The Presentation, Transmission and Outcomes of COVID-19 in Infants and Children

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Abstract

The emergence of a novel coronavirus (SARS-CoV-2) in late 2019 took a global toll, killing hundreds of thousands of people, infecting millions, causing many countries to institute quarantine policies, causing significant mental and financial hardship for many, and thrusting the world into a global recession. The Severe Acute Respiratory Syndrome (SARS) outbreak in the early 2000s was also caused by a highly virulent coronavirus, leading to severe ARDS and death, most commonly in adults. However, the overall global impact of SARS-CoV was much less than that of the current SARS-CoV-2 pandemic. The mechanism of infection of SARS-CoV-2 involves a crucial interaction between the viral capsid protein, known as "spike protein", with the Angiotensin Converting Enzyme 2 (ACE2) receptor on human Type 2 epithelial cells in the alveoli of the lungs. Much has been learned about the pathophysiology of the SARS-CoV-2 virus in adults, since the virus has disproportionally affected them, and resulted in a more severe disease course. Less is known about the pathophysiology of SARS-CoV-2 in the pediatric population although case reports continue to be published describing the presentation, transmission and outcomes of infants and children with COVID-19. In general, the disease course is milder in the pediatric population although severe inflammatory disease has been described and children have died from COVID-19. PubMed and Medline are two highly trusted medical search engines that were utilized to identify published literature outlining the presentation, transmission and outcomes in pediatric cases of COVID-19.

COVID-19 Introduction

The novel coronavirus pandemic has made an unprecedented impact on human history, changing the lives of many people across the world. With its high degree of infectivity, paired with potentially fatal respiratory and hematological consequences, physicians and researchers were quick to explore the pathogenesis, presentation, and outcomes in adult and pediatric patients with confirmed SARS-CoV-2.

Coronavirus belongs to a family of positive-sense, single-stranded RNA viruses characterised by a helical protein capsule[1]. Figure 1[2] outlines the pathogenesis of SARS-CoV-2 in infecting the human body as well as its activation of the innate immune system and complement pathways. The first step in the pathophysiology of the virus occurs with the binding between SARS-CoV-2 surface protein, known as "spike protein", and receptors on epithelial cells, most commonly the Angiotensin-Converting Enzyme 2 (ACE2) Receptor[3]. ACE2 is a metalloprotein that can be found in many tissues throughout the body including the nasal epithelium, vascular endothelium, kidney, and spleen, but is most abundant in the alveolar pneumocytes of the lung and enterocytes of the small intestines[4]. The virus interacts with the human host cells either in the nose or mouth through respiratory droplets. Following the binding of SARS-COV-2 with the ACE2 receptor, receptor mediated endocytosis occurs and introduces the virus into the host cell. At this time, viral mRNA results in the production of viral RNA replicase. This enzyme is responsible for the rapid replication and production of the virus RNA and its necessary cellular proteins. The synthesized cellular components are then packaged into a new virus and undergo exocytosis, where they can travel through the bloodstream and infect multiple organs. Upon exocytosis, the host cell dies. In addition, the foreign viral antigens can also bind to Toll-Like Receptors (TLRs) on immune cells, increasing the release of proinflammatory cytokines and chemokines. Cytokines can cause fever. Chemokines will recruit more immune cells, specifically white blood cells, into the tissues increasing mucous production. This produces symptoms that include cough, shortness of breath and, in severe cases, Adult Respiratory Distress Syndrome (ARDS).

The inconsistency between the severity of COVID-19 in the adult and pediatric populations was first described in China. In February 2020, a study in China reported that of its 44,672 cases of confirmed COVID-19, only 0.9% were in children up to 10-years-old[5]. Due to the involvement of SARS-CoV-2 spike protein and the ACE2 receptor in humans, research into the correlation between infectivity, severity of infection and ACE2 expression was conducted. Since ACE2 functions as the receptor for SARS-CoV-2 spike proteins in the respiratory and gastrointestinal tract, individuals with high ACE2 levels are more susceptible to infection by the virus[5]. ACE2 receptors play a modulatory role in the body, downregulating the renin-angiotensin-activating-system (RAAS). Angiotensin II is a crucial component in the RAAS pathway that acts to increase blood pressure via vasoconstriction and induce pro-inflammatory actions[6]. ACE2 converts Angiotensin II to particles that counteract the pro-inflammatory properties of Angiotensin II[6]. The engagement of SARS-CoV-2 with the host causes downregulation of ACE2 receptors and, therefore, unregulated activation of RAAS[7]. When local tissue-based RAAS is stimulated in the lungs, pulmonary hypertension, pulmonary edema and worsened tissue injury occurs[5]. Paradoxically, however, studies have also demonstrated that, upon infection, high ACE2 levels may protect the individual and result in a less severe presentation[5]. Increased ACE2 receptor expression is associated with decreasing the life-threatening consequences of COVID-19, SARS and H5N1 influenza[5]. This includes extensive lung damage from sepsis and acid aspiration[5]. Therefore, increased ACE2 levels in the lungs ultimately causes decreased lung injury[5]. Further exploration of the correlation between age, ACE2 expression, and severity of infection could aid to explain the differences in presentation, morbidity and mortality between adults and children.

The question as to children with COVID-19 have a milder disease than adults is unknown, but various theories have emerged. Children may have increased immunity as a result of antibodies produced against other common viruses such as influenza, parainfluenza and adenovirus[8]. These antibodies could cross-react with SARS-CoV-2 and provide additional protection to the pediatric population[8]. Additionally, the expression of ACE2 receptors significantly may decrease with age as describe in rats[5]. In a cohort study from New York, ACE2 gene expression on the nasal epithelial cells were lowest in children under 10-years-old and increased

in a linear fashion as age increased[9,10]. Figure 2[9] displays the relationship between ACE2 gene expression and age in nasal epithelial cells. The low expression of ACE2 in the nares may protect children from infection with SARS-CoV-2[9,10]. The maturity of the ACE2 receptor signaling pathways may also differ between children and adults. The more immature ACE2 receptor in children may prevent SARS-CoV-2 from binding to it as readily as the mature enzyme found in adults[11]. This could further explain why children have experienced more positive outcomes than the adult population.

Presentation in Children

While the spectrum of clinical manifestations is yet to be fully described, adults and children both typically present with varying degrees of respiratory illness and gastrointestinal upset. One retrospective epidemiological study from Wuhan China categorized the presenting signs and symptoms into disease severity in Figure 3[11].

A study from Wuhan, China recorded that approximately 94% of their pediatric patients were either asymptomatic, mild or moderate cases[11]. Another study found that of the children who develop symptoms, 5% experienced dyspnoea or hypoxaemia and only 0.6% progressed to ARDS[12]. In contrast, a cohort study in Wuhan, China reported that 40% of adult patients with confirmed COVID-19 developed ARDS, and of these patients, 52% subsequently died[13]. Children with COVID-19 can present with lymphocytosis, leukopenia, thrombocytopenia, elevated Creatinine Kinase-MB fraction[14], and elevated procalcitonin levels[15]. Elevated procalcitonin are not common in adults[15]. Lung CT findings in adults and children with COVID-19 appear to differ. Pediatric lung CT scans show areas of focal consolidation surrounded by a halo, while adult findings include ground glass opacities with bilateral consolidation in peripheral zones[15]. An example of a lung CT scan from a pediatric and adult scan with confirmed COVID-19 is shown in Figure 4[15] to illustrate the difference.

Interestingly, COVID-19 in pediatric patients often presents with dermatological signs in the absence of respiratory symptoms. The lesions are being described as chilblain-like papules[16]. Chilblains are painful, itchy, red papules that arise in response to inflammation of small blood vessels commonly located in the

hands and feet[17]. A study in Lombardy, Italy reported that 20% of its pediatric COVID-19 cases presented with skin manifestations including erythematous rash, urticaria and chickenpox like papules[18]. These lesions have been more frequently reported on the feet than hands[16].

The recent emergence of a Kawasaki-like illness has also been linked to confirmed SARS-CoV-2 in children. Kawasaki disease is an acute vasculitis that occurs in children with severe complications including coronary artery aneurysm[19]. Clinical diagnosis is made based on the presence of the following symptoms: fever, exanthema, lymphadenopathy, conjunctival injection, and changes to the mucosae and extremities[19]. A study in Bergamo, Italy reported that upon the emergence of COVID-19 they saw a 30-fold increase in the number of cases of Kawasaki disease compared to the same month in the previous 5 years[20]. This finding suggests that SARS-CoV-2 elicits an immune response that triggers the development of Kawasaki disease[20].

Transmission

Similar to the adult population, the spread of SARS-CoV-2 in children occurs through respiratory droplets, either through sneezing, coughing or direct contact with a person infected with the virus[3]. Previous studies of intra-uterine transmission of SARS indicated no transmission among infants born to mothers who developed SARS infection during pregnancy[21]. In Huijun Chen et al's study of the potential intrauterine vertical transmission of 2019-nCoV, samples of the amniotic fluid, cord blood, neonatal throat swab and breastmilk were taken and tested for the virus at the time of delivery of six women with confirmed COVID-19[21]. All tests were negative, suggesting that intra-uterine transmission of the virus did not occur[21]. Horizontal transmission from mother to infant after birth can occur. The risk of horizontal transmission between mother and neonate can be reduced by temporary separation after birth[22]. New reports have also shown elevated levels of IgM in neonates born to COVID-19 positive mothers, but these findings will need to be confirmed[14].

With regards to breastfeeding, the World Health Organization currently states that it is safe for mothers with COVID-19 to breastfeed, so long as they practice the necessary hygiene[23]. This includes

wearing a mask when possible, washing their hands both before and after they breastfeed, and thoroughly cleaning surfaces and objects that they came into contact with[23]. The American College of Obstetricians and Gynaecologists adds that if a woman is using a manual or electric breast pump, proper cleaning measures of both the pump and the mother's hands must be followed[22]. They also suggest consideration that an uninfected individual feed the baby until the mother is well enough to do so[22]. Antibodies to SARS-CoV-2 have been detected in the breastmilk of COVID-19 positive mothers, which may actually offer a protection against the virus to a newborn baby through passive immunity[14].

In addition to respiratory droplet transmission, SARS-CoV-2 can be transmitted via the faecal-oral route among children. In children who are COVID-19 positive, faecal sheading of the virus can occur for several weeks[12]. ACE2 receptors are highly expressed in colonocytes, another route for viral infection and disease progression[7].

Outcomes in Children

A study in Wuhan, China outlined the severity of pediatric cases of confirmed SARS-CoV-2 by age group[11]. Figure 5 outlines the study's findings and offers a comparative view between the severity of infection and age of patient[11]. Over half of the "critical" patients observed in the study were neonates < 1 years old, indicating that this group is the most vulnerable pediatric patient group to progress to a critical state[11]. Although uncommon, severe cases of COVID-19 in neonates and children have been reported as one case study outlines the development late-onset of sepsis. This is thought to have occurred as a result of undetected COVID-19 and goes to show that a negative SARS-CoV-2 test at birth does not rule out the possibility of obtaining the infection through horizontal transmission[24]. The infant was subsequently treated with Hydroxychloroquine and Azithromycin and discharged on day 9 without supplemental oxygen[24]. Among the pediatric population, there are particular groups at increased risk for development of severe/critical COVID-19. Additional risk factors for severe disease in pediatric patients include an immunocompromised state and pre-existing respiratory disease[12].

Conclusion

In December 2019, the novel coronavirus pandemic caused an unexpected turn in the world, dramatically changing the lives of millions of people. Research into the pathophysiology of SARS-CoV-2 demonstrated a strong link between the viral capsid spike protein and ACE2 receptors in the nasal epithelium, pneumocytes in the alveoli of the lower airways, as well as the gastrointestinal tract. It has been shown that ACE2 expression is lowest in young children and increases with age, contributing to the theory that children have shown protection to the virus. The development and function as well as the intracellular immune response produced by ACE2 is also less in children than in adults. The severity of the disease is also related to the extent of differentiation and maturation of the ACE2 receptor in the lungs[25]. The degree of differentiation of the ACE2 receptor in the lungs should be explored in pediatric populations to potentially explain the lower degree of infectivity[25].

The presentation of pediatric COVID-19 is primarily asymptomatic or mild. Symptoms commonly include fever, myalgia, fatigue, cough and rhinorrhea and GI symptoms such as diarrhea. Dermatological findings such as chilblain-like papules have also been described. A Kawasaki-like illness has also been observed and linked to the outbreak of COVID-19. Lab analysis demonstrates leukocytosis, lymphopenia, thrombocytopenia, elevated creatinine kinase-MB fraction as well as elevated procalcitonin. On CT scans of the thorax, the lungs commonly show a focal area of consolidation surrounded by a "halo" area. Ground-glass opacities and areas of peripheral consolidation in the lung have also been described. The highest risk pediatric population are neonates < 1 years old and those with pre-existing respiratory conditions. Transmission between the pediatric population occurs via respiratory droplets and potentially by faecal-oral route. There are currently no studies that support vertical transmission or transmission through breastmilk. On the contrary, breastmilk may be providing some protection against SARS-CoV-2 to newborns through passive immunity. Finally, the overall outcomes of COVID-19 cases in pediatric settings are better than in adults.

The primary limitation to literature review includes small sample sizes and insufficient data due to the lower number of affected children. As more data is collected and analyzed, physicians will be able to gain

better insight into the pathogenesis and pathophysiology of this novel coronavirus. A comparison between the immune response, lung maturation, ACE2 expression, and co-morbidities in the adult population could shed light on why pediatric cases of COVID-19 appear milder. Further data is required to resolve the milder impact of COVID-19 in pediatric cases. For now, it is imperative that pediatricians are familiar with the wide variety in presentation to better detect pediatric cases of COVID-19. They should acknowledge the different means of transmission in order to decrease the spread among children and between children and adults. Detailed research surrounding the physiology of the positive outcomes of COVID-19 in children can be used to explain why the adult population exhibits a worse prognosis.

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Appendix

Figure 1: A detailed diagram outlining the pathogenesis and interaction between SARS-CoV-2 and the human host[2]

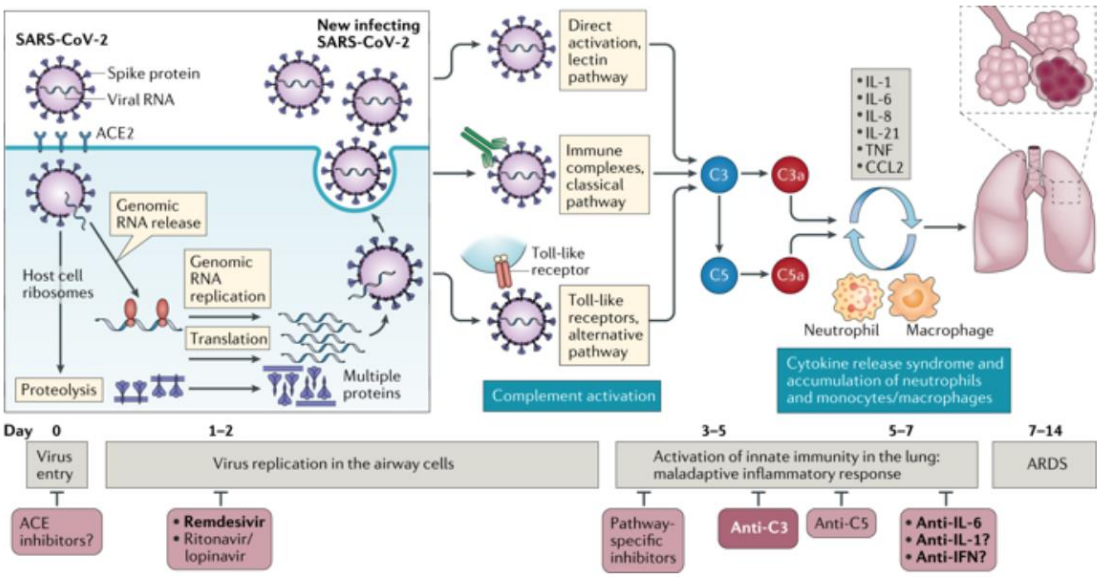

Figure 2: ACE2 gene expression in the nasal epithelium by age[9]

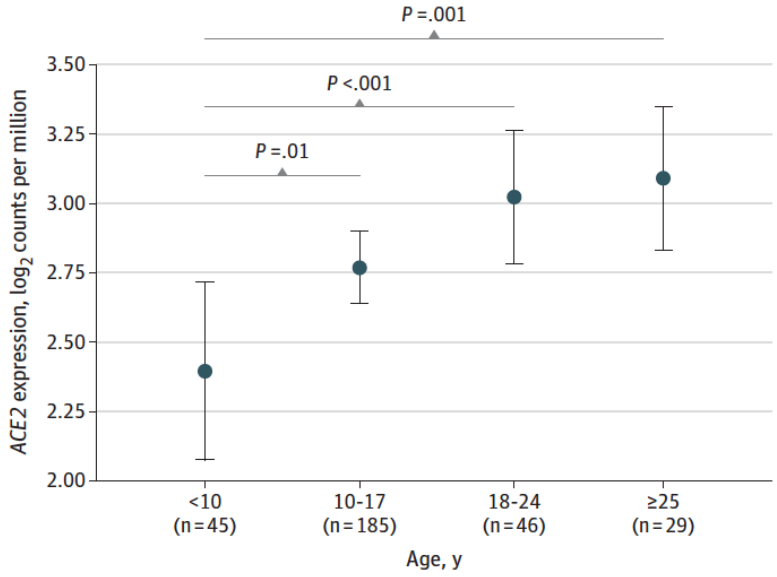

Figure 3: Grading the Symptoms of Pediatric Cases of COVID-19[11]

Grading	Description of Symptoms
Asymptomatic	No signs and symptoms, normal chest imaging. Confirmed positive with SARS-CoV-2 nucleic acid test.
Mild	*Upper respiratory tract infection* including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing. On exam, patients may show signs of congestion of the pharynx, however, examination of the chest yields no abnormal auscultory findings. Additionally, some cases may have no fever and will present only with digestive symptoms such as nausea, vomiting, abdominal pain and diarrhea.
Moderate	*Lower respiratory tract infection/pneumonia* with fever and cough. Cough is often characterized as dry initially but can progress to productive in some cases. Wheeze occurs occasionally, but shortness of breath and other signs of hypoxaemia are notably absent. In certain cases, patients diagnosed with moderate disease have no clinical signs or symptoms, but CT-chest demonstrated (subclinical) lung lesions.
Severe	*Pneumonia with rapid progression* – similar initial presentation to moderate disease (pneumonia and gastrointestinal symptoms) with rapid progression (around 1 week of the symptom onset) to significant dyspnoea and central cyanosis. Oxygen saturation is usually less than 92%, with other manifestations of hypoxia.
Critical	*Acute respiratory distress syndrome (ARDS) or respiratory failure.* Other critical conditions that may develop include shock, encephalopathy, myocardial infarction or congestive heart failure, coagulopathy and acute kidney injury. As with other aetiologies of multi-organ dysfunction/failure, a critical presentation of COVID-19 can be life-threatening.

Figure 4: A comparative look at the CT scans of the thorax on patients with confirmed COVID-19. Image A, B, and C were obtained from a 64-year-old female, and D was taken from a 1-year old infant[15].

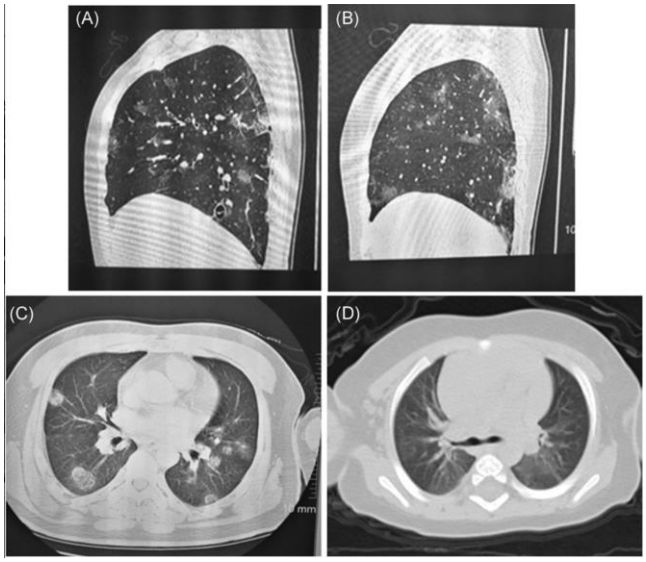

Figure 5: The Severity of Pediatric Cases of COVID-19 by Age Group in Wuhan, China[11]

Age Group*	Asymptomatic	Mild	Moderate	Severe	Critical	Total
<1	7(7.4)	205(18.8)	127(15.3)	33(29.5)	7(53.8)	379(17.7)
1-5	15(16.0)	245(22.5)	197(23.7)	34(30.4)	2(15.4)	493(23.0)
6-10	30(31.9)	278(25.5)	191(23.0)	22(19.6)	0(0)	521(24.3)
11-15	27(28.7)	199(18.2)	170(20.5)	14(12.5)	3(23.1)	413(19.3)
>15	15(16.0)	164(15.0)	146(17.5)	9(8.0)	1(7.7)	335(15.7)
Total	94	1091	831	112	13	2141(100)

Data is presented with a number and a percent (%). *Two cases had missing values.