



Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement

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Abstract

Since the outbreak of 2019 novel coronavirus infection (2019-nCoV) in Wuhan City, China, by January 30, 2020, a total of 9692 confirmed cases and 15,238 suspected cases have been reported around 31 provinces or cities in China. Among the confirmed cases, 1527 were severe cases, 171 had recovered and been discharged at home, and 213 died. And among these cases, a total of 28 children aged from 1 month to 17 years have been reported in China. For standardizing prevention and management of 2019-nCoV infections in children, we called up an experts' committee to formulate this experts' consensus statement. This statement is based on *the Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Standards (the fourth edition)* (National Health Committee) and other previous diagnosis and treatment strategies for pediatric virus infections. The present consensus statement summarizes current strategies on diagnosis, treatment, and prevention of 2019-nCoV infection in children.

Background

In December, 2019, a cluster of pneumonia cases, who were later proven to be caused by a novel coronavirus (named as "2019-nCoV"), emerged in Wuhan City, Hubei Province, China. By January 30, 2020, 9692 confirmed cases and 15,238 suspected cases have been reported around 31 provinces and cities in China. Among the confirmed cases, 1527 were severe cases, 171 had recovered and been discharged

at home, and 213 died. Twenty-eight confirmed cases aged from 1 month to 17 years had been reported in China [1].

Coronavirus (CoV) belongs to the *Coronaviridae* family, *Nidovirales* order. CoVs are divided into four genera: α -, β -, γ -, and δ -coronavirus. α - and β -coronaviruses only infect mammals, whereas γ - and δ -coronaviruses mainly infect birds, with a few infecting mammals. Human CoVs include α -coronaviruses (229E and NL63), β -coronaviruses (OC43 and HKU1), the Middle East respiratory syndrome-related coronavirus (MERS-CoV), severe acute respiratory syndrome-related coronavirus (SARS-CoV), and 2019-nCoV. The 2019-nCoV belongs to the β -coronavirus genus [2], which includes bat-SARS-like (SL)-CoVZC45, bat-SL-CoVZXC21, SARS-CoV, MERS-CoV, and 2019-nCoV. Current studies have revealed that 2019-nCoV may originate from wild animals, but the exact origin remains unclear.

2019-nCoV infected patients are the main infection sources. However, we also should attach importance to asymptomatic cases which may play a critical role in the

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transmission process. Respiratory droplets and contact are the main transmission routes [3]. Close contact with symptomatic cases and asymptomatic cases with silent infection are the main transmission routes of 2019-nCoV infection in children.

People of all ages are susceptible to 2019-nCoV. The elderly and those with underlying chronic diseases are more likely to become severe cases. Thus far, all pediatric cases with laboratory-confirmed 2019-nCoV infection were mild cases, and no deaths had been reported.

For standardizing the prevention and treatment of 2019-nCoV infections in children, we called up an experts' committee to formulate this consensus statement. This statement is based on *the Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Standards (the fourth edition)* (National Health Committee) and other previous diagnosis and treatment strategies for pediatric virus infections.

Clinical manifestations

Based on the current epidemiological data, the incubation period of 2019-nCoV infections ranges from 1 to 14 days, mostly ranging from 3 to 7 days. Current reported data of pediatric cases revealed that the age of disease onset ranged from 1.5 months to 17 years, most of whom had a close contact with infected cases or were family cluster cases [4]. Infected children might appear asymptomatic [5] or present with fever, dry cough, and fatigue, and few have upper respiratory symptoms including nasal congestion and running nose; some patients presented with gastrointestinal symptoms including abdominal discomfort, nausea, vomiting, abdominal pain, and diarrhea.

Most infected children have mild clinical manifestations. They have no fever or symptoms of pneumonia with a good prognosis. Most of them recover within 1–2 weeks after disease onset. Few may progress to lower respiratory infections. No newborns delivered by 2019-nCoV infected mothers have been detected positive; and no newborn cases have been reported yet. It should be noted that clinical manifestations in pediatric patients should be further defined after collecting more pediatric case data. Furthermore, the number of confirmed infected cases will increase after a wide use of pathogen analysis.

Data from adults reveal that severe cases often develop dyspnea one week after disease onset. Severe cases may rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis, and coagulation dysfunction [6, 7]. Although no deaths in children have been reported up to now, the potential risk of death should be highlighted. Though clinical symptoms in pediatric patients are relatively milder compared with those in adult patients, ARDS and death cases also occurred in infected children during the SARS and MERS epidemics [8–11].

Auxiliary examinations

Laboratory examination [3]

1. In the early phase of the disease, white blood cell count is normal or decreased, with decreased lymphocyte count; liver enzymes, muscle enzymes, and myohemoglobin levels are increased in some patients.
2. Most patients display elevated C-reactive protein level and erythrocyte sedimentation rates, and normal prolactin levels.
3. Severe cases show high D-dimer levels and progressively decreased blood lymphocytes counts.
4. Samples from throat swabs (better using nasopharyngeal swab in children), sputum, lower respiratory tract secretions, stool and blood, etc. are tested positive for 2019-nCoV nucleic acids.

Chest imaging examination [3]

Suspected cases or confirmed cases should undertake chest X-ray examination as soon as possible. Chest CT scan is required when necessary. In the early stage of disease, chest images show multiple small plaques and interstitial changes, which are obvious in the lung periphery, further deteriorate to bilateral multiple ground-glass opacity and/or infiltrating shadows. Lung consolidation may occur in severe cases. Pleural effusion is rarely seen.

Diagnosis

Suspected cases

2019-nCoV 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 Wuhan city and neighboring areas, or other areas with persistent local transmission within 14 days prior to disease onset;
2. Children with a history of contacting patients with fever or respiratory symptoms who have a history of contact with patients from Wuhan city and neighboring areas, or other areas with persistent local transmission within 14 days prior to disease onset;
3. Children who are related with a cluster outbreak or close contact with 2019-nCoV infected cases;
4. Newborns delivered by confirmed 2019-nCoV-infected mothers.

Clinical manifestations

1. Fever, fatigue, dry cough; 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 lymphocyte count;
4. No other pathogens are detected which can fully explain the clinical manifestations.

Confirmed cases

Suspected cases who meet any one of the following criteria [3]:

1. Respiratory tract or blood samples tested positive for 2019-nCoV nucleic acid using RT-PCR;
2. Genetic sequencing of respiratory tract or blood samples is highly homologous with the known 2019-nCoV.

Clinical classifications

1. Asymptomatic infection (silent infection)
Children tested positive for 2019-nCoV, but without manifestations of clinical symptoms or abnormal chest imaging findings.
2. Acute upper respiratory tract infection
Children 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
Children with or without fever, respiratory symptoms such as cough; and chest imaging indicating pneumonia, but not reaching the criteria of severe pneumonia.
4. Severe pneumonia
Meeting any of the following criteria [3, 12–15]:
 - (1) Increased respiratory rate: ≥ 70 times/min (< 1 year), ≥ 50 times/min (≥ 1 year) (after ruling out the effects of fever and crying);
 - (2) Oxygen saturation $< 92\%$;
 - (3) Hypoxia: 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.

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 critical cases

According to the experiences in diagnosis and treatment of community-acquired pneumonia in children, children with a history of contact with severe 2019-nCoV infected cases, or with underlying conditions (such as congenital heart disease, bronchial pulmonary hypoplasia, respiratory tract anomaly, with abnormal hemoglobin level, severe malnutrition), or with immune deficiency or immunocompromised status (under long-term use of immunosuppressants) who meet any one of the following criteria may become severe cases:

1. Dyspnea: respiratory rate > 50 times/min for 2–12 months old; > 40 times/min for 1–5 years old; > 30 times/min in patients over 5 years old (after ruling out the effects of fever and crying);
2. Persistent high fever for 3–5 days;
3. Poor mental response, lethargy, disturbance of consciousness, and other changes of consciousness;
4. Abnormally increased enzymatic indexes, such as myocardial enzymes, liver enzymes, lactate dehydrogenase;
5. Unexplainable metabolic acidosis;
6. Chest imaging findings indicating bilateral or multi-lobe infiltration, pleural effusion, or rapid progression of conditions during a very short period;
7. Infants younger than 3 months;
8. Extrapulmonary complications;
9. Coinfection with other viruses and/or bacteria.

Differential diagnosis [3]

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 of 2019-nCoV with other viruses and/or bacteria should be considered in diagnosis.

Treatment

Treatment locations

1. Based on their medical conditions, suspected patients should be isolated in a single room or self-isolated at home following the doctors' advice.
2. Confirmed cases can be admitted in the same ward.
3. Critically cases should be admitted to ICU as soon as possible.

General treatment

The general treatment strategies include bed rest and supportive treatment; ensuring sufficient calory and water intake; maintaining water electrolyte balance and homeostasis; monitoring vital signs and oxygen saturation; keeping respiratory tract unobstructed and inhaling oxygen when necessary; measuring blood routine, urine routine, C-reactive protein, and other blood biochemical indexes including liver and kidney function, myocardial enzyme spectrum, and coagulation function according to patients' conditions. Blood gas analysis and timely re-examination of chest imaging should be performed when necessary.

Symptomatic treatment

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 performed. 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.

Oxygen therapy

When hypoxia appears, 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.

Antiviral therapy

Interferon- α [3, 16–28]

Interferon- α can reduce viral load in the early stage of infection which can help to alleviate symptoms and shorten the course of disease. Based on our clinical research and

experiences of using interferon- α in treating bronchiolitis, viral pneumonia, acute upper respiratory tract infection, hand foot mouth disease, SARS, and other viral infections in children, the recommended usage is as follows:

1. Interferon- α nebulization: interferon- α 200,000–400,000 IU/kg or 2–4 μ g/kg in 2 mL sterile water, nebulization two times per day for 5–7 days;
2. Interferon- α 2b spray: applied for high-risk populations with a close contact with suspected 2019-nCoV infected patients or those in the early phase with only upper respiratory tract symptoms. Patients should use 1–2 sprays on each side of the nasal cavity, 8–10 sprays on the oropharynx, the dose of interferon- α 2b per injection is 8000 IU, once every 1–2 hours, 8–10 sprays/day for a course of 5–7 days.

Lopinavir/litonavir [3, 29, 30]

Lopinavir/litonavir has been tried to apply to the treatment of adult patients with 2019-nCoV pneumonia, but its efficacy and safety remain to be determined.

Usage of other agents

Antibiotics [3, 12]

Avoiding irrational use of antibiotics, especially in combination with broad-spectrum antibiotics. Paying close attention to the changes of conditions in children with coinfection of bacterial or fungal infection; actively collecting samples for pathogen analysis and timely or rational use of antibiotics or anti-fungal drugs.

Arbidol [31], oseltamivir [32] and other anti-influenza drugs

Arbidol is administrated for adults infected with 2019-nCoV; however, its efficacy and safety remain unclear. Oseltamivir and other anti-influenza agents can be applied for patients coinfecting with other influenza virus.

Other drugs [3, 12]

Glucocorticoids

The use of glucocorticoids should be based on the severity of systemic inflammatory response, degree of dyspnea, with or without ARDS, and the progress status of chest imaging results. Glucocorticoids can be used in a short period

(3–5 days). The recommended dose of methylprednisolone should not exceed 1–2 mg/kg/day.

Immunoglobulin

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

Treatment of severe and critically ill cases [3, 12]

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 2 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.

Traditional Chinese medicine

This disease belongs to the epidemic disease category of Traditional Chinese Medicine and results from contracting epidemic pathogens. Different regions can refer to the following plans for dialectical treatment according to the patient’s conditions, local climate features, and physical characteristics of children.

Clinical treatment period

1. Asymptomatic infection:

- (1) Therapeutic methods: strengthening the healthy and dispelling pathogenic factors;
- (2) Recommended prescription and drugs: modified Yupingfeng powder in combination with Buhuanjin Zhengqi powder composed of 9–12 g

of *Zhihuangqi* (Prepared Astragalus), 6–9 g of *Chaobaizhu* (Roasted Rhizoma *Atractylodis Macrocephalae*), 3–9 g of *Houpo* (Official *Magnolia Bark*), 6–9 g of *Cangzhu* (*Atractylodes lancea*), 6–9 g of *Chenpi* (*Pericarpium citri reticulatae*), 3–6 g of *Jiangbanxia* (Ginger processed *pinellia*), 6–9 g of *Huoxiang* (*Agastache rugosus*), 6 to 9 g of *Fuling* (*Poria cocos*), and 3–6 g of *Zhigancao* (Prepared *Liquorice Root*).

2. Old and damp tightening the lung:

- (1) Clinical manifestations: aversion to cold, fever or no fever, dry cough, sore throat, nasal congestion, tiredness and fatigue, nausea and retching, loose stool, pale tongue or reddish tongue with whitish-greasy fur, floating, and soft pulse;
- (2) Therapeutic methods: dispersing lung to promote pathogenic factors, detoxify, and dispel dampness;
- (3) Prescription and drugs: modified Qingqi decoction composed of 6–9 g of *Cangzhu*, 3–9 g of *Houpo*, 6–9 g of *Chenpi*, 6–12 g of *Huoxiang*, 3–9 g of *Banxia*, 3–9 g of *Xingren*, 9–15 g of *Suye*, 6–9 g of *Jiegeng*, 6–9 g of *Guanzhong*, 6–9 g of *Fuling*, 3–6 g of *Shengjiang*, and 3–6 g of *Gancao*.

3. Plague poison obstructing lungs:

- (1) Clinical manifestation: fever persists or chill and fever alternate; cough with little or yellow phlegm; shortness of breath holds back; abdominal distension constipation. The tongue is red, while the moss is yellow and greasy or yellow and dry. Slide number of arteries and veins;
- (2) Therapeutic methods: detoxification, opening and closing, clearing the lungs, and dampness;
- (3) Prescription and drugs: modified Xuanbai Chengqi decoction composed of 6–9 g of *Huoxiang*, 10 g of *Cangzhu*, 3–6 g of *Zhimahuang*, 3–9 g of *Chaoxingren*, 15–30 g of *Shengshigao*, 10 g of *Gualou*, 3–6 g of *Jiujun* (to be added later in preparation), 6–9 g of *Huangqin*, 6–9 g of *Fuling*, 6–9 g of *Danpi*, 6–9 g of *Shichangpu*, and 3–6 g of *Chuanbei*.

4. Inner blocking causing unconsciousness and collapse:

- (1) Clinical manifestation: dyspnea, lethargy, restlessness, cold and sweat in limb, dark purplish tongue, thick and slimy fur or dry fur, big floating and unstable pulse, cyanosis in fingerprints, and reaching for the Mingguan point (distal phalanx);

- (2) Therapeutic methods: opening the blocking and solidification dysfunction, detoxifying, and reviving the unconscious;
 - (3) Prescriptions and drugs: modified Shenfu decoction plus Shengmai drink composed of 3–6 g of *Renshen* (radix ginseng), 6–12 g of *fuzi* (radix aconiti Praepareta) (to be decocted one hour first), 6–12 g of *Shanzhuyu* (Fructus Corni), 10 g of *Maimendong* (Radix ophiopogonis), and 3–6 g of *Rougui* (Cinnamomum cassia), to be taken with Angong Niu Huang Pill.
5. Qi deficiency of both the lung and spleen.
- (1) Clinical manifestation: feeble cough, lassitude and asthenia, spontaneous sweating, poor appetite, loose stool, pale tongue with whitish and slippery fur, thready, and weak pulse;
 - (2) Therapeutic methods: nourishing the lungs and strengthening the spleen, nourishing qi, and dehumidifying;
 - (3) Prescription and drugs: modified LiuJunZi decoction composed of 15 g of *Zhihuangqi* (Prepared Astragalus), 10 g of *Xiyangshen* (American Ginseng), 10 g of *Chaobaizhu* (Roasted Rhizoma Atractylodis Macrocephalae), 6 g of *Fabanxia* (Rhizoma Pinelliae preparatum), 6 g of *Chenpi* (Pericarpium citri reticulatae), 3 g of *Chuanbei* (Tendrill-leaved fritillary bulb), 15 g of *Fuling* (Poria cocos), 6 g of *Huoxiang* (Agastache rugosus), and 3 g of Sharen (Fructus amomi) (to be added in later).

Psychotherapy

Psychological counseling plays an important role in disease recovery. If patients (especially older children) show mood swing, fear, or psychological disorders, active psychological intervention and treatment are needed.

Release and discharge criteria [3]

Confirmed patients can be discharged from isolation or transferred to the corresponding departments for treatment of other diseases if all the following criteria are met:

1. The body temperature returns to normal longer than 3 days;
2. The respiratory symptoms improve obviously;

3. The detection of respiratory pathogenic nucleic acid is negative for two consecutive times (the sampling interval is at least 1 day).

Suspected patients can be discharged from isolation when the detection of respiratory pathogenic nucleic acid is negative for two consecutive times (the sampling interval is at least 1 day).

Prevention [33–35]

Novel coronavirus infection is a new communicable disease with an emergent outbreak that affects all populations. 2019-nCoV infection has been classified as category B infectious disease legally but managed as category A infectious disease. It is paramount to implement infection control practices by infection source controlling, transmission route blocking, and susceptible population protection.

Controlling infection sources

Patients infected with 2019-nCoV are the main infection sources. Children infected by novel coronavirus should be isolated at home or admitted to designated hospitals under the guidance of healthcare workers depending on the severity of their medical conditions. Try to provide single rooms for isolated children, and reduce the chance of contact with the co-residents. There are enormous demands for room ventilation, necessary cleaning, and disinfection work for the articles used by children. Equally crucial is the need of equipment with disposable masks and properly disposal after use when taking care of the sick.

Blocking transmission routes

1. Preventing transmission by respiratory droplets and contact: Cover mouth and nose with napkin or towel when coughing or sneezing. Wash hands for children frequently, or teach children seven-step washing technique. Try not to touch mouth, nose, or eyes before cleaning hands thoroughly after returning from public places, after covering the mouth when coughing, before eating or after using toilet; regularly disinfecting toys by heating at 56 °C for 30 min, 75% alcohol or chlorine-containing disinfectants, and ultraviolet rays.
2. Reduce exposure to infection: Avoid public transport at epidemic areas, and wear masks when going to crowded or poorly ventilated public places; avoid touching or eat-

ing wild animals, and going to markets selling with live animals.

- Children's health monitoring: Children with a history of close contacts of infected patients need to be monitored for body temperature and clinical features routinely. When presenting with suspicious symptoms, children should be taken to a designated hospital for screening. Newborns delivered by infected mothers must complete a pathogen test and be isolated in a single ward or at home according to their medical conditions.

Boosting immunity

Balanced diet, oral health, adequate exercise, regular rest, avoiding excessive fatigue, and boosting immunity are the powerful measures to preventing infection, as well as maintaining emotional stability and mental health. Vaccination is an effective way to prevent virus infection. The research and development of anti-virus vaccines has been carried out in China at present.

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Compliance with ethical standards

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