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SARS-CoV-2 infection in children – Understanding the immune responses and controlling the pandemic

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Abstract

In December 2019, a cluster of patients with severe pneumonia caused by a novel coronavirus (SARS-CoV-2) emerged in the city of Wuhan, China. The disease is now termed coronavirus disease 2019 (COVID-19). In the early reports, the patients were mainly middle-aged and elderly men, and children appeared to be less susceptible to this infection. With modern and efficient transportation, the disease quickly spread to almost all corners of the world and the mortality far exceeds those caused by severe acute respiratory syndrome coronavirus (SARS) or Middle East respiratory syndrome coronavirus (MERS). As the number of children with COVID-19 gradually increases, the disease has been documented in premature babies, infants, children and adolescents. Severe and fatal cases in children are relatively rare. The burden of disease in children has been

relatively low, but the high proportions of asymptomatic or mildly symptomatic infections in children deserve careful attention. Clear understanding of the immune responses to the virus in children and the transmission potential of asymptomatic children are of paramount importance for the development of specific treatments and vaccine in order to effectively control the ongoing pandemic.

KEYWORDS: SARS-CoV-2, children, coronavirus, immune response, pandemic

1. INTRODUCTION

Human coronavirus is an important agent causing mild to severe respiratory tract infections in humans. In December 2019, an outbreak of severe pneumonia due to a novel coronavirus emerged in Wuhan, Hubei province of China.[1] In the past 2 decades, two coronaviruses, namely severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS) have caused outbreaks of severe respiratory infections in community and healthcare settings around the world.[2] Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is the latest one among the 7 coronaviruses known to cause human disease. The number of reported cases has been increasing rapidly since it was first detected. As of 15 April 2020, SARS-CoV-2 is responsible for more than 2 million cases and 125,000 deaths around the world. [3] This review focuses on SARS-CoV-2 infection in children in order to provide reference for the understanding of the biology of this infection which is important for development of measures to control this pandemic.

2. HUMAN CORONAVIRUS

Coronaviruses (CoVs) are enveloped positive sense RNA viruses that can be found in humans, and other mammals as well as birds and they can cause respiratory, enteric, hepatic, and neurologic diseases.[4,5] Seven coronavirus species are known to infect humans.[6] Four of them, namely HKU1,

NL63, 229E and OC43, are prevalent and typically cause common cold symptoms in immunocompetent individuals. Both innate and adaptive immune responses are essential to control and eliminate CoVs infections. CoVs infect macrophages and monocytes, and then macrophages present CoVs antigens to T cells, followed with T cell activation and differentiation. This process is accompanied by the production of cytokines associated with different T cell subsets leading to immune response amplification.[7] The subsequent specific T cell activation and humoral responses lead to effective viral clearance.[8] Early data from adult patients recovering from COVID-19 showed that they would mount an IgM response by one week after the onset of disease while a peak IgG response was reached by 2 weeks.[9]

CoVs were previously thought to be of low pathogenicity in humans, and they usually cause mild upper respiratory tract infections.[10] However, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 have changed this perception, because these coronaviruses are highly infectious and can result in diseases with high fatality rates.[10-12] SARS-CoV was identified as a human CoV that causes severe acute respiratory syndrome in 2002-2003. It emerged in Guangdong province, China, and subsequently spread to 26 countries and regions, resulting in 774 deaths and 8098 cases over a period of nine months.[13] A decade later, the MERS-CoV, also of bat origin, emerged in Saudi Arabia with dromedary camels as the intermediate host and infected 2494 people with 858 deaths and the fatality rate was 34%.[14] Children represented less than 5% of all patients infected with these two coronavirus.[13-14] Since December 2019, the number of people infected with SARS-CoV-2 has been increasing rapidly around the world,[14] and the WHO declared this outbreak as a pandemic on 11 March 2020. SARS-CoV, MERS-CoV and SARS-CoV-2 all belong to the group of beta coronavirus. SARS-CoV was effectively contained by early identification and isolation of infected cases so that chain of transmission was stop.[15-18] MERS-CoV has a natural intermediate host (camel),[19] and there have been periodic small-scale outbreaks primarily in the Middle East. MERS is associated with the highest case fatality rate, but infectivity is rather low. In contrast, SARS-CoV-2 is highly contagious but the mortality rate is lower than those of

SARS-CoV and MERS.[20]

3. SARS-CoV-2 INFECTION IN CHILDREN

3.1 Clinical features of SARS-CoV-2 infection

Infants and children of all ages are susceptible to SARS-CoV-2 infection. A recent review by the Chinese Center of Disease Control and Prevention with 72,314 subjects documented that only 2% of the 44,672 confirmed cases of COVID-19 were children and adolescents aged 0-19 years.[21] The incidence of SARS-CoV-2 infection in children is lower than that in adults, and the feature of familial clustering is well documented.[22] Current data revealed that the median incubation period of SARS-CoV-2 infection in children is 3~7 days (range 1-14 days). In contrast with infected adults, most children have a milder clinical course characterized by fever, cough, fatigue, myalgia, vomiting, diarrhea. These symptoms usually resolve within 7-10 days. [23] Unlike other viral respiratory diseases in children such as those caused by respiratory syncytial virus or asthmatic exacerbations precipitated by human rhinovirus, wheezing is not a common feature of COVID-19 in children while alveolar consolidation is the most common presentation. [23-24] Furthermore, none of the infected children seen at the Wuhan Children's Hospital had underlying asthma; therefore, childhood asthmatics do not appear to be have higher risk for severe SARS-CoV-2 infection. [23] The proportion of infected children requiring intensive care is approximately 2%. [23-24] Fever is present in less than half of the infected patients while asymptomatic infections have been reported to occur in at least 20% of infected children. [23-24] Elevation of inflammatory markers such as C-reactive protein or procalcitonin, and lymphopenia were less common in children.[23,25] Although the radiological findings in infected children are similar to those in adults, the changes are less severe. Localized or bilateral ground-glass opacity, and patchy, flocculent or nodular shadows are the most common findings. [23-24] In patients recovering from the infection, prolonged fecal shedding of viral particles up to 5 weeks in adult and pediatric patients have been documented.[26-27] Further studies to determine the infectious potentials of feces from patients are needed. Although

SARS-CoV-2 has strong person-to-person transmission potential between adults, and from adults to children, the transmission potential from children to others is still unclear. In particular, it is important to determine the transmission potential of asymptomatic children to clarify their role in propagating the infection in the community level.

3.2 Differences of epidemiology, clinical manifestations, and immune responses between infected children and adults

Children are underrepresented in the total burden of SARS-CoV-2 infections, and their clinical manifestations are less severe than those in adults. Both data from China and US showed that only about 2% of all cases were under 18 years of age while 18-20% of the Chinese or US populations are under 18 years of age. [21-24] For outbreaks of viral infections, the spread of respiratory viruses in schools is usually very common. The SARS-CoV-2 outbreak in China coincided with the Chinese New Year Holidays and school suspension was extended for more than 2 months. School suspension might be one of the most important factors resulting in a lower transmission of illness between children. As the disease is frequently mild or asymptomatic in children, there may be many asymptomatic infections among children resulting in a factitiously low number of infected children. Furthermore, the lockdown in different cities and communities would greatly limited the transmission among children. [28] Sero-epidemiological studies will help to determine the true infection rate in children.

It is intriguing that SARS-CoV-2 behaves similar to SARS-CoV and MERS that it seems to cause milder disease than in adults and it may be explained by the possible differences of immune response to the virus. [29] The severity of SARS-CoV-2 infection is a result of a complex interplay between the ability of inhibiting viral replication early on and possible damage induced by an overactive immune response leading to immunopathological injuries to different organs. A high viral load early in the illness, and subsequent excessive innate immune response and cytokine

storm have been thought to be important in the pathogenesis of severe disease in adults due to SARS and MERS. [2,10-12] The exact reasons why children do not mount such cytokine response are not clear. [10,11,30] Although respiratory virus infections including other coronavirus are frequent in childhood, early data suggest that there was little, if any, cross protection from antibodies of other common coronavirus (NL63, 229E, OC43, HKU1) against SARS-CoV-2. [9,31]

Another possible reason for milder infection in children is that the virus receptor in children may be qualitatively or quantitatively different from those in adults. S protein is the viral protein that mediates the entry of CoVs into host cells. [32] Receptor-binding domain (RBD) within the S1 domain mediates binding to the cognate host cell receptor. The tissue tropism of CoVs is determined by the S protein interaction with the receptors on host cells and SARS-CoV-2 enters different human cells through the angiotensin converting enzyme 2 (ACE2) receptor. [33] A recent study showed that SARS-CoV-2 S protein has higher affinity to ACE2 than SARS-CoV S protein. [34] ACE2 is widely distributed in the small intestine, heart, kidneys, lungs, and testes. The development, distribution and function of ACE2 protein in children may be different from those in adults. Studies have shown that intracellular response induced by ACE2 in alveolar epithelial cells in children is lower than that in adults.[35] Furthermore, underlying comorbid conditions are less common in children. All these reasons may partly explain the lower degrees of severity of the disease in children.

With regards to the ages of infected children, infants under one year of age were found to be overrepresented in data from China. [21,23] In the cohort of infected children from Wuhan Children's Hospital, 18% of all cases were infants under 1 year of age. Early results reported by the US CDC also showed that 15% of all COVID-19 cases were under 1 year of age. [24] The exact reasons explaining the susceptibility of infants remain to be explored. Infections in neonates have also been reported, but vertical transmissions from infected mothers to newborns were rather uncommon. In a study with 33 mothers infected in late pregnancy, only three newborns infants (9%) were subsequently confirmed to be infected. In line with the disease in other pediatric age-groups, their illness was not severe. [36] Although most children with severe diseases usually

have some predisposing factors, there are rare fatal cases of previously healthy children and one must ask the question whether there are any host immune-related factors resulting in more severe diseases in a small percentage of otherwise healthy children. [21,23,24]

4. TREATMENT AND VACCINE

To date, no specific antiviral treatment effective against COVID-19 is available. Regarding patients infected with SARS-CoV-2, the treatment is primarily supportive. [37] There are many clinical trials registered in both the International Clinical Trials Registry platform or the Chinese Clinical Trial Registry aiming to evaluate the efficacy and safety of targeted medicine for treating COVID-19 and the potential pharmacological treatments have been extensively reviewed recently. [38,39] All the potential drugs have not been tested systematically in children, and proper clinical trials testing the efficacy of these drugs in children are needed.

Immunotherapy is regarded as an effective method for treatment of different infectious diseases. Many monoclonal antibodies against different viruses have been developed in recent years and many more are in the research pipeline. [40] Appropriately powered clinical trials are needed to determine if the use of various monoclonal antibodies is beneficial or not. Clear understanding of the important early immune response in suppressing viral replication and the subsequent control of appropriate innate and adaptive immune responses are needed in order to develop more targeted treatment in different stages of COVID-19. [41]. Limited open labeled study with the use of convalescent plasma donated from patients who have recovered from the infection suggested that such treatment might be useful in adult patients with severe disease.[42] Proper assessment of the efficacy of such treatment in children with severe disease is needed.

Within two months of the SARS-CoV-2 outbreak, at least 37 biopharmaceutical companies or academic sectors are pushing at a rapid pace to develop effective vaccine using various

platforms including mRNA, DNA, adenoviral vector and recombinant protein[43]. Careful evaluation in each step of vaccine development will be crucial. This includes finding target antigen(s), immunization route, correlated-immune protection, animal models, scalability, production facility, target product profile (TPP), outbreak forecasting and determination of the target population. International collaboration as well as technology transfer between research groups will also facilitate SARS-CoV-2 vaccine development to quickly move forward. Zika virus outbreak has provided several important lessons. In order to speed up the development of vaccine during ongoing outbreak, preclinical studies of SARS-CoV-2 vaccine candidates may need to be performed in parallel with clinical trials. However, before entering clinical testing, researchers and the regulatory agencies must assess the production process and preclinical information to ensure volunteers' safety.[44] The protective effects of ACE2 on ARDS is not yet clarified and further studies are needed to determine if drugs targeting the ACE2 receptor may have any role in the management of COVID-19. [45]

5. PREVENTION AND CONTROL

In 2003, SARS outbreak was eventually contained by public health measures without specific treatment or vaccination. The control of SARS-CoV-2 turns out to be more problematic and the presence of large proportions of patients with mild or no symptoms is likely an important reason because the identification and isolation of infected individuals become more difficult. The experience of lockdown of the city of Wuhan and Hubei province in China does provide a few lessons, whether these measures used were effective will be debated for many years to come. Nevertheless, a recent comprehensive analysis of laboratory confirmed cases in Wuhan demonstrated a temporal relationship of dramatic reduction of community spread with progressive introduction of traffic control, social distancing, home confinement, centralized quarantine, and universal symptom survey. [28] A similar country-wide analysis also demonstrated the possible effects of these public health measures in reducing the number of cases in China. [46] Such

multi-faceted public health measures, however, may not be easily replicated elsewhere due to social, legal, and political differences among different countries and such drastic measures are associated with huge economic implications. Nevertheless, until effective vaccine and specific treatments are available, early identification of infected cases, proper isolation of patients, and social distancing remain the most important measures to minimize transmission of this infection worldwide.

6. CONCLUSION

Children of all ages are susceptible to SARS-CoV-2 infection and infants appears to be at higher risk while asymptomatic infections are more common in older children and adolescents. The clinical course of SARS-CoV-2 infection in children is milder than that in adults, and most children with severe diseases have underlying comorbid conditions. Although many theories have been put forward, the exact reasons for a milder nature of the disease in children are not clear. A clear understanding of the underlying immune response to SARS-CoV-2 infection and disease severity in different age groups, and the factors associated with resistance against infection will facilitate the development of effective treatments and vaccine to control the ongoing pandemic.

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