

## Update on COVID-19 in Children

Elif Güdeloğlu, Hasan Tezer

Gazi University Faculty of Medicine, Department of Pediatric Infectious Diseases, Ankara, Turkey

### ABSTRACT

Since the start of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, it has been clear that most children who have been infected with the virus remain asymptomatic or very mildly ill. Since asymptomatic children are less often examined, the true prevalence of asymptomatic SARS-CoV-2 infection is probably underestimated. Children rarely get anosmia/ageusia, yet it is the best indicator of a positive SARS-CoV-2 test. Children with coronavirus disease-2019 (COVID-19) generally have a lower risk of hospitalization and potentially fatal consequences. Immunization with effective and safe vaccine in children and adolescents is likely to provide protection against severe COVID-19 infection. Recent results from COVID-19 vaccine studies indicate good efficacy and tolerability in children.

**Keywords:** COVID-19, COVID-19 in children, pandemic, SARS-CoV-2

### Introduction

In December 2019 in Wuhan, China, the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) made its first appearance before fast spreading throughout the world. On March 11, 2020, the World Health Organization (WHO) declared coronavirus disease-2019 (COVID-19) a pandemic (1). As of November 10<sup>th</sup>, 2022, 14,950,786 pediatric COVID-19 cases had been reported in the USA, making up 18.3% of all cases and occurring at a rate of 19,864 instances per 100,000 children (2).

All ages, including children, are susceptible to SARS-CoV-2 infection. Numerous pediatric investigations have described the multiple unusual clinical manifestations of children with COVID-19 during the pandemic. Although pediatric age groups have also reported fatal cases, the illness appears to affect children less severely than it affects adults (3). Asymptomatic, mild, or moderate disease is present in approximately 90% of pediatric patients. The true incidence of COVID-19 pediatric infections may have been underestimated at the time because of the high percentage of asymptomatic children and low testing rate (2). Additionally, 6.7% of cases may be severe. Generally, the disease has a severe course in patients younger than 1 year and with underlying disease (3).

Five SARS-CoV-2 variants, including Alpha, Beta, Gamma, Delta, and Omicron, as reported by the WHO, have been identified as of September 11, 2020. All age groups experienced an increase in infectivity due to variations, particularly Delta and Omicron. Recent research has demonstrated that Omicron variations are less severe but more contagious than prior SARS-CoV-2 variants, and that they replicate more readily in the upper respiratory tract than in the lower respiratory tract (4).

**Address for Correspondence:** Elif Güdeloğlu MD, Gazi University Faculty of Medicine, Department of Pediatric Infectious Diseases, Ankara, Turkey

**Phone:** +90 (507) 796 37 87 **E-mail:** dreelif55@hotmail.com **ORCID ID:** orcid.org/0000-0002-3818-017X

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Several studies have been conducted on the diagnosis and treatment of COVID-19. However, there are not enough studies to study pediatric patients (5).

### Clinical Manifestations

When compared to adult cases, pediatric COVID-19 cases typically present with milder symptoms and reduced risks of hospitalization and death. Furthermore, a substantial percentage of children with COVID-19 infections have no symptoms. Between 15% and 65% of pediatric COVID-19 cases have been observed to be asymptomatic (6).

According to the child's age, COVID-19 has a different clinical presentation. Fever (46%), cough (37%), headache (15%), diarrhea (14%) and sore throat (13%) were the most common symptoms in children under nine years of age. Children between the ages of 10 and 19 years are more likely to have symptoms similar to COVID-19 in adults, including headache (42%), cough (41%), fever (35%), myalgia (30%), sore throat (29%), and shortness of breath (16%) (6). Although fever and cough are the most commonly reported symptoms in children with COVID-19, other lower respiratory tract diseases, such as pneumonia and bronchiolitis, are also observed (3).

Since angiotensin-converting enzyme-2 (ACE-2), the SARS-CoV-2 receptor, is also present in other organs such the kidneys, adipocytes, heart, brain, enterocytes, and liver COVID-19 is a systemic illness that affects numerous organs. Extrapulmonary symptoms of COVID-19 may be brought on by ACE-2-linked signaling pathways (3).

Children with COVID-19 have rarely had cutaneous abnormalities documented (6). Cutaneous manifestations may include painful lesions of the fingers and feet as well as a rash (maculopapular, urticarial, or vesicular). Changes are typically seen on the feet (74%-100%) but have also been reported to occur on the hands (6).

The clinical spectrum of COVID-19 severe illness presentation in pediatrics is similar to that in adults. Children may show multi-system organ failure, encephalopathy, myocarditis, shock, acute renal failure, coagulopathy, and neurological involvement (including Guillain-Barré syndrome, cerebral edema, and stroke) (6).

Risk factors for serious diseases are categorized by age group. Children aged 2 to 17 years are at risk for chronic lung illness, neurological problems, cardiovascular disease, obesity, and diabetes. Additionally, infants under 1 year of age had the highest prevalence of hospitalization and severe COVID-19 compared to other age groups (7).

### Post-infectious Complications

#### • Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C or multisystem inflammatory syndrome in children, is a rare but possibly fatal COVID-19 consequence (8). Significant cardiovascular, gastrointestinal, and mucocutaneous abnormalities characterize the presentation, which shares significant characteristics with Kawasaki illness, septic shock, and toxic shock syndrome (9). Clinical and laboratory characteristics are used in the case definition of MIS-C to identify suspected or confirmed cases. The case definitions used by the WHO and Centers for Disease Control and Prevention (CDC) differ slightly. Both categories share the same features, including a fever (duration varies), elevated inflammatory markers, at least two indications of multisystem organ involvement, proof of SARS-CoV-2 infection or exposure, and the exclusion of other possible sources of inflammation. Additionally, the child must have serious clinical signs necessitating hospitalization according to the CDC case criteria (8,9).

Supportive treatment should be a part of the regimen to maintain haemodynamic stability and guarantee appropriate systemic perfusion. For the quick identification and treatment of any arrhythmias, continuous cardiac monitoring is necessary. Typically, immediate empiric broad-spectrum antibiotic treatment should be initiated on patients who present with severe multisystem involvement and shock while awaiting culture findings (9). For most patients with MIS-C, intravenous immune globulin (IVIG) and/or glucocorticoids can be used in the treatment. Patients are considered refractory to initially therapy, if they do not show improvement within 24 h of treatment. For MIS-C patients who do not react to IVIG plus low- to moderate-dose steroids, pulse-dose steroid therapy, infliximab (a tumor necrosis factor inhibitor), or anakinra [an interleukin-1 (IL-1) inhibitor] may be administered (10).

Thrombosis is more likely in patients with MIS-C. Because of the risk of thrombosis, low-dose aspirin may be added to the treatment regimen. Additionally, patients with a current or past history of venous thromboembolism usually require therapeutic anticoagulation with low-molecular-weight heparin (9).

Despite the lack of long-term follow-up data, the prognosis for MIS-C is good because most children make complete clinical recovery. Generally, death rates range from 1 to 2 percent. Most kids with cardiac involvement recover function by the time they are released from the hospital. After discharge, cardiology should be performed on children with heart problems (10).

### • Long COVID-19

A significant number of people who had an acute SARS-CoV-2 infection are now suffering from various persistent symptoms because of the COVID-19 pandemic. This group consists of patients whose symptoms began during or shortly after COVID-19, persisted for at least four weeks, and could not be accounted for by any other condition. Several terminology, including “post-COVID conditions”, “long COVID”, “postacute sequelae of SARS-CoV-2 infection”, “post-acute COVID-19”, “chronic COVID-19”, and “post-COVID syndrome”, have been used to describe prolonged symptoms following COVID-19 (11).

On “long COVID”, there is not much information available in pediatrics. However, most children’s symptoms appear to last no more than 12 weeks (12).

Physical symptoms that last after covid 19 are common and frequently involve weakness, breathlessness, chest pain, and coughing. Anosmia, joint discomfort, headache, rhinitis, dysgeusia, poor appetite, dizziness, myalgias, sleeplessness, alopecia, sweating, and diarrhea are less frequent chronic physical complaints. Additionally, patients may report psychological or cognitive issues such post-traumatic stress disorder, anxiety, depression, and difficulties concentrating. A COVID-19 follow-up visit is not routinely recommended in patients with mild-to-moderate disease who do not require hospitalization unless the patient requests it or has persistent, progressive, or new symptoms. The need for further investigation is determined by the severity of the disease, previous abnormal tests performed during the illness and current symptoms. Routine retesting of patients for active infection with SARS-CoV-2 for which hospitalization is not required, is not recommended. Instead, non-test-based approaches to eliminate infectious measures are preferred (11).

### Vaccinations

A large portion of the world must develop virus immunity in order for this pandemic to be over. Also using vaccination to perform this is the safest option. Within the less than a year after the outbreak began, numerous research teams have developed vaccines to prevent SARS-CoV-2. The challenge now is to make these vaccines accessible to people worldwide. It is critical that all individuals receive the necessary protection, not just those in rich countries. Worldwide, 12.94 billion doses have been given; today, 1.93 million are given every day. 68.2% of people worldwide have received at least one dose of the COVID-19 vaccination, whereas only 23.6% of people in low-income countries have (13). The COVID-19 vaccination

should be administered to all children to avoid the disorder. CDC recommends COVID-19 vaccines for everyone ages 6 months and older, and boosters for everyone ages 5 years and older if eligible. Table 1 lists the eleven vaccines that the WHO authorizes for use in emergencies. Four vaccines have been approved for use in Turkey and their characteristics are described in Table 2 according to current data (14,15). Although that is known that many countries in the world have inactivated COVID vaccine applications for the pediatric age group, Pfizer-BioNTech COVID-19 vaccines, Nonavax and Moderna COVID-19 vaccines are among the COVID-19 vaccines approved for use in children (16,17).

The bivalent vaccines, also referred to as “updated boosters” contain two mRNA components of SARS-CoV-2 which has been approved by the US Food and Drug Administration (FDA), according to a report published on August 31, 2022. Following this announcement, the FDA amended the emergency use authorizations (EUA) for Moderna COVID-19 Vaccine, Bivalent and Pfizer-BioNTech COVID-19 vaccine, Bivalent to allow their use as a single booster dose in younger age groups. Pfizer-BioNTech COVID-19 vaccine, Bivalent is approved for administration in children up to five years of age or at least two months following the completion of booster vaccination, while Moderna COVID-19 vaccine, Bivalent is approved for administration in children up to six years of age (18). Bivalent vaccines, which have been started to be used by many countries such as America and Canada, but are not yet available in our country, should be made available, especially for populations at risk (17).

Although the vaccines are well tolerated by children and adolescents, except injection site pain, fever and fatigue, some cases of myocarditis/pericarditis have occurred among adolescents and young adults, particularly males, following routine use of mRNA vaccines (18). However, most cases of myocarditis and pericarditis are mild, self-limiting and resolve without complications (16,18).

### Diagnosis

#### • Laboratory Tests

Real-time reverse transcriptase polymerase chain reaction detection of SARS-CoV-2 nucleic acid is one of the most efficient methods for diagnosing COVID-19 (19).

Compared with other hospitalized patients, children who require admission to the Pediatric Intensive Care Unit experience greater rates of elevations in C-reactive protein (CRP), procalcitonin, pro-B-type natriuretic peptide, and platelet count. Organ dysfunction was linked to elevated CRP, a higher white blood cell count, and thrombocytopenia (20,21).

**Table 1.** Eleven vaccines granted emergency use listing by WHO (16)

| Protein subunit   | RNA-based         | Non-replicating viral vector | Inactivated                   |
|---|-------------------|------------------------------|-------------------------------|
| - Serum Institute of India: Covovax (Novavax formulation)               | - Moderna         | - CanSino                    | - Bharat BioNTech: Covaxin    |
| -Novavax  | - Pfizer/BioNTech | - Janssen                    | - Sinopharm (Beijing): Covilo |
| -Serum Institute of India: Covishield (Oxford/ AstraZeneca formulation) |                   | -Oxford/AstraZeneca          | -Sinovac: CoronaVac           |

WHO: World Health Organization

**Table 2.** Four vaccines approved for use in Turkey (17)

| RNA-based                    | Non-replicating viral vector | Inactivated   |
|------------------------------|------------------------------|---|
| - Pfizer/BioNTech: Comirnaty | Gamaleya: Sputnik V          | - Health Institutes of Turkey: Turkovac<br>- Sinovac: CoronaVac |

In adult patients with COVID-19, hyperinflammation was related to poor outcomes and was accompanied by elevated lactate dehydrogenase, D-dimer, IL-6, CRP, and ferritin and decreased lymphocyte count, platelet count, and albumin levels (22).

#### • Radiographic Findings

In children with mild or moderate disease, radiographic results (ground glass opacity and consolidation, respectively) may be normal or suggestive of viral/bacterial processes. The American College of Radiology currently advises against using a routine chest X-ray or computed tomography (CT) to diagnose COVID-19 (23).

Chest X-ray is recommended to establish an imaging baseline and assess for alternative diagnosis for clinical symptoms that range from moderate to severe and require hospitalization. Chest CT should only be used to answer specific clinical concerns or to explain worsening clinical deterioration. It is not recommended to use it as the initial diagnostic procedure for pediatric patients with known or suspected COVID-19 pneumonia because children are more radiation sensitive than adults (24).

#### Management of COVID-19

The cornerstone of therapy for COVID-19 patients is supportive care. The self-isolation should occur at home, at a COVID-19-approved health facility, or in a community facility. In addition to providing age-appropriate nutrition and hydration, antipyretics should be used to manage fever and pain. Patients with mild COVID-19 are not advised to receive antibiotic treatment or prophylaxis (25).

Most children with COVID-19, including those with severe disease, recover with supportive care. The children have been excluded from most clinical trials involving COVID-19 treatment

protocols, so there is currently little data to support treatment recommendations in this age group. Decisions about the use of antiviral therapy should be made in consideration of the disease's severity, clinical course, current data of its efficacy, and any underlying diseases that might increase the risk for progression. Additionally, it can be necessary for children who have a mild-to-moderate illness and an underlying condition that increases the risk of contracting a severe illness (26).

Remdesivir, a nucleotide analog found to be effective against SARS-CoV-2 in vitro, has been approved by the FDA in patients over the age of 12 with severe disease necessitating hospitalization despite not been advised for use in children by the WHO (27).

The FDA has approved the drug baricitinib for emergency use in children patients older than two years old who are hospitalized with COVID-19 and need oxygen, ventilator support, or extracorporeal membrane oxygenation.

Bamlanivimab-etesevimab, a monoclonal antibody treatment, has been approved by the FDA for use in infants under the age of two who are hospitalized with mild-to-moderate COVID-19 and at risk of the condition progressing to severe disease. Hydroxychloroquine, which was used in the first months of the pandemic, is no longer recommended for COVID-19 treatment (25).

The use of glucocorticoids for immune-mediated COVID-19 problems is decided on a case-by-case basis based on the severity of the illness (25). The advantages and risks of glucocorticoids for pediatric patients are unknown, although they have been related to decreased mortality in adult patients (26). Low-dose glucocorticoids may be necessary for some children with severe or critical COVID-19 who need mechanical ventilation or additional oxygen and have risk factors for disease progression at the time of admission;

the therapy's duration is up to 10 days or until discharge, whichever is shorter (26).

Despite limited data on the advantages and risks of tocilizumab, which is a monoclonal antibody, in children with COVID-19, an EUA has been granted by the FDA for this drug, which reduces inflammation by blocking the IL-6 receptor, for use in hospitalized patients under two years of age who require extracorporeal membrane oxygenation, supplemental oxygenation, or mechanical ventilation (non-invasive or invasive) (25).

When compared with adult COVID-19 infections, pediatric infections are often milder and have reduced the risks of hospitalization and mortality. Fever and cough are still the most prevalent clinical signs, but other symptoms, including "COVID toes", anosmia, and croup, are also possible. Post-infectious problems in children, such as MIS-C and long

COVID, are a possibility. It is strongly recommended to use vaccination as a kind of prevention. The mainstays of diagnosis and treatment continue to be symptomatic management and respiratory nucleic acid amplification tests.

### Ethics

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: E.G., Concept: H.T., Design: H.T., Data Collection or Processing: E.G., Analysis or Interpretation: H.T., Literature Search: E.G., H.T., Writing: E.G.

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