# CHAPTER 18

# THE CLINICAL FEATURES IN PEDIATRIC PATIENTS WITH COVID-19

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## INTRODUCTION

Chinese scientists identified the pathogen as Coronavirus after the first serious pneumonia cases were discovered in Wuhan, China, in December 2019. In January 2020, it was understood that the world encountered an acute respiratory distress virus that had not been encountered before. At first, it was named novel coronavirus 2019. However, it was later dubbed SARS-CoV-2 after it was discovered that the virus's genetic structure was close to that of the SARS coronavirus. On January 30, 2020, the World Health Organization declared a global emergency. On March 11, 2020, the epidemic was declared a pandemic . It has been announced that it is a new type of coronavirus that has typical features of the coronavirus family such as SARS-CoV and MERS-CoV, causes severe respiratory failure, and is classified in the Beta coronavirus genus. People in the seafood wholesale industry were the first to be infected with Covid-19. This virus, like SARS-CoV and MERS-CoV, is a zoonotic infection, meaning it can be transmitted from animals to humans. Because of its ability to spread from person to person, the disease spread quickly. SARS-CoV-2 is spread through droplets or inanimate surfaces contaminated by these droplets.

Although other transmission routes such as fecal-oral spread have not been fully clarified, pediatric cases with persistent PCR positivity in fecal samples have been reported despite regression of symptoms, and it has been suggested that it may be beneficial to expect PCR negativity in nasopharyngeal swabs as well as rectal swabs and stool samples in orderto determine the duration of isolation in children. Although infected symptomatic people are the primary source of transmission, the contribution of asymptomatic carrier people to the transmission has resulted in a rapid spread. The contagiousness of people infected with SARS-CoV-2 in the presymptomatic period may pose difficulties for disease control. In a study conducted in Singapore with 243 patients over a period of two months, it was found that there was contagiousness before 1–3 days from the onset of symptoms in the epidemiological clusters, and the importance of social distance in preventing SARS-CoV-2 transmission was emphasized.

## CLINICAL FINDINGS

COVID-19 disease is effective in all age groups and the incubation period is between 1 and 14 days. Symptoms occur within 5-6 days on average. Most cases occur after contact with family members or sick people. The symptoms of COVID-19 in children and adults are similar but may differ in frequency. Most children are asymptomatic and severe illness is uncommon. Also, most children experience mild to moderate illness. The disease heals after seven to fifteen days. The number of severe cases is low. Severe clinics are more popular in immunocompromised children and the young age groups. In a review of 61 studies involving all age groups, at least one-third of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections were asymptomatic . In a study conducted on children with COVID-19 under the age of 20, it was reported that both genders were affected equall. In another study involving 7480 children with PCR-positive COVID-19, the weighted mean age was 7.6. Fever and cough were among the most common complaints in children admitted to the hospital, accompanied by gastrointestinal symptoms such as sore throat, fatigue, muscle pain, trouble breathing, headache, runny nose, and, in some cases, vomiting and diarrhea. Symptoms in infants include feeding difficulties and undetectable fever. The most common gastrointestinal symptoms in children are diarrhea, vomiting and abdominal pain. Cutaneous manifestations are rare and include urticarial, maculopapular, vesicular eruptions, and transient livingo reticularis.

In a study of 17877 patients aged 0-19 years conducted in the United States of America, the symptoms were listed according to age groups as follows: frequency of symptoms in children aged 0 to 9 years; Fever, cough, or shortness of breath 63% (Fever 46%, Cough 37%, Shortness of breath 7%), Myalgia 10%, Rhinorrhea 7%, Sore throat 13%, Headache 15%, Nausea/vomiting 10%, Abdominal pain 7%, Diarrhea 14%, Loss of smell or taste 1%. Among children aged between 10 to 19 years, the frequency of symptoms was as follows: Fever, cough, or shortness of breath 60%, Fever 35%, Cough 41%, Shortness of breath 16%, Myalgia 30%, Rhinorrhea 8% Sore throat 29%, Headache 42%, Among children aged between 10 to 19 years, the frequency of symptoms was as follows: Fever, cough, or shortness of breath 60%, Fever 35%, Cough 41%, Shortness of breath 16%, Myalgia 30%, Rhinorrhea 8%, Sore throat 29%, Headache 42%, Nausea/vomiting 10%, Abdominal pain 8%, Diarrhea 14%, Loss of smell or taste 10%.

The hospitalization rate of pediatric cases is between 6–20%, and the rate of admission to intensive care is 0.58–2%. The effect of comorbid diseases on the course of infection in children has been stated in some publications. In a study involving eight patients between the ages of 2 months and 15 years, it was stated that only one of the patients had an underlying acute lymphocytic leukemia. In a study involving 25 pediatric patients diagnosed with COVID-19 and hospitalized, 2 patients had a severe course. These two patients were between 0-1 years old. In addition, these patients had congenital heart disease and metabolic diseases. In another study, it was reported that among 171 pediatric patients, three of them required follow-up in the intensive care unit; and hydronephrosis, acute leukemia, and intussusception were comorbid in each of them. COVID-19 infections were examined in the clinics of 7480 children under the age of 18 with PCR positive, and 1475 of them were classified for the severity of symptoms. Of these classified cases, 15 percent were asymptomatic, 42 percent mild, 39 percent moderate (pneumonia without hypoxemia), 2 percent severe (dyspnea, central cyanosis, hypoxemia), and 0.7 percent critical (acute respiratory disorder syndrome, respiratory failure, shock).

Different hypotheses describe the mild path of COVID-19 infection in children. One of them is that SARS-CoV-2 uses ACE-2 receptors, and these receptors decrease with age, as detected before in animal studies. The other is that children's airways are healthier, children do not smoke, are less exposed to toxic gases, underlying diseases are less common, and have a more active innate immune system. Another theory is that the younger age group has

frequent viral infections, and the immune system responds more effectively to SARS-CoV-2 with these stimuli.

## LABORATORY FINDINGS

Laboratoryfindings are variable in COVID 19 cases. In a report evaluating blood parameters in children, 69.6% of the patients had normal leukocyte counts, while an increase in the leukocyte count was observed in 15.2%, lymphopenia was detected in only two patients. In another study with PCR-positive COVID-19 cases younger than 18 years of age, it was found that most of the children had normal complete blood counts, but 17 percent had lymphopenia and 13 percent had neutropenia. High C-reactive protein (CRP) and procalcitonin were found in about one-third. High levels of serum aminotransferases and lactate dehydrogenase (LDH) levels were one of the common abnormalities. Kidney dysfunction can occur in children with severe illness. In a study involving 52 children, serum creatinine was higher than the upper reference range (ULRI) in 24 of them (46%). Of these patients, 15 met the criteria for acute kidney injury (AKI). Most of these 15 cases were seen in children with Multisystem inflammatory syndrome in children (MIS-C) admitted to the intensive care unit. However, these patients did not need transplantation and returned to normal levels with treatment.

## DIAGNOSIS

Taking the rightsample at the right time with the appropriate technique increases our success for the diagnosis of COVID-19. Because it is difficult to distinguish SARS-CoV-2 from viruses acquired from other populations with a single symptom or symptoms, and co-infection is common. Much work is needed to increase the reliability of polymerase chain reaction (PCR) in diagnosis. The detection percentage of the virus was found to be higher in nasopharyngeal samples than in oropharyngeal samples. It was stated by the Centers for Disease Control and Prevention that nasopharyngeal samples should be preferred primarily. If an oropharyngeal sample is to be taken, it would be appropriate to take it in combination with a nasopharyngeal swab. Samples, if possible, from the lower respiratory tract should be repeatedly taken from patients whose first RT-PCR sample taken from the upper respiratory tract is found to be negative, but whose clinical suspicion persists. It is

quite difficult to produce SARS-CoV-2 in vitro and is often used for vaccine and drug studies research. Detection of antibodies caused by COVID 19 in the blood is very important in detecting past infections and determining their epidemiology. It has been stated that serology should not be used as the only diagnostic test. In another study, high sensitivity and specificity were determined by examining nucleocapsid protein from nasopharyngeal samples of RT-PCR positive patients by fluorescent immune chromatographic method.

### Radiological Diagnosis

Imaging findings may differ. It may occur before the patient's complaints. In radiological diagnosis, plain radiographs in children may not show abnormal findings in the early period or mild involvement. In a review of 674 PCR-positive, COVID-19 infected children who were imaged, approximately 50 percent had abnormalities. In COVID-19, predominantly bilateral, rarely unilateral, subpleural ground-glass opacities and consolidation areas can be detected in tomography. In a study conducted to show the differences of imaging findings in children from the adult age group, involvement was found bilateral in 10 patients and unilateral in six patients. Subpleural involvement was detected in all patients with tomography findings, and consolidation surrounded by 50% air crescent sign, 60% ground glass image, 20% and 15% small nodules were detected, as well . In the same study, co-infection was found in 40% of the patients. The presence of co-infection in children with COVID 19 may change imaging and the use of imaging alone may be insufficient for diagnosis. In a study involving 107 pediatric patients, the radiological findings were listed as ground glass in 33%, local patchy involvement in 19%, bilateral patchy involvement in 12%, and interstitial changes in 1%. Typical signs of other respiratory viral infections (hyperinflation, peribronchial signs) have not been reported.

## RISK FACTORS FOR SEVERE ILLNESS IN CHILDREN

Children with concomitant medical problems are at higher risk of severe illness than healthy children. These risk factors are obesity, severe genetic disorders, severe neurological disorders, hereditary metabolic disorders, sickle cell anemia, congenital heart disease, diabetes, chronic kidney failure, asthma, and other chronic lung diseases, down syndrome, malignancy, or immunosuppression due to drugs that weaken immunity. In one study, 42 percent of

children hospitalized with COVID-19 had less than 1 underlying condition, the most common of which were obesity, chronic lung disease, and premature. In another study, 22 percent of patients had comorbidity in the evaluation of 587 PCR-positive children. The most common comorbidities are asthma (45%), congenital heart disease (23%), immunosuppressive (12%), hematological or oncological diseases (6%), and chronic lung disease.

## MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

In international studies, different concepts and case definitions are used for multisystem inflammatory syndrome (MIS-C) in children associated with COVID-19. The case definition for MIS-C is still unclear. Other clearly defined inflammatory syndromes such as Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome in children have clinical features that are both similar to and different from MIS-C cases. MIS-C can cause shock and multi-organ failure.

The European and US Centers for Disease Prevention and Control (CDC) provides a case definition, clinical findings, severe disease and multi-organ involvement (two or more), exclusion of differential diagnoses, and within four weeks before the onset of symptoms or the newly proven SARS-CoV- 2 infection or COVID-19 exposure.

The incidence of MIS-C is not yet clear. COVID-19 is assumed to be a rare complication in children. In one study, the incidence of SARS-CoV-2 infection was 322 per 100,000, and the incidence of MIS-C was detected as 2 in 100,00. It is assumed to be caused by an uncontrolled immune response to the virus in Kawasaki disease (KD), macrophage activation syndrome (MAS), MIS-C, and cytokine release syndrome. It appears to have a different immune phenotype than KD and MAS. Most of the affected children have positive serology while the PCR test for SARS-CoV-2 is negative; this result suggests that MIS-C is associated with an immune abnormality that occurs following an acute infection. Refractory fevers (median duration of four to six days) 100%, gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) 60-100%, rash 45-76%, conjunctivitis 30-81%, mucous membrane involvement 27-76%, neurocognitive symptoms (headache, drowsiness, confusion) 29-58%, respiratory symptoms 21-65%, sore throat 10-16%, myalgia 8-17%, edema in hands and feet 9-16%, lymphadenopathy 6-16% were present. Most patients go to the hospital due to fever for 3-5 days. In a study, 10% of 186

patients had a three-day fever, 13% had a four-day fever, and 78% had a five-day fever.

Gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhea are more common and distinct and may mimic appendicitis in some children. Terminal ileitis has been found on abdominal imaging and/or colonoscopy in some children.

Respiratory symptoms (tachypnea, dyspnea) are often due to shock. Some children may need free oxygen or positive pressure ventilation, but severe pulmonary involvement (acute respiratory distress syndrome) is uncommon. Neurocognitive symptoms are common and may include headache, drowsiness, confusion, and irritability. A minority of cases go to the hospital with more severe neurological symptoms such as encephalopathy, seizures, coma, meningoencephalitis, muscle weakness .

At admission, 59 (66%) of 89 of the patients with suspected or proven MIS-C had lymphopenia; high proBNP levels in 74 out of 82 (90%), high troponin levels in 63 out of 89 (71%), high C-reactive protein levels in 98 out of 98 and high d-dimer levels in 86 out of 94 (91%) was observed. Laboratory findings of inflammation appear to be related to the severity of the disease. Children with shock had higher CRP, neutrophil levels, lymphocyte counts, and serum albumin values, as well as higher cardiac markers than non-shock pediatric patients, according to a study.

Chest radiographs of many patients were normal. Abnormal findings included pleural effusions, patchy consolidations, focal consolidation, and atelectasis. Chest CT (when available) usually has findings similar to those on a chest radiograph. Few patients had nodular ground glass opacification. Abdominal ultrasound or CT images included free fluid, ascites, ileitis, mesenteric lymphadenopathy/adenitis, and pericholecystic edema.

In one study, 10 (10%) of 79 MIS-C patients hospitalized in the intensive care unit required mechanical ventilation. The median time from symptom onset to hospitalization was four days. Intravenous immune globulin (IVIG) treatment was given to 69 patients, systemic glucocorticoid therapy to 63 patients) and vasopressor therapy to 61 patients; systemic glucocorticoid and IVIG treatment was given to 48 patients.

## TREATMENT

After the SARS-CoV-2 epidemic was declared, treatment became very important. Antiviral treatments and vaccines have become mandatory. Also, the

development time for new agents was very short. For this reason, it has been tried to find an effective agent against COVID 19 among the drugs used for different indications. Among antiviral agents, lopinavir/ritonavir, interferon, arbidol and oseltamivir have been tested in different patients. However, evidence-based information in the pediatric age group is insufficient and these treatments should not be used routinely, except in critically ill patients, since most of the infection is asymptomatic or mild.

## Antiviral Treatments

### Hydroxychloroquine, chloroquine

It has been stated that chloroquine and hydroxychloroquine, which are used in the treatment of malaria and autoinflammatory diseases, inhibit viral and endosome fusion in vitro studies by affecting the endosomal pH and glycosylation of host receptors, and their anti-inflammatory effect may have a positive effect on the clinical course. The efficacy of hydroxychloroquine in treating COVID-19 is uncertain. Hydroxychloroquine is not licensed for this indication, and its emergency use authorization for the treatment of COVID-19 has been revoked in the United States. It is ideally used only in the context of clinical research with hospitalized patients. Due to the insufficient data on the use of hydroxychloroquine in children and the risk of life-threatening side effects such as QT prolongation, our national guideline states that it should be used in severe cases and children with accompanying risk factors, accompanied by ECG monitoring.

### Favipiravir

Favipiravir is an RNA polymerase inhibition agent known to be effective on ebola and influenza. It is known from studies on ebola that this drug, whose side effects are known to be mild and self-limiting, is more effective at high doses. In the comparison between 120 patients using arbidoland 116 patients using favipiravir, there was no difference in the clinical recovery time of favipiravir compared to arbidol. It has been reported that the most common side effect is hyperuricemia. Data on the use of favipiravir in children with COVID-19 are insufficient. In cases where treatment is required, the Favipiravir tablet can be crushed and given by mixing with foods, making it easier for children to use.

### Remdesivir

It is a broad-spectrum antiviral agent developed against RNA viruses such as flavivirus and coronavirus. remdesivir is a prodrug of a nucleotide analog that

inhibits RNA-dependent RNA polymerase and has activity against coronaviruses. Reported side effects of remdesivir include nausea, vomiting, and transaminase elevations. Studies on its use in the treatment of COVID-19 are ongoing. In a multi-center study conducted in China, 158 of the patients diagnosed with microbiologically and radiologically proved COVID-19 were given remdesivir and 78 placebo patients were included. Faster clinical improvement was observed in the group receiving remdesivir, but no statistically significant difference was found. In the United States, remdesivir has been approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19 requiring hospitalization in adults and children aged 12 years weighing 40 kg; with an emergency use permit, it is also available to other children hospitalized with suspected or laboratory-approved COVID-19 weighing 3,5 kg . The normal duration of treatment for children with severe illness is up to 5 days; the period can be extended up to 10 days for critically ill children who do not recover after five days. Remdesivir should not be co-administered with hydroxychloroquine or chloroquine because co-administration may reduce the antiviral activity of remdesivir.

### Lopinavir/ritonavir

The first publications about the use of lopinavir-ritonavir in the treatment of SARS-CoV2, a protease inhibitor used in HIV treatment, are not reliable since they were made on a small number of patients. In a study of 199 adult patients, lopinavir-ritonavir and standard supportive therapy were compared and lopinavir-ritonavir was not found to be effective. Giventhe lack of efficacy and adverse pharmacodynamics, the routine use of lopinavir-ritonavir is not recommended.

## Other Treatments

### Corticosteroids

The use of glucocorticoids for immune-mediated complications of COVID-19 is made on a case-by-case basis based on the severity of the disease. There are reservations about the side effects of corticosteroids, the risk of secondary infection and decreased viral clearance, and the use of steroids. It is not routinely recommended for COVID-19 treatment, except for some critical patients. Although glucocorticoids have decreased mortality in adult patients, studies are ongoing in children. The benefits and risks are uncertain. In a series of eighth cases published on COVID-19 pediatric patients, it was reported that

supportive treatments and corticosteroids were used in five patients, three of these patients recovered completely, and two patients continued their treatment. In the "Infectious Diseases Society of America" COVID-19 treatment guideline, the dosage schedule for steroid use is given.

### Antisitokine and immunomodulatorytherapies

Other adjunctive treatments for COVID-19 immune-mediated complications are determined on a case-by-case basis, in conjunction with the rheumatology and infectious diseases departments, depending on the severity of the disease and when indicated. In the treatment of children with COVID-19, immune modulators (IL-6 inhibitors (Tocilizumab), interferon-beta 1b, plasma obtained from recovering patients can be given. In severe clinical COVID-19 patients, an increase in proinflammatory cytokines and cytokine storms have been reported to worsen the clinical picture. IL-6 plays a key role in this pathway. Tocilizumab, effecting through IL-6, is an agent used in the treatment of rheumatological diseases. In a study conducted on 20 patients, clinical improvement was reported in 91% of the patients with a single dose of tocilizumab treatment . There is a need for large-scale, controlled studies on the use of these agents.

### Immunoglobulin, convalescent plasma

It has been stated that plasma taken from donors who recovered from COVID-19 infection was transfused to critically ill patients, patients had a clinical benefit in a case series of five patients, and it may be beneficial to conduct further research on this subject. It is emphasized that there should be an increase in the number of patients who have had COVID-19 infection and recovered in the donor pool for immunoglobulin treatment. In another study, three critically ill patients who received high-dose immunoglobulin showed clinical improvement.

### Monoclonal antibody therapy

Bamlanivimab, or casirivimab/imdevimab is recommended for monoclonal antibody therapy for COVID-19. Bamlanivimab, casirivimab/imdevimab are highly neutralizing monoclonal antibodies produced by recombinant DNA technology. Risk factors should be considered in children being treated. The benefits and risks in children are uncertain. Children treated with bamlanivimab or casirivimab/imdevimab should continue to isolate themselves and follow infection control measures. The US Food and Drug Administration has

granted emergency use for 12-year-old children diagnosed with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Bamlanivimab and casirivima/imdevimab can be used in patients older than 12 years and weighing 40 kg with certain risk factors for mild, moderate, severe disease and hospitalization.Bamlanivimab and casirivimab/imdevimab should be administered as soon as possible after a positive SARS-CoV-2 test and within 10 days of symptom onset. In a study of 452 patients, bamlanivimab reduced the risk of hospitalization compared to placebo. Nausea and infusion-related adverse effects (itching, flushing, rash) have been reported, but these are uncommon and mild. An interim analysis of the first 275 patients in a multicenter, randomized, placebo-controlled study, casirivimab-imdevimab reduced the viral load, and the rate of medically attended visits (e.g., emergency room, telemedicine, and face-to-face visits; hospitalization) over 29 days.

## HOW SHOULD CHILDREN BE MANAGED AT HOME?

Children with documented or suspected Covid-19 and mild symptoms (e.g fever, cough, pharyngitis, other respiratory symptoms) should usually be treated at home unless they have a chronic condition that increases the risk of serious illness. Management focuses on preventing infection (isolation), monitoring clinical deterioration, and supportive care.

## CONCLUSION

As a result, COVID-19 seems to have a mild course in the pediatrics age group, but it is important to distinguish these children from COVID-19 infected adults, as severe clinical follow-up can be observed in children with chronic diseases, malignancy, or immunosuppression. Careful follow-up of this age group gains importance as a significant portion of severe cases are reported in infants. Since the patient group, which has an asymptomatic and mild clinical course, including children, has a very important role in the spread of the disease, it is important to pay attention to social distance in the society, to take preventive measures and to eliminate new sources of infection by screening contact cases.

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