



Updated diagnosis, treatment and prevention of COVID-19 in children: experts' consensus statement (condensed version of the second edition)

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Abstract

In the early February, 2020, we called up an experts' committee with more than 30 Chinese experts from 11 national medical academic organizations to formulate the first edition of consensus statement on diagnosis, treatment and prevention of coronavirus disease 2019 (COVID-19) in children, which has been published in this journal. With accumulated experiences in the diagnosis and treatment of COVID-19 in children, we have updated the consensus statement and released the second edition recently. The current version in English is a condensed version of the second edition of consensus statement on diagnosis, treatment and prevention of COVID-19 in children. In the current version, diagnosis and treatment criteria have been optimized, and early identification of severe and critical cases is highlighted. The early warning indicators for severe pediatric cases have been summarized which is utmost important for clinical practice. This version of experts consensus will be valuable for better prevention, diagnosis and treatment of COVID-19 in children worldwide.

Keywords Children · COVID-19 · Infection · SARS-CoV-2 · Treatment

Introduction

In the early February, 2020, we called up an experts' committee to formulate the first edition of consensus statement on diagnosis, treatment and prevention of coronavirus disease 2019 (COVID-19) in children, which has been published in World Journal of Pediatrics [1]. With accumulated experiences in diagnosis and treatment of COVID-19 in children, we have updated the consensus statement and released the second edition recently. The current version in English is a condensed version of the second edition of consensus statement on diagnosis, treatment and prevention of COVID-19 in children.

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Compared with the adult patients, the number of pediatric patients was lower with milder symptoms and better prognosis. According to the COVID-19 situation report issued by World Health Organization (WHO) on 28 February 2020, pediatric cases in China accounted for 2.4% of 55,924 confirmed cases [2]. There was a death reported as of March 8, 2020 [3]. Up to now, COVID-19 pandemic affects more than 185 countries around the world. China is under the risk of transmission of imported cases, which brings a new challenge in containing the epidemic in children. With more and more pediatric cases confirmed around the world, this updated version of expert's consensus statement from China is utmost important for clinical experience sharing. The statement will help pediatricians throughout the world in better diagnosis and treatment of COVID-19 in children.

Etiology

The description of severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) can be referred to the first edition of statement [1].

Route of transmission

Respiratory droplets and close contact are the main transmission routes of infection. When exposed to high concentration of aerosol for a long time in a relatively enclosed environment, aerosol transmission may occur. Live SARS-COV-2 can be isolated from the feces and urine in infected patients; the viral nucleic acid clearance in the feces was later than nasopharyngeal swabs. So attention should be paid to the aerosol or contact transmission caused by environmental pollution of feces and urine.

Close contact with infected patients with or without symptoms is the main transmission route of SARS-CoV-2 infection in children. Pediatric patients are mostly clustered cases. There is no direct evidence of vertical mother-to-child transmission, but newborns can be infected through close contact [1, 4].

Susceptible population

Children of all ages are susceptible to SARS-CoV-2 infection. Children with underlying diseases (such as congenital heart, lung and airway disease, chronic heart and kidney disease, malnutrition, hereditary metabolic diseases, immunodeficiency disease, tumor, etc.) are likely to become severe cases [1, 4].

Pathological changes

According to the current available pathological findings of adult patients, lung and immune system are mainly damaged. Among them, the lungs appear with varying degrees

of consolidation. Serous fluid, fibrin exudate and hyaline membrane formation were found in alveolar cavity. Alveolar septum is hyperemia and edema, mononuclear cell and lymphocyte infiltration and intravascular transparent thrombosis can be seen. Mucous and mucus plug formation can be seen in bronchial lumen of the lung [4–6].

Clinical manifestations

The incubation period of SARS-CoV-2 infection ranges from 1 to 14 days, mostly ranging from 3 to 7 days.

Fever, dry cough, and fatigue are the main clinical manifestations. A few children have upper respiratory symptoms such as nasal congestion, runny nose, and sore throat. Some infected newborns and children may have atypical symptoms, presenting as gastrointestinal symptoms such as vomiting, diarrhea or only poor spirit and shortness of breath.

Most children have relatively mild clinical symptoms without fever or pneumonia. They usually recover within 1–2 weeks. Severe pediatric cases show obvious dyspnea, and may rapidly progress to acute respiratory distress syndrome, septic shock, refractory metabolic acidosis, coagulation dysfunction and multiple-organ failure. Those who progress into severely and critically ill diseases may have low to moderate fever even without obvious fever during the disease.

Laboratory findings

Laboratory examinations [1, 4, 7, 8]

Blood testing

1. In the early phase of the disease, white blood cell count is normal or decreased, with decreased lymphocyte count; liver enzymes, lactate dehydrogenase, and myohemoglobin levels are increased in some patients. Troponin level is increased in some severe patients.
2. Most patients display elevated C-reactive protein level and erythrocyte sedimentation rate, but with normal parathyroid hormone-related protein level.
3. Severe patients show increased levels of D-dimer and ferritin, and progressively decreased blood lymphocytes counts.
4. Severe or critical patients may have increased levels inflammatory factors such as IL-6, IL-4, IL-10, TNF- α .

Pathogen analysis

SARS-CoV-2 nuclear acid test

SARS-CoV-2 can be detected in blood, feces, anal swabs and other specimens. For improving the positive test rate, collect sputum sample, and collect lower respiratory tract secretion samples in patients under tracheal intubation. Samples should be sent for test as soon as possible.

Blood SARS-CoV-2 antibody detection

Serum SARS-CoV-2 specific antibodies IgM and IgG test positive for two consecutive times is helpful for diagnosis. However, negative antibody tests cannot exclude infection at the early stage of disease onset. Non-specific reactions must be ruled out for positive IgM antibody detection. The diagnostic value of IgM and IgG detection needs further evaluation, because it takes a certain period for the body to produce serum-specific antibodies and reach the detection threshold after virus infection and the kinetic features of serum-specific antibody production after the virus infection are still unclear. Antibody test can be used for retrospective auxiliary diagnosis and seroepidemiological surveys.

Chest imaging examination

Digital X-ray photography

X-ray photography is not recommended as the first choice, because it is easy to missed diagnosis. Infected pediatric patients commonly have no abnormal X-ray imaging results at the early stage of disease onset. Only those severe cases or those at the progression stage show “white-lung” pattern. X-ray photography can be used for reviewing and comparison [9, 10].

CT scanning

To enhance the imaging features of CT examination in each stage, to observe pulmonary imaging changes in children more clearly, were commend using a spiral CT volume scan of 16 rows or more to reconstruct a thin layer of 1.0–1.5 mm, with standard algorithms and bone algorithms being the best [9, 10].

1. Early stage: Mostly appearing with single or multiple localized ground-glass opacities in the form of light cloud or fine mesh, with thickened blood vessels shadows inside the lesions. A few presenting with localized consolidation, located under the pleura or near the bron-

chial blood vessel bundles; among them, the periphery of the subpleural lung is the most commonly affected, and most are located in the bilateral lower lobes.

2. Progressive stage: Few patients have increased ground-glass shadows, or the affected area enlarged tending to merge, thus presenting with large-scale consolidation (rarely seen in patients).
3. Severe or critical stage: Very rarely seen in patients who have diffused consolidation of unilateral or bilateral lungs and accompanied with ground-glass opacities, bronchial inflation signs; pleural effusions are rarely seen.
4. Absorption stage: the original lesions completely absorbed and improved, the interstitial fibrosis is rarely seen.

Diagnosis

Suspected cases [1, 4, 8]

According to the global trend of disease outbreaks, we update the epidemiological history that requires close attention in clinical practice as follows. COVID-19 should be suspected in patients who meet any one of the criteria in the epidemiological history and any two of the criteria in clinical manifestations.

Epidemiological history

1. Children with a travel or residence history in a community with infected cases reported in China or a country or region with a serious epidemic within 14 days prior to disease onset (With the global pandemic of COVID-19, imported cases deserve attention).
2. Children with a history of contacting patients infected with SARS-Cov-2 within 14 days prior to disease onset.
3. Children with a history of contacting patients with fever or respiratory symptoms from communities with reported cases in China or countries or regions with serious epidemic within 14 days prior to disease onset;
4. Clustered cases: two or more cases with fever and/or respiratory symptoms within 14 days in small groups (such as family members, school classmates, etc.);
5. Newborns delivered by mothers with confirmed infection.

Clinical manifestations

1. Fever, fatigue, dry cough, and/or other respiratory symptoms; some pediatric patients may have low-grade fever or no fever.

2. With above-mentioned chest imaging findings (refer to the section of *Chest imaging examination*).
3. In the early phase of the disease, white blood cell count is normal or decreased, or with decreased lymphocytes count.
4. No other pathogens are detected which can fully explain the clinical manifestations.

Confirmed cases [1, 4, 8]

Suspected cases who meet any one of the following criteria:

1. Testing positive for SARS-CoV-2 by real-time PCR.
2. Genetic sequencing of respiratory tract or blood samples is highly homologous with the known SARS-CoV-2.
3. Both serum-specific antibodies IgM and IgG are positive.
4. Serum-specific antibody IgG changed from negative to positive or increased fourfolds or higher than that in the acute phase during the recovery period.

Clinical classifications [1, 4, 8]

1. Asymptomatic infection (silent infection)

Testing positive for SARS-CoV-2, but without clinical symptoms or abnormal chest imaging findings.

2. Acute upper respiratory tract infection

With only fever, cough, pharyngeal pain, nasal congestion, fatigue, headache, myalgia or discomfort, etc., and without signs of pneumonia by chest imaging or sepsis.

3. Mild pneumonia

With or without fever, with respiratory symptoms such as cough; and chest imaging indicating changes of viral pneumonia, but not reaching the criteria of severe pneumonia.

4. Severe pneumonia

1. Polypnea : ≥ 60 times/min (< 2 months), ≥ 50 times/min (2–12 months), ≥ 40 times/min (1–5 years), ≥ 30 times/min (> 5 years) (after ruling out the effects of fever and crying).
2. Oxygen saturation < 92% under a resting state.
3. Dyspnea: assisted breathing (moans, nasal flaring, and three concave sign), cyanosis, intermittent apnea.

4. Disturbance of consciousness: somnolence, coma, or convulsion.
5. Food refusal or feeding difficulty, with signs of dehydration.
6. Pulmonary high-resolution CT (HRCT) examination showing bilateral or multi-lobe infiltrates, rapid progression of disease in a short period or with pleural effusion.

5. Critical cases

Those who meet any of the following criteria and require ICU care:

1. Respiratory failure requiring mechanical ventilation.
2. Shock.
3. Combined with other organs failure.

Early identification of severe and critical cases

High-risk children and early warning indicators are highlighted in this edition.

High-risk children [1, 4, 8, 11]

According to the current accumulated experiences in managing confirmed COVID-19 pediatric patients and experiences from diagnosis and treatment of community-acquired pneumonia in children, children who meet any of the following criteria are at high-risk to become severe or critical cases:

1. Patients with a contact history of cases with severe COVID-19.
2. Patients with underlying diseases, such as congenital heart, lung and airway diseases, chronic heart and kidney diseases, malnutrition, tumors, diabetes, immunodeficiency or hyp immunity, hereditary metabolic diseases, etc.
3. Patients who are under long-term medication of immunosuppressants.
4. Infants under 3 months.

Early warning indicators

Early warning indicators for severe or critical diseases are as followings:

1. Increased respiratory rate (RR): > 50 times/min (2–12 months), > 40 times/min (1–5 years), > 30 times/

min (> 5 years) (after ruling out the effects of fever and crying).

2. Persistent high fever for 3–5 days, a disease course longer than 1 week, and no improvements in symptoms or signs or progressive exacerbation.
3. With poor mental response, lethargy, etc.
4. Significantly reduced and/or progressively decreased peripheral blood lymphocytes.
5. Progressively increased enzymatic indexes, such as myocardial enzymes, liver enzymes, lactate dehydrogenase.
6. Unexplainable metabolic acidosis.
7. Significantly increased D-dimer, IL-6, IL-10, and ferritin levels.
8. $SpO_2 \leq 95\%$ under the resting state.
9. Extrapulmonary complications.
10. Co-infected with other viruses and/or bacteria.

Differential diagnosis [1]

Differential diagnosis should be made to distinguish from influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus, rhinovirus, human metapneumovirus, SARS coronavirus, and other known viral infections, as well as mycoplasma pneumoniae and chlamydia pneumonia and bacterial pneumonia. The coinfection with other viruses and/or bacteria should be considered in diagnosis.

Treatment

General treatment and monitoring [1, 4, 8]

Detailed information can be referred to the first edition [1]. In this edition, we highlight maintaining microecosystem balance. Meanwhile, based on the pathological changes obtained from adults and referring to the special physiological structural characteristics of children, attention should be paid to appropriate humidity of airways.

Symptomatic treatment [1, 4, 8, 12, 13]

The patients with high fever should be actively controlled. If patients' body temperature exceeds 38.5 °C with obvious discomfort, physical cooling (warm water bath, use of antipyretic patch, etc.) or antipyretic drug treatment should be given. Common drugs include: ibuprofen orally, 5–10 mg/kg every time; acetaminophen orally, 10–15 mg/kg every time. Keep children quiet and administrate sedatives immediately when convulsions or seizure occur. Disperses phlegm when with increased respiratory secretions. Since mucus and mucus plug may occur in the lungs of patients revealed by pathological analysis in adults,

use of expectorant drugs can reduce or avoid respiratory tract obstruction. Commonly used drugs include: inhalation of acetylcysteine solution by nebulization, each 3 mL (0.3 g), 1–2 times/day for 5–7 days; Inhalation of ambroxol hydrochloride solution by atomization (ambroxol hydrochloride solution mixed with normal saline according to a ratio of 1:1, at 1 mL (< 2 years), 2 mL (2–12 years), 3 mL (> 12 years), 1–2 times/day for 5–7 days. According to the airway secretion, closed tracheal suction can be used if necessary after nebulization.

Oxygen therapy

When hypoxia occurs, effective oxygen therapy should be given immediately including nasal catheter, mask oxygen. Nasal high-flow oxygen therapy, and non-invasive or invasive mechanical ventilation should be undertaken when necessary [1].

Antiviral therapy [1, 14–23]

Children are a special group and the clinical manifestations of pediatric cases are relatively mild. Though some antiviral drugs are under clinical trial in infected adults, antiviral drugs without clear evidences of safety and efficiency are not recommended to be used in pediatric patients. The revised antiviral drug therapy remains to be interferon- α (IFN- α) sprays and aerosol inhalation. We do not recommend using lopinavir/ritonavir, ribavirin or chloroquine phosphate in pediatric patients.

IFN- α can reduce viral load, and early use can help to reduce symptoms and shorten the disease course. The recommended usage is as follows:

1. IFN- α spray: 1–2 sprays on each side of the nasal cavity, 8–10 sprays to the oropharynx for 8–10 times/day, with a treatment course of 5–7 days. According to previous evidences, interferon- α sprays can be used to high-risk children who had close contact with suspected patients or those with upper respiratory tract symptoms in the early stage of virus infection; and the daily dosage should not be less than 800,000 International Units (IU).
2. IFN- α nebulization: IFN- α 200,000–400,000 IU/kg or 2–4 μ g/kg, 2 mL of normal saline, atomization inhalation, 2 times/day, at a treatment course of 5–7 days.

Use of other antiviral drugs [1, 4, 14–23]

In the retrospective studies in abidol, no effects have been found in improving symptoms and shortening clearance time of viral nucleic acid in respiratory specimens have been found. Arbidol has been administrated for confirmed cases;

however, the efficacy still needs to be confirmed. Attention should be paid to its adverse effects such as nausea, diarrhea, elevated liver enzymes, bradycardia.

Oseltamivir and other anti-influenza agents can be added for COVID-19 patients coinfecting with other influenza virus.

Traditional Chinese medicine treatment

Please refer to the detailed information in the first edition [1].

Treatment of severe and critical cases [1, 4, 24–27]

On the basis of symptomatic treatment, we should actively prevent and treat complications, underlying diseases, secondary infection, and provide organ function support as indicated.

Respiratory support

Children who undergo non-invasive mechanical ventilation for two hours without improvements in conditions, or cannot tolerate non-invasive ventilation, with increased airway secretions, severe cough, or hemodynamic instability, should be subjected to invasive mechanical ventilation promptly. The invasive mechanical ventilation should adopt low tidal volume “lung protective ventilation strategy” to reduce ventilator related lung injury. If necessary, prone position ventilation, lung recruitment, or extracorporeal membrane oxygenation (ECMO) can be applied.

Circulation support

On the basis of full fluid resuscitation, improve microcirculation, use vasoactive drugs, and monitor hemodynamics if necessary.

Glucocorticoids

According to the degree of systemic inflammation, dyspnea, combination with ARDS and chest imaging exacerbation, glucocorticoids can be used in severe cases for a short period of time (3–5 days); and the recommended dose should not exceed 1–2 mg/kg/day equivalent to methylprednisolone.

Blood purification therapy

The blood purification system includes plasma exchange, adsorption, perfusion, blood/plasma filtration, etc. It can remove inflammatory factors and block “cytokine storm”, thus reducing the damage of inflammatory reaction to the body, and can be used for treating severe and critical patients in the early and middle stages of cytokine storm.

Immunoglobulin

Immunoglobulin can be used in severe cases when indicated, but its efficacy needs further evaluation.

Bronchoscopy

When severe and critical cases have obvious airway obstruction, bronchoscopy and lavage can be performed under the three-level protective measures.

Anticoagulation therapy

Children with significantly increased D-dimer and at high risk of thrombosis can be treated with low molecular weight heparin calcium at an early stage; and anticoagulant therapy can be given if necessary.

Convalescent plasma therapy

Convalescent plasma therapy can be used in children with a very fast exacerbation of conditions, and those with severe and critical diseases.

Prevention

Detailed information on prevention of infection in children can be referred to the first edition [1]. We highlight the following visiting and accompanying policy in ward for pediatric patients.

1. Strict visiting and family members accompanying policy. In principle, visiting and accompanying are not allowed. However, hospitals should fully evaluate the age span of children admitted, differences in care needs, children’s compliance with treatment, allocation of nursing human resources, possible secondary risks and hazards, etc.
2. Children are not allowed to leave the isolation ward on their own. If visiting children in critical condition is needed, visitors must take the protective measures the same with healthcare workers. Patients should wear protective clothing to go into the ward along with the specified route during the specified time; and hand hygiene must be strictly implemented at the same time.
3. The quarantine measures for visitors are the same with those for patients. They should also be kept at home or in isolation for 14 days. During this period, they should undertake health monitoring, wear masks, reduce close contact with their families, eat and drink separately, maintain hand hygiene, avoid going out and receive follow-up tests.

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