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Review Article

COVID-19 in the Children: A Practical Review

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Abstract

Since the outbreak of the new coronavirus infection in December 2019, the China epidemic situation has been initially controlled, but the situation is still grim globally. In this pandemic, compared with adult cases, children have relatively fewer cases, milder symptoms with better prognosis. The spread of risks poses new challenges for approaching, prevention and treatment in the children. This review summarizes the early medical information in order to further guide the management of children with COVID-19 infection.

Keywords: COVID-19; Children; Coronavirus Pneumonia

Introduction

Since December 2019, a new coronavirus pneumonia epidemic has appeared in Wuhan City, Hubei Province. With the spread of the epidemic, other cases in China and many overseas countries have also found such cases. The epidemic situation in most provinces in china has eased, but the number of outbreaks globally is on the rise. On March 11,2020 WHO have made the assessment that COVID-19 can be characterized as a pandemic [1]. According to published data, children appear to be less likely develop COVID-19. Fortunately, affected children also had a milder symptoms and fewer complications than adults [2]. Children can be considered as silent victims of this disease. While the Centers for Disease Control and Prevention (CDC) currently reports that the risk of exposure to COVID-19 is low for young ages, research makes it clear that, children are more vulnerable to the emotional impact of traumatic events that disrupt their daily lives compared to adults [3]. Since children, especially those who are younger, need closer care, quarantining them is very difficult. There is no proven antiviral agent against COVID-19 in the children. Understanding of the recent experiences in diagnosis and management of the COVID-19 in pediatrics will improve the early diagnosis and managing, cure rate, reduce the mortality rate, and avoid hospital infection as much as possible.

Etiology

COVID-19 are coronaviruses of the genus β, which have an envelope, particles that are round or oval, often polymorphic, with a diameter of 60 - 140 nm and the genetic characteristics are significantly different from SARS-CoV and MERS-CoV. COVID-19 has more than 85% homology with bat SARS-like coronavirus (bat-SL-CoVZC45). When isolated and cultured *in vitro*, the new coronavirus can be found in human respiratory epithelial cells in about 96 hours, while it takes about 6 days to isolate and culture in Vero E6 and Huh-7 cell lines [4].

Epidemiology

According to the report of the World Health Organization (WHO): As of March 25, 2020, a total of 41,3467 confirmed cases

were reported globally in 199 countries, territories and 1 international conveyance (the *Diamond Princess* cruise ship harboured in Yokohama, Japan) [5]. Amidst the COVID-19 outbreak, everyday life has changed and will continue to change for most people globally with a basic reproductive number estimated to be from 2.21 to 3.32 and a mortality rate of around 2.3% [4,6].

Current research shows that the 2019 new coronavirus may come from wild animals, and more evidence suggest that its host may be bat and the intermediate host has not been identified, but its final source remains to be further studied [7]. Respiratory droplets and close contact transmission are the main routes of transmission. There is a possibility of aerosol transmission in a relatively closed environment (less than 2 meters) with prolonged exposure (more than 15 minutes) to high concentrations of aerosol. Moreover, as the COVID-19 can be isolated in feces and urine, although it is not yet known whether other non-respiratory body fluids from an infected person including vomit, urine, breast milk, or semen can contain viable, attention should be paid to aerosols or exposure to environmental pollution caused by feces and urine [8].

Although children can also be infected with respiratory infections infected with the virus, constant hand-to-mouth contact with the face and mouth can play an important role. The sources of infection in children seen so far are mainly family cluster symptomatic patients those involved with COVID-19. Asymptomatic patients can also be a source of infection. Moreover, they are not routinely tested, so the prevalence of asymptomatic infection not well understood. In the recent published study 13% of RT-PCR-confirmed cases of COVID-19 infection in children were asymptomatic [2]. These asymptomatic children should be given more attention as they can easily transmit the virus.

Case definition

Case and contact definitions in the children are available based on existing information and are updated regularly as new information is collected. Countries may need to adjust their definitions based on their epidemiological conditions.

Suspect case

A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g. cough, shortness of breath) AND A history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset OR having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset OR requiring hospitalization in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case

A suspect case for whom testing for the COVID-19 virus is inconclusive or could not be performed for any reason.

Confirmed case

A child with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms [9].

Clinical manifestations

The incubation period is the same as adults, and is from 1 to 14 days, and in most of them are 3 to 7 days. Similar to other pneumonias caused by coronaviruses, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), children with COVID-19 appeared to be less involved and their symptoms are relatively mild [10]. The main manifestations are fever, dry cough, runny nose and sore throat. A few patients have symptoms such as nasal congestion and myalgia. Patients with severe disease usually have dyspnea and/ or hypoxemia one week after the onset of their symptoms, and can quickly progress to acute respiratory distress syndrome (ARDS), septic shock, and multiple organs failure [11-13]. There may be low to moderate fever, even without obvious fever. Some pediatric patients were asymptomatic A recent study found that near half of the pediatric patients had no systemic symptoms and no severe cases were seen in them. They had fewer fevers and milder fatigue but presented with more coughs and runny noise compared to the adults [14].

Some children and neonatal cases may have atypical presentation, manifested as gastrointestinal symptoms such as loss of appetite, nausea, vomiting and diarrhea. These group of atypical patients may have a delayed diagnosis and a worse clinical outcome compared to those without digestive symptoms [12].

Differential diagnosis

The mild manifestations of COVID-19 infections in the children needs to be distinguished from upper respiratory tract infections caused by other viruses. COVID-19 pneumonia should be mainly differentiated from respiratory syncytial virus influenza virus, adenovirus and mycoplasma pneumoniae infections [11]. Co-infec-

tion with some of the mentioned pathogens has also been reported [15]. Co-infection is more common in pediatrics compare to the adults [13].

It should also be distinguished from non-infectious diseases such as vasculitis, dermatomyositis, and organizing pneumonia. Based on the published data, children with CPVID-19 had fewer upper respiratory symptoms (cough and pharyngeal congestion) but pneumonia was more frequent and compared to those infected by the SARS they had much milder disease [12].

All suspected pediatrics cases should have two negative RT-PCR consecutive tests (at least 24 hours apart) and the negative specific IgM and IgG antibodies 7 days after the onset of the disease to rule out the diagnosis for COVID-19 and differentiate from other respiratory virus infections.

Laboratory and diagnostic testing

In the early stage of the onset, the total number of white blood cells in the peripheral blood is normal or decreased. Most of the patients have elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and the normal procalcitonin level. Some children may have increased liver enzymes, lactate dehydrogenase (LDH), muscle enzymes, and myoglobin. Decreased number of the lymphocytes and increased D-dimer may occur in the progressive phase.

Children with severe and critical illness also may be accompanied by elevated levels of inflammatory factors such as interleukin (IL) -6, IL-4, IL-10, tumor necrosis factor (TNF) -α and troponin [12].

COVID-19 nucleic acid can be detected in nasopharyngeal and oropharyngeal swabs, sputum, feces and blood using RT-PCR or in next generation study (NGS) methods as a new inspection method [16].

Detection of lower respiratory tract specimens (bronchoalveolar lavages or sputum) is more accurate than those from the nasopharynx and then throat samples [15]. Detection of RNA in blood and prolong virus RNA shedding in the stool may be a marker for illness severity and need for hospitalisation [18,19].

Detection of the COVID-19 IgM and IgG serum-specific antibodies can help confirm the diagnosis. COVID-19 specific IgM antibodies begin to show positive after 3 - 5 days of onset, and the recovery period of IgG antibody titers is 4 times or more higher than that of the acute phase. Thus, negative results early in the onset of disease cannot exclude the infection as It takes a certain time to generate serum-specific antibodies and reach the detection threshold after virus infection. Moreover, the kinetic characteristics of serum-specific antibody production are unclear, so the diagnostic value of IgM and IgG detection needs further evaluation [20].

Chest imaging

Plain chest X-rays are easy to miss as there are usually no abnormal findings at the initial stage. In children with a mild disease, routine use of CT might not be warranted. But suspected moderate to severe cases should undergo chest CT examination as soon as possible. Lung abnormalities at CT in the pediatrics are similar but more modest to those seen in adults [21].

In the chest CT examination, multiple small patchy shadows and interstitial changes appeared early. Furthermore, it develops bilateral, peripheral or subpleural multiple ground glass opacities (GGO) and crazy paving [22]. Although peribronchial distribution and bronchial wall thickening were not common in both pediatrics and adults, it was more prevalent in children [14].

In severe cases, pulmonary consolidation with surrounding halo sign may occur, but nodules, lymphadenopathies and pleural effusion are rare [13].

Clinical severity

1. **Mild:** Low grade fever, minimal symptoms, normal chest imaging and Laboratory data and Spo_2 more than 95%.
2. **Moderate:** Fever, tachypnea but less than 60 per minute, abnormal chest imaging (< 50% lung involvement on imaging) and laboratory data and Spo_2 in range of 92 to 95%.
3. **Severe:** High grade fever, tachypnea (more than 60 per minute), respiratory distress (grunting, nasal flaring, intercostal or suprasternal retractions), lethargy and/or convulsions, poor feeding, abnormal chest imaging (>50% lung involvement on imaging) and laboratory data (elevation of lactic acid, IL-6 and C-reactive protein), cyanosis and Spo_2 less than 92%.
4. **Critical:** Respiratory failure, acute respiratory distress syndrome (ARDS), shock, or multiorgan system dysfunction.

Risk factors

The risk factors among the pediatric age group consider as: Infants under 3 months of age, have underlying diseases (congenital heart disease, bronchopulmonary dysplasia, respiratory malformations, abnormal hemoglobin, severe malnutrition, etc.), have immunodeficiency or long-term use of immunosuppressants.

Treatment

Suspected and confirmed cases should be isolated with effective isolation and protection conditions and treated in designated hospitals. Suspected cases should be treated in a single room and isolated. Multiple confirmed cases can be admitted to the same ward. They should be placed in the private ward with a negative air pressure that has a minimum of 6 air changes per hour. Critical cases should be admitted to specialised COVID-19 pediatrics intensive care unit (PICU) as soon as possible. Due to the insufficient evidence for treating COVID-19 in children, these suggestions should not replace clinical judgement at the bedside.

Support treatment

The treatment is mostly supportive in children with COVID-19 infection and are included as: Complete bed rest, Fluid-sparing resuscitation and calorie intakes to maintain hydration and nutritional supports; closely monitoring of the vital signs including oxygen saturation and give humidified oxygen if necessary, by nasal cannula, simple mask OR non-rebreather masks. Continuous monitoring of blood pressure, intake-output, peripheral capillary refills, cardiac and neurological status. Empiric antibiotics if suspicion for secondary infection [11].

Management of hypoxemic respiratory failure

High-flow nasal catheter oxygen therapy or non-invasive ventilation can be considered when patients have respiratory distress and/or hypoxemia cannot be relieved after receiving standard oxygen therapy. If the condition does not improve or worsens within a short time (1 - 2 hours), tracheal intubation and invasive mechanical ventilation should be performed. Treatments for COVID-19 patients who admitted in the PICU are included:

1. Early and rapid sequence intubation using video laryngoscopy (where possible) to avoid use of aerosolizing bag-mask valve or NIPPV.
2. Minimize circuit breaks and use high-efficiency particulate air (HEPA) filters between endotracheal tubes and CO_2 detectors.
3. Use lung-protective ventilation strategies protocol.
4. Prone and paralyze as needed. Prone ventilation should be performed for more than 12 hours per day. If prone position mechanical ventilation is not effective, if conditions permit, extracorporeal membrane pulmonary oxygenation (ECMO) should be considered as soon as possible.

Medical treatment

No specific medical treatment for COVID-19 is currently US Food and Drug Administration (FDA) approved in the pediatrics. The National Institutes of Health (NIH) began a randomized controlled trial for the treatment of COVID-19 patients with the investigational antiviral drug Remdesivir. The FDA has been working closely with other academic centers and studies are underway to determine the efficacy in using chloroquine to potentially reduce the duration of symptoms, as well as viral shedding, which can help prevent the spread of COVID-19. Tocilizumab, an IL-6 inhibitor may have a role in the cytokine storm and for patients in shock [23].

Although clinical trials of some drugs are performed in adult cases, based on the lower incidence, relatively milder clinical manifestations and by considering the toxic side effects of these drugs, they should not be used without clear and effective evidence.

Prognosis

The largest cohort of more than 44,000 persons with COVID-19 from China showed that the overall case fatality rate was 2.3% but was about 50% in those patients with the critical disease [24].

Judging from the current pediatric cases, most patients have a good prognosis, and a few patients are critically ill. Epidemiological characteristics of 2143 pediatric patients in china showed that the clinical severity was low in 94% of cases (asymptomatic, mild or moderate disease), severe disease was seen in 5%, and only < 1% having critical disease. Only one (< 0.1%) death was reported in a patient less than 18 years old [2,24].

Conclusion

Despite the high incidence of the disease, children appear to be less likely to be involved in recent outbreaks. Children have a lower rate of severe illness. In comparison to adults, the severity of the disease is lower. More child protection, more housing, early school closures, and early family members' quarantine protocols can all help reduce the incidence of childhood illness. No specific medi-

cal treatment for COVID-19 is currently approved in pediatrics. The base of their treatment is supportive care, oxygenation supports, maintain the nutritional needs, starting antibiotics for bacterial superinfections.

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Volume 4 Issue 6 June 2021