

# A new classification of clinical findings and treatment options of SARS-CoV-2 infection in children from China

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## Abstract

Since December 2019, cases of SARS-CoV-2 coronavirus infection have been reported in Wuhan, Hubei province, and the epidemic continues to spread. SARS-CoV-2 infections in children seem to progress more mild and slowly as compared to adult courses with severe and some times fatal outcome. Severe or fatal cases in children are yet not described supposing any molecular difference in viral-receptor binding between spike protein and angiotensin II receptor. This manuscript presents a first and completely new classification of clinical findings and treatment options in children infected with SARS-CoV-19 virus.

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## Introduction

SARS-CoV-2 virus was first described in 2003 and not a new entity, mostly controlled in S4 laboratories. Globally, more than 462.684 cases of COVID-19 infections have been reported, including 20834 deaths (date 26/03/2020). 2401 deaths worldwide were found in the last 24 hours (25/3-26/3/2020) indicating the aggressive and killing potential of the virus. It caused great loss of human life and economy [1,4].

According to incomplete statistics, as on February 7, 2020, 285 children with SARS-COV-2 pneumonia and 10 newborns were reported to have been diagnosed in China.

Epidemiological investigations suggest that people are generally susceptible to SARS-COV-2, and some children have a clear family gathering history [2,3].

On March 3, the national health commission said in the updated "coronavirus infection pneumonia treatment plan (implementation of the seventh edition)" that children and infants also have the disease.

The symptoms of some children and neonates are not typical, presenting as vomiting and diarrhea and other gastrointestinal symptoms or only showing as weak spirit and shortness of breath. Children with mild symptoms only showed low fever, mild fatigue, and no pneumonia.

Easily confused with human infection of upper respiratory tract, the main transmission routes of children infection are droplets, contact and transmission of feces and urine of the digestive tract. Conjunctival transmission has also been reported.

In traditional Chinese medicine, children are considered to be delicate and young in Yin and Yang. Neonates and children are more susceptible to new coronavirus infection due to their immature physiological and anatomical characteristics and immune functions.

Therefore, the new crown infection appears different from the adult cases.

Especially young children, and the younger the age, the less easy to find, once the onset of the disease, the progress is faster, the incubation period of the shortest 1 day that onset with up to 14 days.

The characteristics of the new crown in children are: 1, fewer cases than adults, 2, mild cases, 3, good prognosis, 4, no death cases have been reported so far.

The incubation period is 1 day at the minimum and normally 14 day at the maximum. Some Chinese reports shed light on an incubation period up to 24 days.

According to the clinical characteristics of the existing cases in children, the Chinese Journal of Pediatrics recommends the following five clinical types:

1. Asymptomatic infection
2. Light weight
3. Common type
4. Heavy duty
5. Critical type

**a) Asymptomatic infection:** The child has no clinical symptoms and signs. Chest imaging examination is normal, but the 2019-nCoV nucleic acid test was positive, sex, or serum-specific antibody positivity, was retrospectively diagnosed as infection.

**b) Mild:** Mainly presenting with acute upper respiratory tract infection, including Fever, fatigue, myalgia, cough, sore throat, runny nose and sneezing. Physical examination showed pharyngeal hyperemia and no positive signs in the lungs.

Part of children may not have fever, or with or only nausea, vomiting, abdominal pain and diarrhea; gastrointestinal symptoms.

**c) Common type:** Presenting as pneumonia. Often have fever and cough, most at the beginning of the cough, after the cough for sputum, part of the wheeze, but no obvious call of shortness of breath and other hypoxia, lung can be heard and sputum or dry rales and (or) wet rales. Some children do not have any clinical symptoms and signs, but chest CT showed pulmonary lesions, which were subclinical [5].

**d) Severe:** Early fever and cough and other respiratory symptoms, can be accompanied by diarrhea and other gastrointestinal symptoms, often in 1 week or so disease progression, with dyspnea, central cyanosis or pulse without oxygen. Blood

oxygen saturation showed  $<0.92$  oxygen degree manifestations.

**e) Critical type:** Children can rapidly progress to acute respiratory distress, acute respiratory distress syndrome (ARDS) or respiratory failure which can also be accompanied by shock, encephalopathy, myocardial injury, or heart failure.

Multiple organ dysfunctions such as exhaustion, coagulation dysfunction and acute kidney injury is possible in these cases.

### **Laboratory and imaging examination**

Clinical characteristics of infection in children (incubation period: 1 d, maximum: 14 d):

The clinical characteristics of the confirmed cases of infection in children are fever and cough, as well as fatigue, myalgia, nasal congestion, runny nose, sneezing, sore throat, headache, dizziness, nausea, vomiting, abdominal pain and diarrhea (only frequent vomiting in 45-day-old infants), which usually disappear within 1 week. The obvious period of symptoms is 1 ~ 2 weeks after the disease, and the time of detoxification can last 3 ~ 4 weeks or longer [4].

Although the incidence of serious children is low, but enough to warn pediatricians to pay attention to close monitoring, especially for children with basic diseases, such as congenital heart disease, kidney disease, diabetes, blood system and immune diseases, and strive for early identification and timely treatment.

### **Clinical types of cases in children**

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### **(A) General laboratory inspection**

**Blood routine:** The white blood cell count and the absolute number of lymphocytes in children were mostly normal. CRP was normal or mildly elevated temporarily, procalcitonin (PCT) was normal. Significant increases in CRP, lactate dehydrogenase (LDH), and serum ferritin are indicative of worsening or worsening of the disease.

Blood biochemistry and coagulation function are present in severely ill children with elevated levels of liver enzymes, myoglobin and myoglobin, decreased albumin, or coagulation disorders and elevated d-dimers. There were no clinical symptoms and signs, chest imaging examination were normal, but NCP nucleic acid test was positive, or serum specific antibody positive retrospective diagnosis of infection.

### **(B) Chest X-ray**

Imaging changes are sub substantial, cloudy or ground glass changes, with polymorphic characteristics. In the early stage, there were no abnormal changes and the rate of missed diagnosis was high. With the progress of the disease, it can be manifested as bronchitis or bronchiolitis changes or there are localized plaques, in severe cases, diffuse multiple consolidations of both lungs.

### **(C) Chest CT:**

The disease changes quickly, deteriorates quickly, the convalescent lung shadow absorption is also fast, can become 2 to 3 days thin. CT examination shows changes in multiple shapes and parts. In the early stage, the lumpy shadow can be single lung or double lung, with the characteristics of one side and the other, as well as bronchopneumatic syndrome.

According to the course of the disease, it can be divided into the following four stages:

(1) Early lesions were localized, which were subsegmental or segmental patchy shadows and ground glass shadows distributed under the pleura, with or without interlobular septal thickening. Early detection of small, thin lesions in the lateral lung or close to the pleura cannot completely rule out NCP pneumonia.

(2) In the progressive stage, the lesions increased in number and expanded in scope, involving multiple pulmonary lobes, and some lesions became solid, which could coexist with ground glass or striated shadows.

(3) In the critical stage, diffuse lesions were found in both lungs, mainly in the form of consolidation, with a few presenting as "white lung" and bronchial air signs. Pleural effusion and pneumothorax are rare.

(4) In the recovery period, the absorption of the original lesions improved. Pathologically, there is

no severe fibrosis in the lungs, and there is obvious inflammation and a lot of mucus. Therefore, some patients with clinical phlegm are not too much, but very thick, obstructing normal ventilation. Pathologically, the pulmonary fibrosis is not severe, but the inflammation is severe and there is a lot of mucus. This suggests that some clinical patients although not too much sputum, but very sticky, obstructing normal ventilation.

### ***Pathological findings of adult autopsy and biopsy***

1) The lungs are the main damaged organs despite the multi-organ damage, and the lungs show different degrees of consolidation. Serous, fibrinous exudation and hyaline membrane formation were observed in the alveolar cavity.

2) Exsudate cells are mainly mononuclear and macrophages, which are easy to see polynuclear giant cells. Type 2 alveolar epithelial cells proliferate markedly, with some cells exfoliated. Inclusion bodies are seen in type 2 alveolar epithelial cells and macrophages. This is a hyperemic, edematous species of alveolar septa with mononuclear and lymphocyte invasion and clear intravascular thrombosis. Focal hemorrhagic necrosis of lung tissue is seen here with a hemorrhagic infarction. Partial alveolar exsudate is institutionalized and interstitial fibrosis occurs.

3) Part of the epithelium of the bronchial mucosa in the lung was detached, and mucus and myxic acid could be seen in the lumen. A few alveoli are overinflated, and the alveolar septa ruptures or the lumen forms. The bronchial mucosal epithelium and type 2 alveolar epithelial stroma are seen here under electron fiber microscopy. Coronavirus particles, immunohistochemical staining showed that part of alveolar epithelium and macrophages were positive for novel coronavirus antigen, and rt-PCR detected positive nucleic acid of novel coronavirus.

4) Denatured and necrotic cardiomyocytes can be seen in the heart and blood vessels, and a few monocytes, lymphocytes or neutrophils can be seen in the stroma. Partial vascular endothelial shedding, intimal inflammation and thrombosis.

### **Basic principles**

The "four early" principle of early recognition, early isolation, early diagnosis and early treatment is emphasized.

1. Clinical suspected and confirmed cases should be isolated as soon as possible.
2. Treatment options are determined according to the severity of the illness: asymptomatic infection and mild cases, especially those in the foci, can be considered for home isolation treatment and ensure supervision and medical guidance when they do not have the conditions for hospitalization, common cases require hospitalization, and severe and critically ill children must be admitted to the pediatric intensive care unit. Early oxygen inhalation, vitamin D supplement and probiotics are recommended in the treatment.

### **General treatment**

Symptomatic treatment includes oxygen therapy, antiviral treatment, treatment of severe and critical types (respiratory support, loop support, other organ function support, glucocorticoids, intravenous immunoglobulin (IVIG), rational use of antimicrobial drugs and traditional Chinese medicine treatment.

### **Etiological examination**

#### **Virus nucleic acid testing**

Viral nucleic acid detection is the main method of NCP etiology diagnosis, and positive is the basis of diagnosis. It shall be carried out in the P2 laboratory, and the operator shall implement three levels of protection.

#### **1. Sample collection:**

Respiratory tract samples with the highest positive rate should be collected first, including upper respiratory tract samples (nasopharyngeal swabs and swabs) and lower respiratory tract samples (sputum, tracheal aspiration and bronchoalveolar lavage fluid). For suspected severe cases, negative samples of a single upper respiratory tract cannot exclude the diagnosis, so it is recommended to increase samples of the lower respiratory tract or repeatedly collect samples of the upper respiratory tract [4]. The diagnostic value of other samples such as blood (with a lower positive rate than

respiratory secretions) and faeces and urine should also be assessed for infection in children.

#### **2. Detection method:**

Fluorescence quantitative reverse transcription Polymerase chain reaction with detection of virus-specific antibodies. At present, there is still a lack of detection reagent, which can be used in clinic after the development of detection reagent. According to the diagnostic criteria of SARS coronavirus infection [6], two doses of serum or plasma were taken in the acute phase and the convalescence phase to detect virus-specific antibody, and it was observed that the titer of specific antibody was  $\geq 4$  times higher than that of antibody, which was helpful for retrospective diagnosis. Single test can be used for epidemiological investigation. V. diagnostic criteria According to the current situation of epidemic situation and the clinical characteristics of children infected cases, the following diagnostic criteria for epidemiological classification, surveillance cases, suspected cases and confirmed cases are proposed.

#### **Epidemiological classification**

Epidemiological history is an important basis for the early identification and diagnosis of children infected cases. According to the current epidemic situation, it is recommended to be divided into three grades: high, medium and low risk.

(1) The high-risk cases were suspected or confirmed cases of NCP infection that had been in close contact within 14 days before onset;

(2) The medium-risk patients were residents or communities with clusters of NCP pneumonia;

(3) Low risk is the general epidemic area outside the foci and without cluster disease in the residential community. Asymptomatic children at high risk are monitored and children at medium or low risk are monitored for any of the following. (1) fever; (2) respiratory symptoms or fatigue, nausea, vomiting, abdominal discomfort and diarrhea.

(4) Suspected cases:

4.1) the newborn born to the mother with new crown infection is a suspected case

4.2) children at high risk who meet 2 of the following 3 criteria are suspected cases.

Surveillance cases at medium and low risk were suspected after exclusion of influenza (no effect of standard oseltamivir phosphate 2 d) and other common respiratory pathogens.

(5) Confirmed cases: On the basis of meeting the standards of suspected cases, samples such as respiratory tract swabs or secretions, blood, feces and urine were taken to test for positive NCP nucleic acid. The viral gene sequencing is highly homologous to the known NCP.

## Conclusion

SARS-CoV-2019 coronavirus is responding to an outbreak of respiratory disease caused by a novel unknown coronavirus that was detected in China in December 2019 and which has now been detected in more than 100 locations internationally, including in the United States (1-7) and has led to 462,684 infections worldwide and 20834 deaths (WHO, 26/03/2020).

The virus has been named SARS-CoV-2 and the disease it causes has been named coronavirus disease 2019 (abbreviated COVID-19) (1-9). SARS-CoV-2 was described the first time in 2003 and not a new entity, controlled in S4 laboratories. COVID-19 infections have a slightly more preponderance in male. On January 30, 2020, the International Health Regulations Emergency Committee of the World Health Organization (WHO) declared the outbreak a public health emergency of international concern (PHEIC) (10-12).

On January 31, Health and Human Services Secretary Alex Azar declared a public health emergency (PHE) for the United States to aid the nation's healthcare community in responding to COVID-19. On March 13, the President of the United States declared the COVID-19 outbreak a national emergency situation.

To date, the virus is spreading in an exponential way all over the world and affects thousands of people (13). Most often the patients are asymptomatic, some are fatal. Chinese researchers found a higher level of serum amyloid protein in severe cases with lung involvement of more than 10 lung segments.

The situation is serious and devastating, economically and due to health concerns. COVID-19 is rapidly spreading worldwide and the

number of cases in Europe rising with increasing pace affecting several areas of the world. To date, 26/03/2020, 20834 people were dead worldwide (WHO, situation report, 26/03/2020). The speed of people infected with this new target, and this is very atypical and serious, suggest that in a few days and weeks, other countries like China will have similar situations, especially in the European region. The first country involved in the new viral pandemic, Italy, has been ambushed by the rapid spreading of SARS-CoV-2, leading to 7505 deaths (26/03/2020, WHO), more than in country of outbreak -China-. Further countries like Spain and Germany, with to date exponential numbers of SARS-CoV-19 positive tests, push efforts to test as many people they can to get clearer information about asymptomatic SARS-CoV-19 transmitter.

To date no clear guidelines in this disease and infection by SARS-CoV-2 are present, the outbreak is young and vaccination research and drugs to treat this virus are in childhood shoes. Many countries react with strict closing of the borders and by diminishing social contacts and staying at home. Schools, kindergardens and companies were closed for many weeks.

The only way to stop the pandemic situation is to test all individuals as soon as possible to get clearer numbers of asymptomatic cases and keeping them at home by social distance to avoid more transmittance of the novel virus and later for vaccination immunity, to strengthen all healthcare efforts producing a secure and approved vaccine for the people. Herd immunity will not be successful.

In different countries are efforts to make first steps in vaccination research of SARS-CoV-2 (USA, Germany, China). It is a competition of research to be the first to find a secure vaccination or drug to diminish this extraordinary spreading virus. The fact is, vaccination research will react in a sudden and minimal approved manner forced by governmental interests with dispense for animal studies at first, testing new possible vaccines in a hurry in human beings and not to know, what will happen with individual immunity in early and late stadium after vaccination, not to know anything about late complications of vaccination.

In the US, at John Hopkins University, they make first efforts to treat severe cases of COVID-19 with blood from survivors by application of COVID-19 antibody rich donated plasma (convalescent serum).

This therapy was used successful in former SARS epidemics and was introduced a few days ago in the United States.

On the other hand, at the University of Minnesota, Dr. Tignanelli et al. introduced a randomized controlled trial of Losartan (angiotensin II blocker) for patients with COVID-19 requiring hospitalization. SARS-CoV-2 uses Angiotensin II receptor (receptor site) as a portal entry of the lungs. More than 80% of pulmonary ACE2 are situated on type II alveolar epithel cells, which produce surfactant.

Measurement of surfactant levels could be necessary in severe cases in children with SARS-CoV-19 associated ARDS. In children, more than 80% of the angiotensin II receptor belongs to the AT-2 subtype, clinically in less severe cases in children so far. Hypothesis could be, the more AT-1 receptor binding of COVID 19 in adults, the more severe outcome. Angiotensin II receptor blocker could disturb the binding of COVID 19 with spike protein and angiotensin II receptor with his two subtypes (AT I/II). Recent studies in adults shed light on brain damage of COVID-19 with deterioration, loss of speech, loss of taste and presence of COVID-19 triggered necrotic encephalitis (14). To date, these neurological features not found in children. Children seem to have a „guardian angel“ to develop severe COVID-19 infection, but to date, few fatal cases especially in teenagers were found. The infection remains one of the biggest challenges in worldwide health care prevention and treatment(13).

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