACE or ACE2 did not appear to differ in bronchoalveolar lavage in ARDS patients between children or adult populations (31). Thus, children may be protected from serious pulmonary consequences in part by the decreased expression of receptors and other proteins that are essential for viral entry into the respiratory epithelium.

Differences in Immune System:

The immune system is considered immature or weakened in the newborn and the aged, respectively, with reduced antimicrobial activity by neutrophils and macrophages, reduced antigen presentation by dendritic cells, and decreased natural killer cell-mediated defense[17]. On the other hand, the heightened immune response to the virus in many adult patients can lead to the worsening of lung disease with SARS-CoV-2 infection (37). The extent of lung damage in adult patients due to the virus replication and due to the contribution from the overactive immune system still needs to be elucidated. With the 2002 SARS-CoV infection and the relative sparing of children, one of the hypotheses was that the second phase of respiratory deterioration in the infected adults was immune-mediated and not directly related to viral replication, and this phase was muted in children. By using *in vivo*-passaged SARS-CoV in BALB/c mice, Nagata *et al*. showed lethal pulmonary edema and diffuse alveolar damage in adult but not young mice (26). In non-human primates, SARS-CoV-infected aged macaques develop more severe pathology with more vigorous host response to virus infection, with NF-kappaB emerging as a central player (34).

The T-cell response plays an important protective role against respiratory viruses . In 21 adult patients with moderate or severe COVID-19, there was a marked reduction in both $CD4^+$ and $CD8^+$ T-cell population (5) in patients with severe disease compared to those with moderate disease. In a murine model of the SARS-CoV infection using the mouse-adapted SARS-CoV (MA15), Zhao *et al*. showed that a virus-specific T cell response, even in the absence of activation of the innate immune response, was sufficient to enhance survival and attenuate disease (42). In a murine study with senescent mice, $CD4^+$ T-cell (but not $CD8^+$ T-cell)-mediated immunity was crucial for controlling viral replication and disease severity in primary SARS-CoV (6). The profound lymphocytopenia seen in adults compounded by the effects of aging on the adaptive immune response may play a role in the increased virulence of SARS-Cov-2 in adults compared to children (9).

Imbalance in the production pro- versus anti-inflammatory cytokines may also contribute to this process. One such example would be declining levels of IL-10 production with age. IL-10 has an anti-inflammatory role by decreasing macrophage activation as well as the release and activity of inflammatory cytokines, such as IL-6, TNF-α, and IL-1β (7, 24). Adult murine lungs had significantly lower IL-10 and IL-13 levels before infection than young murine lungs and produced high levels of proinflammatory mediators leading to macrophage and neutrophil infiltration and activation (26). Young mice, on the other hand, produced immunomodulatory cytokines like IL-10 and -13 in addition to the pro-inflammatory mediators. In a lung injury model with both LPS and mechanical ventilation, there was a synergistic increase in neutrophil infiltration and IL-1 beta levels in adult but not in juvenile mice (33). Markers known to be involved in the neutrophil response (MPO, IL-6), are one of the hallmarks of ARDS (31). These markers were significantly lower in neonates and children when compared to adults/older adults. This study found that the absolute number of neutrophils is significantly lower in juveniles and suggested that the extravasation of neutrophils was limited in juveniles when compared to adult animals. This could be secondary to lower expression of adhesion molecules such as p-selectin, a result found in human studies as well (17, 19).

Transcriptomic analysis of the lung in aged mice with SARS-CoV infection showed upregulated immune response and cell-to-cell signaling genes (including TNF-α, IL6, Ccl2, Ccl3, Cxcl10), which was sustained even after viral clearance, suggesting an exacerbated host response to virus (2). Wu *et al*. reported high neutrophil counts and lymphocytopenia associated with the development of ARDS in COVID-19 patients (38). In 171 children with CARS-Cov-2 infection fron China, only 3.5% or 6 patients has lymphocytopenia (22).

The immune system may not be impaired but more heavily regulated in the newborn and infancy period due to differences in the modulation of the Toll-like receptor (TLR) pathway or in the generation of regulatory cells (41). Newborns show decreased TLR-induced responses and reduced pro-inflammatory cytokine production compared to adults (18). Pediatric lung and intestinal tissues have a higher proportion of regulatory T cells which in turn may suppress immune responses (35). In conclusion, differences in the immune system activation in children either due to a dampened immune response or activation of a different sect set of immune effectors could be protective in children against the development of severe life-threatening lung disease with SARS-CoV-2 infection.

Other Factors that may Contribute to Age-Based Susceptibility:

Children who develop ARDS have lower mortality (28). On the other hand, adults experience more long-term impairment with permanent alveolar simplification and fibrosis (15). Alveologenesis and microvascular maturation is an ongoing process that continues in the pediatric lung up to 6-8 years of life and by some reports even up to late adolescence. Biological mechanisms related to inflammation and repair in the injured lung are likely to be different in the adult and the pediatric lung. One example is the NF-κB pathway. Differences in the activation of this pathway between adult and neonatal mice were found both in the hyperoxia- and LPS-induced lung injury models (1, 39). Endothelial cell apoptosis and dysfunction with the breakdown of the pulmonary endothelial cell barrier leads to pulmonary edema in ARDS. The pulmonary barrier function was better preserved in neonatal mice compared to adult mice. In response to LPS administration, neonatal pulmonary endothelial cells increased focal adhesion kinase 1 (FAK1) expression leading to better preservation of the pulmonary barrier function (40).

The rapid emergence and universal geographic transmission of SARS-CoV-2, along with the selective, age-associated mortality, render COVID-19 a unique, infectious disease. Insights into age-related variability in pathophysiological processes (**Figure 2**) may offer critical observations, revealing focused paths of therapeutic investigation. Multidisciplinary collaboration between physicians and scientists, engaged in both pediatric and adult pursuits, holds significant promise and should be encouraged.

Figure Legends:

Figure 1: Differences in the clinical course in children and adults with SARS-CoV-2 infection Depiction of the general progression of disease and overarching severity of illness among symptomatic adult and pediatric patients. While the most severe adults progress through the inflammatory phase to profound clinical severity, mild/moderate adults seem to stabilize and recover over a protracted course. Pediatric patients rarely require hospitalization for symptoms and, when more symptomatic early, generally recover quickly. Some children develop a multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. (Figure adapted in part from Siddiqui and Mehra *et al.* COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transpl. 2020 May;39(5):405–7.)

Figure 2: Mechanisms mediating differential susceptibility of adults and children to COVID-19 Increased expression of mediators essential for viral entry into airway epithelial cells (ACE-2 and TMPRSS2) in adults combined with the pro-inflammatory milieu in adults may predispose the adult lung to serious pulmonary injury and progression to ARDS. The pediatric lung has greater expression of immunomodulatory cytokines and possibly a decreased expression of viral entry mediators.

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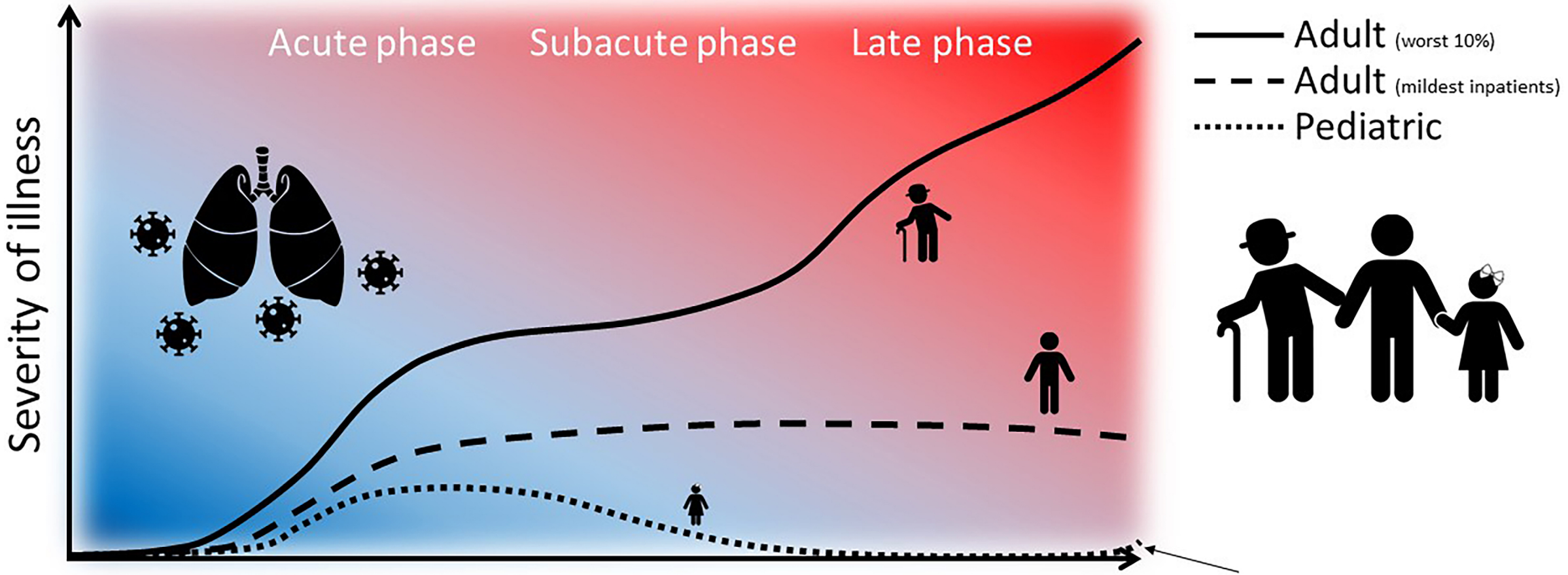

Stage:	Exposure	Viral / initial stage	Progressive / hyper-inflammatory stage		Fibrotic / remodeling stage	Multisystem inflammatory syndrome in children (MIS-C)
Symptoms:	Asymptomatic	Fever, cough, malaise	Shortness of breath	Need for advanced support vs recovery		Fever, rash, vomiting, lethargy
Physiologic effects:	Minimal	Edema, inflammatory cell influx, tracheobronchial irritation	Interstitial and alveolar congestion	Inflammatory cytokine production, cellular hypoxia	Remodeling, fibrosis	Hypotension, multi-organ involvement, elevated inflammatory markers