SARS-CoV-2 infection in children
Çocuklarda SARS-CoV-2 enfeksiyonu

Abstract
SARS-CoV-2, a RNA virus that emerged in December 2019 in the city of Wuhan in China and took hold of the whole world, affects children as well as all age groups. In our country, we started to observe the first cases by March 2020. SARS-CoV-2, which is transmitted by droplets and by way of contact with surfaces contaminated by these droplets, is generally transmitted to children from adults through close contact. There is no known information about other transmission routes such as fecal-oral transmission. Similar to adults, the primary symptoms at presentation include fever, cough, sore throat, malaise, nasal discharge, and rarely, vomiting and diarrhea in children. Although the majority of pediatric patients are asymptomatic or have a mild clinical course, severe cases have been reported in children with underlying chronic diseases. There is currently no specific antiviral treatment against the SARS-CoV-2 virus. Supportive treatment is recommended in children with a mild course, and some treatments are recommended in children with comorbidities or in children who are observed to have a more severe course. Asymptomatic pediatric patients or pediatric patients who have a mild course constitute an important group in terms of transmission of the infection to the advanced age group who carry high risk. Prevention of infection is very important in terms of reducing new cases and alleviating the load on the healthcare system. In order to prevent transmission of SARS-CoV-2, hygienic rules should be pursued in the community, social distancing should be observed, and the family members and contacts of patients who have been diagnosed should be screened and isolated.

Keywords: Children, COVID-19, SARS-CoV-2

Öz
İki bin on dokuz Aralık ayı itibariyle Çin’in Wuhan bölgesinde başlayan, tüm dünyaya etkisi altına alınmış olan bir RNA virüsü olan SARS-CoV-2 tüm yaş gruplarına olduğu gibi çocuklara da etkilemektedir. İki bin yirmi Mart ayı itibariyle ülkemizde de ilk olgular görülmeye başlamıştır. Çocuk hastaların büyük çoğunluğu asemptomatik ya da hafif seyirle ilerlemişlerdir. SARS-CoV-2’si karşı özgün bir antiviral tedavi henüz yoktur. Hafif kliniği olan çocuklarda destek tedavi önerildir, riski升高 olan çocuklarda ise daha da hafif ve bazı tedaviler vardır. Asemptomatik ya da hafif seyirle enfeksiyonu geçiren çocuk hastalar, riskli ileri yaş grubuna yayılmasından önemlidir. SARS-CoV-2’nin yayılmasını engellemek için toplum içinde hijyen kuralları uygulanması, sosyal mesafe dikkat edilmesi ve izole edilmesi gerekir.

Anahtar sözcükler: COVID-19, çocuklar; SARS-CoV-2

Introduction
On January 7th, 2020, Chinese authorities reported that a cluster of severe cases of pneumonia had been observed by December 2019 in the city of Wuhan, in China, and these patients had had contact with an animal market (1). After the causative agent was grown in bronchoalveolar lavage in January 2020, an acute respiratory distress agent was determined through whole genome sequencing that had not been encountered previously, and different laboratories started to study diagnostic tests (2). The virus which was previously named novel coronavirus 2019, was named SARS-CoV-2, because it was recognized that its genetic structure was similar to SARS coronavirus (3). On January 30th, 2020, the World Health Organization (WHO) declared SARS-CoV-2 a global health emergency,
and the epidemic was qualified as a pandemic on January 11th, 2020 (3). In Turkey, we started to detect cases of COVID-19 infection by March, 2020. The WHO reported nearly 3.5 million cases and 239,604 deaths by the beginning of May, 2020 (4).

**Microbiologic properties, infection, and pathogenesis**

The coronavirus family is divided into 4 types including alpha, beta, gamma, and delta. 2019 nCoV is included in the beta corona family together with bat-SARS-like (SL)-CoVZC45, bat-SL-CoVZXC21, SARS-CoV, and MERS-CoV (5). Following the primary assessments, it was thought that SARS-CoV2 originated from an animal. It was found that SARS-CoV2 had more than 80% similarity with SARS-CoV and more than 50% similarity with MERS (6). Coronavirus, which are single-chain enveloped viruses with positive polarity, possess crown-like projections on the surface. SARS-CoV-2 is transmitted by way of droplets or surface contamination by these droplets. Although other transmission routes such as the fecal-rectal route are not clear, pediatric cases with fecal samples showing persisting polymerase chain reaction (PCR) positivity despite regression of symptoms, have been reported, and it has been proposed that waiting for PCR to become negative in rectal swabs and feces samples, as well as nasopharyngeal swabs, would be beneficial in determining the isolation period in children (7). Although the primary source of infection is through symptomatic individuals, a rapid spread has been observed because asymptomatic carriers also contribute to infection. The infectivity of individuals infected with SARS-CoV-2 in the presymptomatic period may create difficulties in terms of disease control. In a study conducted with 243 patients in Singapore in a 2-month period, infectivity was found 1–3 days before symptom onset in the epidemiologic groups specified, and the importance of social distancing in prevention of SARS-CoV-2 infections was emphasized (8). SARS-CoV-2 was shown to enter cells with its spike-like projections by way of ACE-2 receptors found on human cells. ACE-2 receptors are expressed on the cells in the lungs, gastrointestinal system, kidneys, and heart (9, 10). After the virus is presented to T lymphocytes by antigen-presenting cells, the inflammatory pathway continues with the release of proinflammatory cytokines. In some studies, it was shown that cytokine dysregulation played a role in the pathogenesis of the disease. Huang et al. (11) found that the levels of interleukin (IL)-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage infectivity potentiator (Mip)-A, and tumour necrosis factor (TNF)-alpha were increased in relation with the severity of the disease in patients followed up in intensive care units (ICUs). In a series including eight pediatric patients, it was reported that IL-6 and IL-10 levels were markedly increased in patients who had more severe conditions (12). Qin et al. (13) showed that lymphocytes including mainly T lymphocytes were important in the pathogenesis of the disease, lymphopenia was observed in patients with severe disease, and increased neutrophil-to-lymphocyte ratio (NLR) could be helpful in early diagnosis and in the follow-up of disease severity.

**Clinical picture**

All age groups are susceptible to COVID-19. Generally, the main source of infection for children is positive subjects in the family. The incubation period has been estimated to be approximately 3–7 days after exposure (the longest incubation period is 14 days) (11). Infected children may be asymptomatic. Studies showed that fever and cough were the most common symptoms at presentation and these were followed up by sore throat, malaise, muscle pain, dyspnea, headache, nasal discharge, and gastrointestinal symptoms such as vomiting and diarrhea in some patients (14). Although severe clinical picture is observed with a lower rate in children compared with adults, the possibility of a severe clinical picture is higher in children with underlying comorbidity and immunosuppression, and in the younger pediatric age group. Critical disease picture may be observed as respiratory failure, acute respiratory distress syndrome (ARDS), shock, multorgan failure, and encephalopathy. In a study by Dong et al. (15), in which more than 2000 children with suspicious or probable diagnoses were included, COVID-19 was clinically divided into 5 groups as asymptomatic, mild, moderate, severe, and critical, and 94.1% were found to be asymptomatic or have mild or moderate condition; severe cases were most commonly found in the 0–1 year age group and 0.6% of the total cases were critical. Apart from a picture of severe pneumonia, infants with a positive history of contact who presented with a clinical picture of upper respiratory infection and whose symptoms regressed with supportive treatment in a short time were reported, and the importance of interrogating risk factors in infants presenting with fever during the pandemic was emphasized (16).

In adults, it was observed that comorbidities such as cardiovascular disease, diabetes, chronic lung disease, hypertension and cancer increased the mortality rate during the pandemic. Although there is as yet no clear data on the effect of comorbidities on the course of infection in children, underlying diseases were mentioned in different publications. In a study in which the demographic properties of eight critical patients with ages ranging between 2 months and 15 years were specified, underlying acute leukemia was reported in only one of the patients.
Among 171 pediatric patients reported from Wuhan Children's Hospital, three patients needed follow-up in the ICU and all had comorbidities (hydronephrosis, acute leukemia, intussusception) (18). According to the Centers for Disease Control and Prevention (CDC) data, pediatric patients constituted 1.7% of the total number of cases in the United States of America. In 90% of these patients, there was a history of household contact or contact with someone in the community, the remaining 10% had a history of travel. In pediatric patients, the rate of hospitalization has been estimated as 6–20% and the rate of hospitalization in the ICU has been estimated as 0.58–2%. When underlying diseases in childhood were examined, on the other hand, chronic lung disease was found with a rate of 11.6%, cardiovascular disease was found with a rate of 7.2%, and immunosuppression was found with a rate of 2.9 in 345 patients who were COVID-19-positive. These were followed up by chronic liver and renal disease, endocrine diseases, pregnancy and obesity (19).

Another point that should be noted in the childhood age group is the frequency of coinfection. In a study in which 20 pediatric patients were included, coinfection was found in nine children infected with COVID-19 (influenza, mycoplasma, cytomegalovirus, respiratory syncytial virus) and this influenced the patients' clinical pictures (20). The mild course of COVID-19 infection in children has been explained by different theories. One of these theories relates this mild course with the finding that SARS-CoV-2 uses ACE-2 receptors, which were found to be decreased with age in animal studies (21). Another explanatory cause is that children have a healthier respiratory tract, are less affected by conditions such as smoking, toxic gases, and underlying diseases, and have a more active natural immune system (22). More frequent viral infections in the young age group and a more effective response of the immune system to SARS-CoV-2 by way of these stimuli, is also among the theories proposed (23). Beginning from the midst of April, 2020, eight previously healthy pediatric patients showing features similar to atypical Kawasaki and toxic shock syndrome-like pictures, have been reported in the United Kingdom. The mutual characteristics of these patients included fever, rash, conjunctivitis, extremity edema and gastrointestinal symptoms at the time of presentation. There was a history of contact with COVID-19 positive individuals in 4 of the patients who received mechanical ventilation and inotropic support (24). Up to the end of April, 2020, about 100 Kawasaki-like cases had been reported predominantly from European countries. Based on the information about Kawasaki disease, this clinical picture which might be observed 2–4 weeks after SARS-CoV-2 infection characterized by incomplete Kawasaki, toxic shock syndrome-like picture and isolated myocarditis in some patients, was interpreted as a post-infectious hyperinflammatory condition, and it was emphasized that supportive treatment should be administered, in a current publication. In conclusion, pediatricians should be watchful in terms of COVID-19 in patients presenting with these atypical Kawasaki and toxic shock syndrome-like conditions (25).

Probable and definite diagnostic criteria
The definitions of probable and definite cases have been continuously updated in the light of renewed data with updated guidelines from the date when the first case was detected in our country up to the present time. In our national guideline published on April 14th, 2020, the definitions of probable and definite cases were as follows (26).

**Probable case A**
- Presence of fever or at least one of the signs and symptoms of acute respiratory tract infection (cough and respiratory distress) AND
- The clinical picture cannot be explained by another cause/disease AND
- History of having been abroad within 14 days before symptom onset for the patient or for a relative OR

**Probable case B**
- Presence of fever or at least one of the signs and symptoms of acute respiratory tract infection (cough and respiratory distress) AND
- Close contact with confirmed case of COVID-19 within 14 days before symptom onset OR

**Probable case C**
- Presence of fever or at least one of the signs and symptoms of severe acute respiratory tract infection (cough and respiratory distress) AND
- Presence of need for hospitalization [severe acute respiratory infections (SARI)]* AND
- The clinical picture cannot be explained by another cause/disease

*Severe acute respiratory infections (SARI)- Need for hospitalization because of fever, cough, dyspnea, tachypnea, hypoxemia, hypotension, diffuse radiologic findings on lung imaging and change in consciousness in a patient who has developed acute respiratory tract infection in the last 14 days OR

**Probable case D**
- Presence of cough or dyspnea with sudden onset fever and absence of nasal discharge
Definite case
Detection of SARS-CoV-2 by molecular methods in patients who are compatible with the definition of probable case.

Laboratory examinations, microbiologic diagnosis
In hospitalized adult patients who are COVID-19-positive, lymphopenia, increased lactate dehydrogenase and amino-transferase levels, and increased inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), have been commonly found among laboratory findings (25). In a meta-analysis including 3370 patients, infected critical patients were compared with patients with mild clinical course, and the total number of white cells was found to be significantly higher, and lymphocyte and platelet counts were found to be significantly lower in critically ill patients (26). Additionally, biomarkers including CRP, ESR, IL-6 and IL-10, and the enzymes that show cardiac, muscle, and liver injury, and coagulation parameters were found to be significantly high in the critically ill patients and close monitoring of total leukocyte count, lymphocyte count, platelet count, and ferritin and IL-6 levels was recommended. In a publication including 66 patients in which laboratory values in children were reviewed, the total leukocyte count was found to be normal in 69.6% of patients, the leukocyte count was found to be increased in 15.2%, and lymphopenia was found in only two patients (27). The lower rate of lymphopenia in comparison with the adult age group was associated with the low number of pediatric patients with a severe clinical picture included in the study. Increased CRP and increased procalcitonin (PCT) were found in 10.6% to 13.6% of patients.

When making a diagnosis of COVID-19, obtaining appropriate samples at the appropriate time and using an accurate technique increases the success rate. Further studies are needed to determine the diagnostic sensitivity and specificity of RT-PCR and other tests. The percentage of detecting the virus was found to be higher in nasopharyngeal samples compared with oropharyngeal samples (28). The CDC reported that nasopharyngeal samples should be preferred primarily, and if an oropharyngeal sample is to be obtained, it should be obtained in combination with a nasopharyngeal swab (29). In patients whose primary RT-PCR samples are obtained from the upper respiratory tract that are found to be negative, but for whom clinical suspicion continues, a repeated sample should be obtained (a second sample should be obtained from the lower respiratory tract, if possible). It is technically difficult to grow SARS-CoV-2 in cell culture, and this is mostly used in vaccine and therapeutic agent investigations. Serologic methods that detect antibodies in the blood are important in terms of determining past infections and understanding the epidemiology of coronaviruses rather than routine use in the diagnosis. Patients who have asymptomatic infection or mild disease may be later detected with serologic tests, but it has been reported that serology should not be used as a single test in the diagnosis (30). There are different tests that are used for rapid diagnosis with antigen/antibody detection, but these tests are problematic in terms of use in the diagnosis because of inadequate validation. In one study, it was found that many patients who were PCR positive were found to be negative with the rapid test performed in the blood using the lateral flow immunoassay method, and it was interpreted that the rapid test performed using this technique had no place in the primary diagnosis (31). In another study, on the other hand, high sensitivity and specificity were found with fluorescent immune chromatography investigating nucleocapsid protein in nasopharyngeal samples obtained from patients who were RT-PCR positive (32).

Radiologic diagnosis
It was reported that computed tomography (CT) had high sensitivity in the early phase in the diagnosis of COVID-19 in the adult age group, and it was emphasized that serial tomographies in association with history of contact and clinical findings provided early detection of infection in patients with negative RT-PCR results (33). In children, direct radiography may not show abnormal findings in the early stage or in cases of mild involvement. In COVID-19 infection, CT may show predominantly bilateral and rarely unilateral subpleural ground-glass opacities and consolidation areas. In a series including 20 patients in which the differences of imaging in children in comparison with the adult age group were described, bilateral involvement was found in 10 patients and unilateral involvement was found in six patients. Among the patients who had CT findings, subpleural involvement was found with a rate of 100%, consolidation surrounded by air crescent sign was found with a rate of 50%, ground-glass consolidation was found with a rate of 60%, and small nodules were found with a rate of 20% and 15% (20). In this study, coinfection was reported in 40% of patients, and it was emphasized that coinfections in children with COVID-19 might influence imaging, and the use of imaging alone would be insufficient in the diagnosis. In a study in which 171 pediatric children were included, radiologic findings were listed as ground-glass consolidation with a rate of 33%, local patchy involvement with a rate of 19%, bilateral patchy involvement with a rate of 12%, and interstitial changes with a rate of 1% (18). In a study in which 171 pediatric patients were included, the radiologic findings were listed as ground-glass consolidation with a rate of 33%, local patchy involvement with a rate of 19%, bilateral patchy involvements with a rate of 12%, and interstitial changes with a rate of 1% (18).
Treatment
While SARS-CoV-2 is rapidly spreading in the world, we need new antiviral agents for treatment, and a vaccine. As the time for developing new agents is very short, however, drugs used for different indications have come to the forefront. Since the beginning of the epidemic, lopinavir/ritonavir, interferon, arbidol, and oseltamivir have been recommended and these drugs have been tried in different patients. However, evidence-based information is lacking in the pediatric age group, and it is being recommended that these treatments should not be used routinely except for critically ill patients, and supportive treatment should be given to patients with mild symptoms, considering the self-limiting characteristics of the infection (34).

Antiviral treatments
Hydroxychloroquine, chloroquine
In in vitro studies, chloroquine and hydroxychloroquine, which are used in treatment of malaria and autoimmune diseases, were shown to prevent viral endosomal fusion by way of glycosylation of host receptors and by acting on endosomal pH, and it was additionally noted that their antiinflammatory actions might have positive effect on the clinical course (35, 36).

In a study conducted with 36 patients in France, it was found that hydroxychloroquine was effective on SARS-CoV-2, and azithromycin potentiated this action. In a study in which chloroquine phosphate was used in 100 adult patients in China, this drug was shown to be effective by elimination of disease progression and disappearance of microbiologic and radiologic findings (37, 38).

Our national guideline reports that hydroxychloroquine should be used with electrocardiography (ECG) monitoring only in children who have severe disease and accompanying risk factors because there are no sufficient data related to pediatric use of this drug, and there is a risk for life-threatening adverse effects including QT prolongation. The recommended dosage of hydroxychloroquine sulphate is 6.5 mg/kg/dose two times a day on the first day (maximum dose: 400 mg/dose) and 3.25 mg/kg/dose on the 2nd-5th days two times a day (maximum dose: 200 mg/dose) (24).

Favipiravir
Favipiravir is an agent causing RNA polymerase inhibition that is known to be effective on ebola and influenza. This drug, which is known to have mild and self-limiting adverse effects, was shown to be more effective at higher doses in studies performed in relation to ebola (39). In a comparison made between 120 patients who used arbidol and 116 patients who used favipiravir, it was reported that favipiravirin had a significant effect in terms of improving cough and fever compared with arbidol, but there was no difference in the time of clinical recovery, and the drug’s most common adverse effect was hyperuricemia (40). Although data related to use of favipiravir in COVID-19 in children are insufficient, information related to ebola may be directive. Favipiravir tablets can be crushed and mixed with foods, and this creates convenience for use in children. In addition, use of the enzymes that are active in children aged 12 months and over including aldehyde oxidase, which is found in the metabolic pathway of favipiravir, renders use of this drug appropriate in this age group (41).

Remdesivir
Studies related to use of remdesivir, which is a broad-spectrum antiviral agent developed against RNA viruses including flavivirus and coronavirus in the treatment of COVID-19, are ongoing. In a multi-center study conducted in China, remdesivir was given to 158 patients with a diagnosis of COVID-19 confirmed microbiologically and radiologically, and 78 patients were included in the placebo group. Among the two groups in whom additional lopinavir-ritonavir, interferon, and corticosteroids were used, rapid clinical recovery was observed in the remdesivir group, but the difference was not statistically significant (42).

Oseltamivir
Oseltamivir, which is a neuraminidase inhibitor used in the treatment of influenza, has not been shown to have in vitro action against SARS-CoV-2. In China, oseltamivir was also given to patients empirically in the period when the COVID-19 epidemic began because it was influenza season (43).

Lopinavir-ritonavir
There is no publication indicating that lopinavir-ritonavir, which is a protease inhibitor used in the treatment of HIV, has in vitro action against SARS-CoV-2. The first publications on the use of lopinavir-ritonavir were case reports or included a limited number of patients, so they did not give reliable information. In addition, lopinavir-ritonavir and standard supportive treatment were compared in a study conducted with 199 adult patients, and lopinavir-ritonavir was not found to be effective (44).

Arbidol
Comprehensive studies on arbidol, which is efficient in the treatment of influenza and shown to have in vitro action against SARS, are ongoing. In a nonrandomized study conducted with 67 adult patients, a lower mortality rate was found in patients who received arbidol compared with pa-
tients who did not receive arbidol, but more comprehensive studies are needed to specify this drug’s efficacy (45).

Other treatments
Corticosteroids
Although steroid use to limit the inflammatory response in the presence of a picture of acute lung injury and ARDS in critical patients infected with SARS-CoV-2 is a frequently debated issue, there are drawbacks because of the adverse effects, risk for secondary infections, and possibility of delayed viral clearance, and routine use of steroids is not recommended in the treatment of COVID-19 except for some critically ill patients (46). In a case series including eight critical pediatric patients who were COVID-19 positive, it was reported that corticosteroid treatment was used in addition to supportive treatment in five patients, three of whom were discharged and treatment was continued in two patients (12). Steroid use was recommended in the presence of the picture of ARDS in the Infectious Diseases Society of America COVID-19 treatment guideline (47).

Anti-cytokine and immunomodulatory treatments
It has been reported that proinflammatory cytokines are increased in patients with COVID-19 with a severe clinical picture, and the picture of cytokine storm caused by the release of these cytokines influences the clinical course (48). IL-6 has a key role in this pathway. Tosilizumab, which acts by way of IL-6, is an agent used in the treatment of rheumatic diseases. In a study conducted with 20 patients, clinical recovery was reported with a single dose of tosilizumab in 91% of patients (49). We need comprehensive, controlled studies on use of these agents.

Immunoglobulin, convalescent plasma
In a case series including five patients, it was reported that plasma obtained from donors who had had COVID-19 infection and recovered, were transfused to critical patients, the patients achieved clinical benefit and further studies on this issue might be helpful (50). It has been emphasized that the number of patients who have had COVID-19 infection and recovered should increase in the donor pool for immunoglobulin treatment to be effective. In a study in which high-dose immunoglobulin was given to three critical patients, it was reported that the patients achieved clinical benefit (51).

Prevention
It is known that SARS-CoV-2 is transmitted by way of droplets and contact. The low number of children infected in the population may be caused by the asymptomatic course of infection in children. Therefore, children are a risky group in terms of transmitting the infection to the adult age group. Doremalen (52) reported that the virus can stay alive for hours and even days on different surfaces. In another study, it was found that the virus could be found for days on equipment belonging to patients such as gastric tubes and even after the nasopharyngeal samples became negative (53).

We should emphasize that providing hand hygiene by washing hands or by way of alcohol-based hand disinfectants, is vital both in the community and in healthcare institutions. In the community, maintaining social distance, providing appropriate hygiene during coughing and sneezing and using a mask at points where social distancing cannot be maintained, are among the recommendations for prevention (54). In healthcare institutions, precautions to be taken include the use of personal protective equipment (PPE) needed for standard, droplet and contact isolation, providing isolation areas for each patient who is compatible with the definition of ‘probable case’ in units where patients present at or are hospitalized, and banning visits to these areas. Accurate use of PPE is important for the safety of healthcare workers. It was found that a lack of abiding by the correct order while wearing and removing PPE increased healthcare workers’ risk of infecting themselves (55).

In conclusion, COVID-19 seems to have a mild course in children. Given that a severe clinical picture can be observed in children with chronic disease, malignancy or immunosupression, however, it is important to separate these children from adults infected with COVID-19. It is important to monitor infants carefully, because a significant portion of severe cases have been reported in this age group. Paying attention to social distancing in the community, taking preventive precautions, screening individuals who have a history of contact with positive patients and elimination of new sources of infection gain importance, because asymptomatic individuals and patients with mild clinical course (the group in which children are also generally included) have a very important role in terms of spreading the disease in the community.
Hakem Değerlendirmesi: Diş bağımız.

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