

COVID-19 Infection and Children: A Comprehensive Review

Abstract

Nowadays, COVID-19 is in pandemic stage, and concerns about the infection of children are on the rise. At first, it has been believed that children are not at risk while some evidences have shown that the risk of infection is lower in children than adults. The COVID-19 children indicated milder symptoms including cough, fever, sore throat, myalgia sneezing, and fatigue than COVID-19 adults. Lymphopenia, which is prevalent in adult cases, has not been reported in pediatric patients. The COVID-19 can also occur in neonates although vertical transmission from mothers to fetuses during pregnancy is rare. Overall, the outcome is better in children than adults. Thus far, there has been neither specific treatment for eradicating the infection nor any preventative vaccine for COVID-19. Preventive measures such as frequent hand washing, social distancing and wearing face mask are the best ways.

Keywords: COVID-19, pediatric, newborn

Introduction

Coronaviruses are a big family of enveloped, non-segmented and single-stranded RNA viruses.^[1] Two previous coronaviruses, Middle East Respiratory Syndrome (MERS, introduced in 2012) and Severe Acute Respiratory Syndrome (SARS, introduced in 2003) infected 2,429 and 8,000 individuals, respectively.^[2,3] In December 2019, a new coronavirus known as COVID-19 with high transmissibility and infectivity rates was found in Wuhan, China.^[4] Transmission happens through large droplets from coughing or sneezing via both asymptomatic and symptomatic cases.^[5] The droplets can spread over a distance of 1–2 m and remain on surfaces. Inhalation of the droplets and touching contaminated surfaces are the main routes of transmission. Aerosol, fecal-oral, and transplacental transmissions are also hypothesized.^[6,7] The COVID-19, which is a group 2c β -coronavirus, has pangolin as its intermediate host and is inactivated at 56°C heat for 30 min and in 75% ethanol as well as in disinfectants containing chlorine.^[8] The COVID-19 can influence all age groups. The most common affected locations by the virus are nasal cavities and throats.^[9]

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Its basic reproduction number (R0) is between 2 and 3.6, which is the average number of secondary infections produced by an affected case without any protection.^[10,11] An asymptomatic case can infect many others because the incubation period of the COVID-19 is estimated about 14 days.

The stage of the infection is pandemic at this time, and most countries are affected. By March 16, 2020, the number of infected countries was 143 as reported by the World Health Organization (WHO).^[12] The higher rate of the COVID-19 related to pneumonia among males and Asians could be due to their having more angiotensin-converting enzyme 2 (ACE2) receptors.^[13,14] The COVID-19 virus uses SARS–coronavirus and ACE2 receptors to enter into the host cells.^[15]

The COVID-19 presentation ranges from an asymptomatic state to acute respiratory distress syndrome. Most patients have clinical symptoms including shortness of breath, fever, headache, cough, myalgia, and fatigue.^[16] At the end of the first week, based on cytokines levels (IL2, GCSF, IL7, IP10, IL10, MCP1, TNF α and MIP1A), some patients can develop pneumonia and respiratory failure, and in severe cases, death may occur.^[17] Near one-third of patients need intensive care unit admission.^[18] The mortality rate has been reported 2–3%, while it can rise

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as high as 4–11% in patients admitted to intensive care units.^[19]

The COVID-19 is diagnosed using molecular tests on respiratory samples (swab samples from nose and throat, sputum, endotracheal aspirates as well as bronchoalveolar lavage).^[18] Laboratory test results, indicating COVID-19 infection include lymphopenia (a lymphocyte count <1,000) and elevated levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). In some cases, thrombocytopenia and elevated levels of aspartate transaminase/alanine aminotransferase (AST/ALT), prothrombin time, creatinine, D-dimer, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH) are evident.^[18]

Although the chest X-ray can be normal in the early stages, it represents bilateral infiltrates. The computed tomography (CT) scans show ground-glass opacities, infiltration, and subsegmental consolidation. The CT scans from suspected or asymptomatic patients can be abnormal.^[20]

The evidence suggests that this disease was milder among patients outside Wuhan province in China and among those living in countries other than China.^[21]

No specific treatment or prevention has yet been found for the virus. Provision of oxygen may be needed via nasal prongs, high flow nasal cannula (HFNC), face mask as well as non-invasive ventilation, and in severe cases, mechanical ventilation and even extracorporeal membrane oxygenation (ECMO). Based on previous SARS experience, the ribavirin and lopinavir/ritonavir can be administered.^[18] In the case of coinfection, antibiotic or antifungal treatments are recommended. There is no proof of benefit from corticosteroid treatment.^[17] Other possible treatments are interferons (IFNs), intravenous immunoglobulin, and chloroquine.^[22,23] Hydroxychloroquine (an analogue of chloroquine) has indicated *in vitro* efficacy against COVID-19.^[24] Gautret *et al.* found that azithromycin plus hydroxychloroquine is more efficient to eliminate the COVID-19,^[25] but not effective to prevent the disease occurrence.^[26]

According to the European Medicines Agency, as fever is a common and good prognostic symptom, the administration of non-steroidal anti-inflammatory drugs (NSAIDs) is safe for some patients with COVID-19 to control fever.^[27] Lopinavir which is used to treat the HIV and contraindicated in patients with severe hepatic insufficiency has been a useful treatment for SARS and MERS and now for COVID-19 based on some evidences.^[28-30] IFN- α which has antiviral effects inhibits viral spread and replication.^[30] In patients infected by MERS, the combination of INF- α and ribavirin has reduced viral replication and improved clinical responses.^[31] Ribavirin has broad-spectrum antiviral effects on viruses with RNA and DNA. Its intravenous

infusion at a dose of 10 mg/kg every time (2–3 times daily) is recommended for children with COVID-19.^[32]

Remdesivir as an antiviral medication is used for patients with COVID-19 and demonstrates favorable results to shorten the duration of the recovery in hospitalized patients.^[33]

It has been proposed that the Bacillus Calmette-Guérin (BCG) vaccine be effective for preventing COVID-19, whereas a recent study has illustrated that the BCG vaccination does not protect against COVID-19.^[34]

To date, no preventative vaccine has been found for COVID-19; therefore, the best way is to avoid exposure to this virus.^[35] Prevention strategies include: wearing surgical face masks or N-95 respirators, washing hands regularly with soap or 75% alcohol solutions, keeping the room ventilated, avoiding unnecessary communications, staying away from infected person as much as possible, avoiding raw foods, reducing restaurant food deliveries, covering coughs and sneezes with a tissue and then throwing it away in a healthy way, keeping the unwashed hands away from eye, nose and mouth as well as keeping away from animals.^[35,36] Mobile phone usage restriction, especially in health care situations and its proper disinfection are recommended.^[37]

Clinical and Research Effects

COVID-19 and Children

At first, it was supposed that children were immune to COVID-19, but a study in China on 44,672 confirmed cases illustrated that 2% of patients were children aged 0–19 years old.^[38] An Italian study represented that only 1.2% of 22,512 affected cases were children, whereas this infected rate was 5% for children in an American study.^[39]

Children compared to adults have milder symptoms including cough, fever, sore throat, myalgia, sneezing, and fatigue.^[18] A study in China suggested that only 34% of children with confirmed COVID-19 had clinical symptoms.^[40] In children, the fever is less than 38°C,^[41,42] and other symptoms include diarrhea, rhinorrhea, fatigue, tachypnea, vomiting, and tachycardia.^[42] Dong *et al.* reported that out of 2,241 children with confirmed COVID-19 which was more common in children younger than 1 year old, 52% of cases were severe and 0.06% were critical.^[40] In a study from the USA, the intensive care admission rate was 2.5% for COVID-19 children.^[43]

In the other study, 34 (20 females and 14 males) COVID-19 children with the mean age of 8 years were admitted to a hospital in Shenzhen, China. Among them, 26 (76.4%) cases were residents of Hubei province or had a travel history to there, and their most common symptom was fever.^[44]

Zachariah *et al.* reviewed medical records of 50 children with COVID-19 symptoms and expressed that the fever

and respiratory symptoms were the most frequent ones. Gastrointestinal symptoms were found in 6% of cases. Obesity was the most common comorbidity. Infants and immune-compromised patients were not at increased risk of severe disease. Patients with severe form of the disease had significantly higher CRP and procalcitonin (PCT) levels.^[45]

In COVID-19 children, the radiological findings typically indicate ground-glass opacities and nodules mostly in the lower lobe of lungs while the disease is not severe. In about 50–80% of the affected children, the CT scans demonstrate the typical findings.^[46-48]

Xia *et al.* reported consolidation with a surrounding halo in half of the infected children. It was correlated to a higher level of calcitonin (bacterial co-infection) which was only observed in pediatric cases.^[49]

Moreover, there is a difference between pediatric and adult patients in terms of laboratory findings.

The lymphopenia (reduced numbers of CD4 and CD8) which is prevalent and can predict disease severity in adult cases has not often been seen in pediatric patients as well as changes in neutrophil-to-lymphocyte and T-cell subtypes are more common in adults.^[16,47] On the other hand, adult patients with COPD, diabetes, hypertension, and smoking history are at higher risk due to the upregulation of angiotensin-converting enzyme 2 (ACE2) receptor, which is not the case for children.^[50] However, it should be taken care of children with underlying lung diseases such as cystic fibrosis.^[51]

Henry *et al.* stated that among 66 confirmed pediatric cases, near 70% of them had normal leukocyte counts as well as neutrophils and neutrophilia were rare. Furthermore, the elevated levels of CRP and PCT were found in 13% and 10% of the pediatric patients, respectively.^[52] According to a study by Lu *et al.*, ground-glass opacity was present in one-third of the affected children, and near 15% of them had no symptoms or radiological features of COVID-19. Nevertheless, another study demonstrated that 60% of infected children had patchy ground-glass opacities on their CT scans.^[33,42]

Treatments in children are supportive, antibiotic for bacterial superinfection, and anti-viral. Shen *et al.*'s study on hospitalized children with COVID-19 displayed that the lopinavir/ritonavir and azithromycin were used for treatment.^[53]

Shi *et al.* reported the isolation of 2 specific human neutralizing monoclonal antibodies against SARS-CoV-2 from convalescent adult patients.^[54]

Because infected children, like asymptomatic and mild symptomatic individuals, are a source of disease transmission, preventive behaviors are also recommended for them.^[55]

COVID-19 and neonates

Since COVID-19 is in a pandemic stage; hence, the pregnant women are at risk of infection, but whether COVID-19 increases the risk of stillbirth, miscarriage, preterm delivery, and fetal problems is not clear.^[56]

To date, three cases of infected neonates were reported in China.^[47] Although the symptoms are different in neonates, fever, runny nose, cough, respiratory distress and vomiting are reported for them.^[57] In Iran, three neonates were born from infected mothers, two of them died after delivery while their tests were negative.^[56] Chen *et al.* reported no COVID-19 nucleic acid in the placenta or throat of the neonates born from infected women.^[58] In the other study, Chen *et al.* found that pregnant infected women had symptoms similar to non-pregnant cases, and all had live births with no death or pregnancy complications.^[7] Zhang *et al.* compared 16 COVID-19 infected pregnant women with 45 non-infected ones. They achieved similar neonatal outcomes between two groups.^[59]

Yu *et al.* retrospectively reviewed medical records of 7 pregnant women with COVID-19 at a gestational age of 39 weeks. They all had cesarean section within 3 days, and the most common symptoms were fever, shortness of breath, cough, and diarrhea. The outcome was good for all mothers and neonates.^[60]

Conclusion

The COVID-19 can occur in children and neonates. The vertical transmission from infected mothers to neonates is rare, and the outcomes are better in children than adults.

Up to now, there has been no preventative vaccine or specific drug for COVID-19, and the preventive strategies are the main goal.

Ethical approval

This study was approved by the Health Research Institute of Babol University of Medical Sciences (IR.MUBABOL.REC.1399.129).

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Conflict of interest

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