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**From SARS to COVID-19: What we have learned about children infected with  
COVID-19**

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**Abstract**

Coronaviruses, both SARS-CoV and SARS-CoV-2 were firstly appeared in China. They have certain similarities in biological, epidemiological and pathological. To date, the researches have shown that their gene exhibit 79% of identical sequence and the receptor-binding domain structure is also very similar. There have been extensive research performed on SARS, however, the understanding of pathophysiology impact of Corona Virus Disease 2019(COVID-19) is still limited. In the review, we draw upon the lessons learnt from SARS in the epidemiology, clinical characteristics and pathogenesis for further understand the features of COVID-19. By comparing these two diseases, we found, COVID-19 has quicker and wider transmission, obvious family agglomeration, higher morbidity and mortality. Newborns, asymptomatic children and normal chest imaging cases were emerged in COVID-19. Children started with gastrointestinal symptoms may progress to severe condition and newborn whose mother was infected with COVID-19 could have severe complications. The laboratory test data showed, the percentage of neutrophils and the level of LDH is higher, otherwise the number of CD4+ and CD8+T cells is decreased in children's COVID-19 cases. Based on these early observations, as pediatrician, we put forward some thoughts on children's COVID-19 and give some recommendations to contain the disease.

**Keywords**

Coronavirus; SARS; COVID-19; SARS-CoV-2; 2019-nCoV; Children

## Introduction

A cluster of pneumonia patients caused by unknown pathogen which were linked to the seafood wholesale market presented in Wuhan, China, in December 2019. Subsequently, a new coronavirus was identified by sequencing the whole genome of patient samples (Zhu et al., 2020). It was named severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) by the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses (Gorbalenya et al., 2020), and the disease caused by the virus was named Corona Virus Disease 2019(COVID-19) by World Health Organization (WHO).

Of 7 coronaviruses identified from human, HCoV-229E and HCoV-NL63 are belong to  $\alpha$ -coronaviruses, HCoV-OC43, MERS-CoV, SARS-CoV and SARS-CoV-2 are belong to  $\beta$ - coronaviruses. Both SARS-CoV and SARS-CoV-2 were firstly emerged in China. Although the genome-wide similarity was only about 79%, the similarity of the seven conserved domains used for virus identification was as high as 94.6%. It indicates that SARS-CoV-2 belongs to the same genus as SARS-CoV. Additionally, studies showed SARS-CoV-2 could enter cells through Angiotensin-converting enzyme 2(ACE2) receptor on the surface of cell membrane, which was consistent with SARS-CoV (Lu R et al., 2020; Zhou et al., 2020).

84,338 confirmed cases including 4642 deaths were reported in China by 25 April.

2020 (China, 2020). The illness spread to other countries in a short time. 213 countries reported 2,724,809 confirmed cases including 187,847 confirmed deaths by 25 April (WHO). The epidemic situation of COVID-19 remains serious threatened at this stage. SARS-CoV-2 as a new virus, the biological characteristics, epidemiology, pathogenicity and immunity are not illustrated; efficient, fast and accurate detection methods are still lacking; specific drugs and vaccines were still investigational. Children as a special group show different clinical features when compared to adults. Therefore, it has posted a significant challenge for medical community to diagnose and treat children with COVID-19.

As a group of pediatrician we reviewed available information and propose the following thoughts: What are the similarities and differences between SARS and COVID-19 on epidemiology and clinical features? What are the determining risk factors may result in development of mild COVID-19 infection to severe cases? Can the diagnosis and treatment experiences of children with SARS extrapolated useful information and apply to children with COVID-19? Can anti-SARS-CoV antibodies have cross-react with anti-SARS-CoV-2? How to prevent and contain SARS-CoV-2 infection in children? To better explain these questions, we compared the epidemical and clinical features of SARS and COVID-19 in this paper.

## **Research content and Results**

### **1. Epidemiological comparison between SARS-CoV and SARS-CoV-2**

SARS, first emerged in Guangdong, China, in November, 2002, causing global anxiety, had result in 8422 cases with 919 death in 32 countries (Yang et al., 2020). The most cases were concentrated in China, Taiwan, Hong Kong, Singapore and Toronto, Canada (Wilder-Smith et al., 2020). In contrast, by 25, April, over 80,000 confirmed cases and over 4,000 deaths were reported within a matter of 4 months in China. Additionally, 213 countries with more than 2,700,000 confirmed cases and at least 180,000 deaths were reported. The notably increased number indicated COVID-19 had stronger infectivity.

The children with SARS were sporadic and had a clear history of exposure. By contrast, the children with COVID-19 showed clear history of clustering in infected households and community spread. According to incomplete statistics, over 230 children were infected with COVID-19, of 26.8% (69/257) have a history of exposure to Hubei province, 71.2% (183/257) had a clear history of clustering in infected households (Chan et al., 2020).

In the aspect of spreading approaches, both SARS and COVID-19 patients can be transmitted through droplets and contact. Insufficient evidences showed the newborn acquire the SARS or COVID-19 infection through vertical transmission (Chen H et al., 2020; Zhu et al., Xia; Pak C. Ng, 2004). On the other hand, studies suggested SARS may transmitted through aerosols containing viruses (Yu et.al, 2004) and digestive tract (Chinese academy of pediatrics respiratory group, 2003), but it's still unclear

whether COVID-19 patients can be transmitted through these ways. Fecal-oral tract way should not be ignored because studies had showed the positive nucleic acid tests in the feces (Guan et al., 2020; Holshue et al., 2020) even though no case was reported being transmitted through the digestive tract.

In conclusion, we found COVID-19 has quicker and wider transmission, obvious family agglomeration, higher morbidity and mortality. Digestive tract transmission cannot be ignored and maternal-infant vertical transmission is doubtful. It suggested traditional public measures took on SARS may not enough to contain the epidemic of COVID-19, international collaboration and information resource sharing can help to minimize the size of outbreak and reduce the global deaths.

## **2. Clinical features comparison between SARS and COVID-19 and the analysis of special cases**

### **2.1 The general cases comparison between SARS and COVID-19**

After comparing the clinical manifestations (Dong et al., 2020; Leong HN et al., 2006; Leung et al., 2004; Lu X et al., 2020; Fang and Luo, 2020; Pak C. Nga, 2004; Zeng et al., 2003; Xu et al., 2020; Xie, 2006; Zou, 2005), we found, the children including newborns are suspected to COVID-19. The most common symptoms of these two diseases are fever and cough and majority children had good prognosis. But children's COVID-19 cases exhibited less fever and more asymptomatic. The younger children especially newborns affected by COVID-19 had poor outcome, which is different

from children with SARS, which showed the increased age predict poor outcome. Moreover, digestive symptoms can be the first clinical manifestation and those children who started with gastrointestinal symptoms may had severe clinical condition.

## **2.2 A death cases and a critical illness cases.**

There was only one death child with SARS in Guangzhou, China, in 2003. The case is a 10 years old male child who had severe hepatitis before 2months ago. He was closely contacted with a doctor who had consulted with a SARS patient. The child had fever and cough in the early time, with the progressively worse condition, he was died 70 hours after transfer to ICU (Fu et al., 2004). Two child died of COVID-19 for now. The first one is a 10 months old child with intussusception who had multiple organ failure and died 4 weeks after admission(Lu X et al., 2020) and another one is a 14 years old boy from Hubei province(Dong et al., 2020).

The first severe condition child infected with COVID-19 was reported in China. The child is one year and one month old, comes from epidemic area, without clearly family contact history. The onset clinical symptoms were diarrhea and vomiting, which rapidly progressed to acute respiratory distress syndrome, sepsis, shock and acute renal failure. During hospitalized, 3 times of Nucleic acid detection were performed but only the third time revealed positive result. Furthermore, it should be noticed that his family members did not had any clinical symptoms, so the



asymptomatic transmission should be considered (Chen F, 2020).

Therefore, although majority children had mild clinical symptoms and good prognosis, we should not overlook the possibility these children can develop to deleterious serious condition, especially those who has atypical manifestations, basic diseases, long-term use of immune-suppressants and immunocompromised children.

### **2.3 Neonatal cases**

There were no newborn's SARS cases reported in China. 3 newborns with COVID-19 were reported. One had fever at the age of 5 days, another one was diagnosed after a home caregiver (first ill) and the mother were diagnosed, the third one was born to pregnant women with suspect COVID-19, and the nucleic acid test showed positive after 30h when he was born(Lu Q and Shi 2020).

It should pay a great attention that although the low possibility through vertical transmission, the infants whose mother infected with COVID-19 may have adverse reactions, such as fetal distress, preterm delivery, respiratory distress and even death(Chen H et al., 2020). Multidisciplinary team should make collective effort in perform labor room to improve the newborn survival rate.

### **3. Biochemical indicators between SARS and COVID-19**

In general, both of these two diseases had the following characteristics: normal or decreased peripheral blood white blood cells, decreased lymphocytes, mild abnormal

liver function and myocardial enzymes. However, children infected with COVID show higher CRP which is different from children with SARS (Bitnun et al., 2003; Xiong, 2003; Leung et al., 2004; Zeng, 2003).

A large number of studies had shown decreased CD4<sup>+</sup> , CD8<sup>+</sup> T cells, High LDH, higher percentage of neutrophils were positively correlated with the severity and mortality cases of SARS (Duan and Shen 2006). The severe child infected with COVID-19 also showed a significant decrease in T-cell subsets, low level of C3 and C4 in the acute stage of disease (Chen F, 2020). Therefore, the clinical works should monitor and pay attention to these early warning biochemical indicators, which can help us identified server cases.

#### **4. Pulmonary images comparison between SARS and COVID-19**

In general, the pulmonary image of children infected with SARS and COVID-19 are nonspecific in the early stage of disease. However, many children's COVID-19 cases showed normal pulmonary image when compared to children with SARS (Guan et al., 2020; National children's medical center, 2020; Xu et al., 2020). In addition, a few children infected with SARS showed mild clinical symptoms but severe pulmonary radiographic changes (Xiong, 2003), different from children's SARS, part of children infected with COVID-19 had radiologic changes but did not have any symptoms(Lu X et al., 2020). It alerted us, the pulmonary imaging changes should not be ignored, especially those patients who are highly suspected but X-ray revealed normal. The

chest CT detection is feasible to improve the positive rate of pulmonary lesions.

## **5. Treatment comparison of SARS and COVID-19**

Long-term follow-up results showed adult with SARS had different degrees of avascular necrosis of the femoral head, lung function impairment and pulmonary fibrosis. The reason of these outcomes may be related to the usage of large doses of hormones (Xie, 2006). Many Children infected with SARS were treated with hormones too, but recent report had suggested that available clinical evidence does not support the use of corticosteroid to treat patient infecting with COVID-19 (Russell, 2020). Therefore, the widely usage of hormones in children infected with COVID-19 remains to be skeptical. Strictly control the criteria to use hormones in clinical work, severe and critical patients can be used for a short time (Yi, 2020).

## **6. Pathogenesis comparison between SARS and COVID-19**

### **6.1 Invades host cellular mechanisms**

The envelope spiker protein of coronavirus associate with cellular receptors to mediate infection of their target cells and ACE2 is a functional protein of SARS (Li et al., 2003). SARS-CoV-2 and SARS-CoV have similar receptor-binding domain which suggest that SARS-CoV-2 might also use ACE2 as a cell receptor (Lu R et al., 2020; Zhu et al., 2020).

### **6.2 Immune response**

Both children with SARS and COVID-19 showed drastic decrease number of CD4+, CD8+ and CD3+T cells in the blood (Chen F, 2020; Duan, 2006; Luo, 2020). The results suggest that cellular immunity is severely damaged after coronavirus infection. However, the detail mechanisms still need to be investigated.

IFN $\alpha/\beta$  system is a powerful innate immune system with strong antiviral activity. Study had shown that, SARS-CoV not only can block the attack of IFN system, but also actively inhibit the activation of IFN regulator 3 (IRF-3) to prevent the activation of IFN system, and prevent the production of antiviral IFN by the body (Kuri & Weber, 2010). Whether these mechanisms were similar to COVID-19 require additional research.

### **6.3 Nuclear factor**

Membrane protein of SARS-CoV can directly bind to I $\kappa$ B kinase (IKK), inhibit the activity of nuclear factor kappaB (NF-kappaB) and reduce the expression of cyclooxygenase2 (COX-2) gene and other transcription factors to regulate the body's immune and inflammatory responses (Fang et al., 2007). The mechanism on COVID-19 still need to be elucidated.

There is significant deficit knowledge and unanswered questions on SARS-CoV-2, For example, ACE2 is widely distributed in lung, kidney, intestinal and other tissues, why the lung tissue damaged more frequently? Why children with COVID-19 show

mild clinical symptoms? Why children patients with COVID-19 show less change of subtype T-cell level when compared to adults (Duan, 2006)? Whether there were other pathways entering into the cell?

## **Discussion**

Although there are many similarities between SARS and COVID-19 from epidemiology to clinical characters they also show differences (Table 1). The potential reasons of higher transmissibility are as following: (1) The unique biological characteristics of SARS-CoV-2. (2) Children could be the potential infectious source because of mild symptoms which result in wider spread. (3) The asymptomatic children were overlooked. (4) Children with normal pulmonary image were ignored. (5)The false negative result of nucleic acid detection.

Why children infected with COVID-19 have mild clinical symptoms? Why they have none/mild abnormal biochemical indicators and pulmonary image change? The potential reasons are as following: (1) Children has a variety of memory T cells specific to the virus for frequently exposed to a variety of viruses in childhood, and it may has cross-react after SARS-CoV-2 virus infection. (2) Vaccination helps the body form a protective immune response. (3) The immune system of children is still developing, and an inadequate immune defense can prevent excessive host immune damage.

As a group of pediatrician, we learn from SARS and suggest: (1) The possible

transmission in children without/with mild illness should be emphasized. (2) Multidisciplinary and strategic approaches should be used to diagnose children with COVID-19. (3) Isolation measures is mandatory taken in time to the perinatal pregnant women infected with COVID-19 and multidisciplinary service team should be involved to improve the survival rate of newborns. (4)The following warning risk factors of severe cases should be identified early: younger age, higher percentage of neutrophils, higher LDH, decreased CD4+, CD8+T cells and progressive pulmonary image. (5) Considering mild clinical symptoms, imaging examination should not be ignored on children with COVID-19, chest CT can be used to improve the positive rate before the nucleic acid result, especially for those cases whose chest X-radiograph is normal. (6) The method of specimen collection for nucleic acid test should be trained, lower respiratory specimens were advocated to improve the positive rate. (7) The widely administrate of hormones should be cautious. (8) The education about how to prevent SARS-CoV-2 infection should be advocated. (9) More clinical and basic researches is necessary to understand COVID-19. (10)A lager and polycentric clinical database should be built to analysis the children infected with COVID-19. Recent study found that anxiety, depression and stress are common in young people during COVID-19 epidemic (Wang et al., 2020), further research is required to study mental health of young children infected with COVID-19.

## **Conclusion**

Currently, limited data are available on children with COVID-19, defining clinical

characteristics and severity of the disease is an urgent need especially in those countries lack of pediatric patients data. At present, China has made initial progress in containing the spread of COVID-19, but many countries are still suffering from the disease. In this paper, we summarized the difference and similarities between children's SARS and children's COVID-19 from epidemiology to clinical characteristics, at the same time, we provide some suggestions on containing children's COVID-19. On the one hand, we hope to draw upon the experience of containing SARS to mitigate the epidemic. On the other hand, we hope our suggestions could help other countries to identify possible preventive and therapeutic strategies.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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**Ethical Approval**

This study was approved by Chengdu Women's and Children's Central Hospital

Ethics Committee.

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Table 1 The comparison of SARS and COVID-19 in epidemiology and clinical characteristics.

Characteristic	SARS	COVID-19
<b>epidemiology</b>		
transmissibility	lower	higher
exposure characteristics	sporadic, hospital cluster	community spread, family cluster
children spread	no reported	yes
main transmission routes	respiratory droplets, contact, fecal-oral tract	respiratory droplets, contact
possible transmission routes	aerosols	aerosols, fecal-oral tract, vertical transmission
<b>clinical spectrum</b>		
incubation period	2-14 days	1-14 days
age	50 days to 17.9 years	36 hours to 18 years
clinical course	most are mild	most are mild and asymptomatic
Common features	fever, cough, headache, malaise, myalgia, diarrhea	
prognosis	good, one death reported	good, no death reported
<b>newborns born to mother with infection</b>		
first trimester	spontaneous miscarriages, termination of pregnancies	no reported
late second/third trimester	oligohydramnios, severe intrauterine growth retardation, severe gastrointestinal complications	may have adverse reactions, such as fetal distress, preterm delivery, respiratory distress and even death
<b>laboratory tests</b>	normal or decreased peripheral blood WBC, lymphopenia, mild elevated CRP, mild abnormal liver function and myocardial enzymes, decreased CD4 <sup>+</sup> , CD8 <sup>+</sup> T cells	
<b>pulmonary images</b>		
similarity	nonspecific in the early stage; as the disease progress could manifest patch shadow, ground glass shadow, lung consolidation	
difference	mild symptom but severe pulmonary radiographic changes	could be normal
<b>Treatment</b>	severe cases treated with hormones	widely usage of hormones is skeptical, severe and critical patients can be used for a short time

### Highlight

1. We study the features of children's COVID-19 by comparing the children's SARS.

2. There are differences between children's SARS and children's COVID-19.
3. We put forward some thoughts and give some recommendations to contain n children's COVID-19 from a pediatrician's perspective.

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