Review

SARS-CoV-2 infection in pediatric population

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Abstract. In December 2019, in Wuhan (Hubei, China), the first COVID-19 cases due to SARS-COV-2 had been reported. On July 1st 2020, more than 10.268.839 million people had developed the disease, with at least 506.064 deaths. At present, Italy is the third country considering the number of cases (n=240.760), after Spain, and the second for the cumulative number of deaths (n=249.271), after the United States. As regard pediatric COVID-19 cases, more than 4000 cases (have been reported; however, these figures are likely to be underestimated since they are influenced by the number of diagnostic tests carried out. Three pediatric deaths have been reported in Italy to date. We aimed to review the peculiar aspects of SARS-COV-2 infection in the pediatric population. (www.actabiomedica.it)

Key words: children, SARS-CoV-2, COVID-19

Introduction

In December 2019, in Wuhan (Hubei, China), the first coronavirus disease 2019 (COVID-19) cases due to severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) have been reported. On March 11th, 2020, the World Health Organization (WHO) declared the pandemic. On July 8th 2020, more than 11.586.205 million people had developed the disease, with at least 537.701 deaths. At present, US is the first country considering the number of cases (n= 6.007.810) followed by Asia (n= 2.583.393). Europe is the second country for the cumulative number of cases (n= 2.500.288). In this regard, the five countries reporting most cases are Russia (687.862), United Kingdom (285.768), Spain (251.789), Italy (241.819), and Germany (196.944) (1).

As regard pediatric COVID-19 cases, a multicentre cohort study involving 82 participating health-care institutions across 25 European countries reported five hundred eighty-two subjects with PCR-confirmed SARS-CoV-2 infection. Four hundred fifty-four (78%) were contributed by tertiary or quaternary health-care institutions, whereas fifty-four (9%) had been diagnosed in secondary and seventyfour (13%) in primary health-care settings. The median age was 5.0 years (IQR 0·5–12·0) and a sex ratio was 1.5 males per female. One hundred forty-five (25%) had pre-existing medical conditions. Three hundred sixty-three (62%) individuals were admitted to the hospital. Fourty-eight (8%) individuals required ICU admission (1-4).

In a multicentre Italian study of 168 children aged one day to 17 years with SARS-CoV-2 infection, Authors found 2.5% asymptomatic cases (6), while in a

cohort of one hundred italian children with SARS-CoV-2 infection, 21% of children were asymptomatic (7). Specifically, the median age was 3.3 years (range 0–18 years). 40 (40%) of notified pediatric cases were occurring in children younger than 1 year, 15 (15%) occurred in children aged 1-6 years. 21 (21%) confirmed cases occurred in children aged 6-10 year, and 24 (24%) in children older than 10 years. Among all pediatric COVID-19 cases, 57% occurred in males. 27 (27%) had pre-existing medical conditions. 45 (45%) children acquired COVID-19 mainly through close contact with their parents or other family members; 48 (48%) were subjected to other exposure, and only 7 (7%) children reported an unknown exposure. On presentation in emergency department, 79 (79%) children were symptomatic. A total of 12% of children appeared ill, and 54% showed body temperature major than 37.6°C. Cough and no feeding or difficulty feeding were the most common symptoms, 44% and 23%, respectively. Fever, cough, or shortness of breath occurred in 28 of 54 of febrile patients (52%). A total of 4% of the children had oxygen saturation values less than 95% with a imaging evidence of lung involvement. Moreover, of the 9 patients receiving respiratory support, 6 children had coexisting conditions (6). A similar trend was also reported in a monocenter demographic study involving 17 Italian children. Authors showed a slight predominance of COVID-19 in males (58.8%); five children required the home isolation as the symptoms were very mild; 12 were admitted at the hospital: 3 (25%) required low-intensity care, 8 (66.7%) sub-intensive care and 1 (8.3%) ICU admission (5). Totally, 5.010 COVID-19 cases where reported in italian children. 12.5% of notified pediatric cases were occurring in children younger than 1 year, 18.1% occurred in children aged 1-6 years, and 69.4% confirmed cases occurred in children aged 7-17 years. Among all pediatric (<18 years) COVID-19 cases, 2% required hospitalization, especially children younger than 2 years (4.9%). The death rate from Covid-19 in children was 0.2%. Overall, four pediatric deaths have been reported in Italy to date (1-5). Lethality was higher for males than for females in all age groups, with exception of children aged 0-9 years (1-5).

COVID-19 data in children: critical issues

At present, whether data on clinical characteristics and course of the disease are widely available in cohorts of adult patients, limited reports analyzed the pediatric COVID-19 population (8, 9). It is reasonable to hypothesize that the available data-based analysis is not including data from asymptomatic or mildly symptomatic patients, as well as they are likely underestimated as strictly related to the number and sensitivity of the diagnostic tests. Also, the lack of a standardized case definition for COVID can further contribute to the underestimation of the pediatric cases (8, table 1). Moreover, data available regarding the pediatric population should be interpreted with caution as they are often incomplete and/or not adjusted for many confounding factors. In this regard, the results from a large pediatric US study, including more than 2000 patients, with confirmed COVID-19 appear incomplete as the authors provided results related only to 9.4% of cases, 13% of those with underlying diseases, and 33% of hospitalized children (10). Confirming the inconsistency of existing data, Pathak et al. (11) estimated 176.190 SARS-CoV-2–infected children in the USA on April 6th, 2020, basing on the number of children admitted to Pediatric Intensive Unite Care (PICUs) in 19 states (n=79).

In most cases, children acquire COVID-19 mainly through close contact with their parents or other family members, suggesting that an infected child represents a warning sign for a family cluster with SARS-CoV-2 infection (12). As adults, the incubation period in children for COVID-19 is on average 5-6 days, but it can be up to 25 days (13). In contrast, although children show a similar risk of infection to the adults, they are less likely to have mild respiratory symptoms. Asymptomatic infections are not uncommon, representing about 10% of the total pediatric cases (14). Interestingly, preliminary data suggest that children, even if asymptomatic or experiencing mild symptoms, may be a source of viral transmission. In this regard, an Italian study has recently reported that most people infected with COVID-19 (43.2%) were able to infect others, even whether asymptomatic (15).

Clinical symptoms of SARS-CoV-2 infection in the pediatric population

Clinical manifestations of COVID-19 in children range from asymptomatic to mild, moderate, severe, and critical (Table 2). Symptomatic children with COVID-19 were reported to have fever, myalgia, rhinitis, sore throat, cough, and, less commonly, gastrointestinal symptoms such as vomiting, diarrhea, and abdominal pain. Severe COVID-19 in children is rare and associated with tachypnea/dyspnea, central cyanosis, oxygen saturation <92%, tachypnea; gastrointestinal symptoms; impaired consciousness; inability feeding and/or drinking; seizures; sepsis; shock; or multi-organ dysfunction (16).

Table 1. Confirmed case and suspected case definition among worldwide guidelines

Adults
Definition from Chinese Centre Disease Control (CDC)
A suspected or probable case is defined as a case that meets three clinical criteria or 2 clinical criteria and 1 epidemiologic criterion: Clinical criteria: 1. Fever   2. Radiographic evidence of pneumonia or acute respiratory distress syndrome (ARDS)   3. Low or normal blood cell count or low lymphocyte count   Epidemiologic criteria: 1. Living in Wuhan or travel history to Wuhan within 14 days before symptom onset   2. Contact with patients with fevere and symptoms of respiratory infection within 14 days before symptom onset   3. Link to any confirmed cases of clusters of suspected cases
Definition from the USA CDC (February 13rd, 2020)
A. Fever or signs/symptoms of lower respiratory illness (eg cough or shortness of breath) AND close contact with a laboratory-confirmed SARS-CoV-2 patients within 14 days before symptom onset   B. Fever or signs/symptoms of lower respiratory illness (eg cough or shortness of breath) AND a history of travel from Hubei Province, China within 14 days before symptom onset   C. Fever or signs/symptoms of lower respiratory illness (eg cough or shortness of breath) AND a history from mainland China within 14 days before symptom onset
Definition from World Health Organization (WHO) Febraury 27th,2020), which also form the basis for the European Centre Disease Prevention and Control (ECDC) case definition
Suspected cases: A. Patient with acute respiratory infection (fever and at least one sign/symptom of respiratory disease (eg cough, shortness of breathe) AND with no other aetiology fully explains the clinical presentation AND a history of travel to or residence in a country/aerea or territory reporting local transmission of COVID-19 during the 14 days before symptom onset; **OR**   B. Patient with acute respiratory infection AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days before symptom onset; **OR**   C. Patient with acute respiratory infection AND requiring hospitalization AND with no other other aetiology fully explains the clinical presentation

Table 1. Confirmed case and suspected case definition among worldwide guidelines

Children
Case Defintion by the National Clinical Research Center for Child Health, Zhejian University School of Medicine (adapted from. Chen et al.)
A *suspected* or *probable case* is defined as a case that meets 2 clinical criteria and 1 epidemiologic criterion: Clinical criteria: 1. Fever, fatigue, dry cough; some pediatri patients may have no fever 2. Patients with the following chest imaging findings: multiple small patchy shadows and interstitial changes, mostly in the lung periphery; bilateral multiple groud.galls opacity, infiltrating shadows, pulmonary consolidation on chest radiography or groungglass opacities, bilateral segmental consolidation, especially in the periphery on chest CT. 3. Low or normal blood cell count or low lymphocyte count Epidemiologic criteria: 1. Children with a travel or residence in Wuhan City and neighnoring aereas, or other areas with persisten local transmission within 14 days before symptom onset 2. Contact with a history of contacting patients with fever or respiratory symptoms who have a travel or residence history in Wuhan City and patients with fevere and symptoms of respiratory infection within 14 days before symptom onset and neighnoring aereas, or other areas with persisten local transmission within 14 days before symptom onset 3. Contact with a history of contacting confirmed or suspected cases infected with SARS-CoV-2 within 14 days before symptom onset 4. Children who are related with a cluster outbreak: in addition to this patient, there are other patients with fever or respiratory symptoms, including confirmed or suspected cases infected with SARS-CoV-2 5. Newborns deliverid by suspected or confirmed SARS-CoV-2-infected mothers A *confirmed* case is defined as a case that meets any of the following criteria: 1. Troath swab, sputum, stool or blood samples tested positive for SARS-COV-2 nucleic acid using RT-PCR 2. Genetic sequencing of troath sputum, stool or blood samples being highly homologous with the known SARS-CoV-2 3. SARS-CoV-2 granules being isolated by culture from troath sputum, stool or blood samples

Prevalence of severe forms and deaths due to SARS-CoV-2 infection in the pediatric population

In a large Chinese study conducted in children, the authors reported that the prevalence of asymptomatic, mild, moderate, severe and critical forms was 12.9%, 42.1%, 41.0%, and 2.5%, respectively; and less than 1% of the total cases required admission to PICU hospitalization or mechanical ventilation (17).

In another study, the authors reported that the prevalence of severe and critical cases was 5.6% and 0.6%, respectively (16). Similarly, in a US study, only 0.58%-2.0% of the total cases (n=15) required admission to PICU hospitalization (10).

Tagarro et al. found that 25 out of 41 children with confirmed COVID-19 (60%) were hospitalized, and 4 of them (9.7%) were admitted to PICU and 4 (9.7%) needed respiratory support beyond nasal prongs (18). Lastly, Streng et al. reported that 3 out of 33 (9%) children with confirmed COVID-19 were admitted to PICU (19).

Severe outcomes have been reported in children, including SARS-CoV-2 associated deaths. On July 8th, 2020, 4 pediatric deaths (aged range 0-9 years)

Table 2. Clinical manifestations of SARS-CoV-2 infection in the pediatric population

Clinical classification	Clinical manifestations
Asymptomatic	Absence of clinical signs and symptoms Normal lung imaging Positive SARS-CoV-2 nucleic acid test
Mild	Mild clinical symptoms Upper respiratory tract infections (feverm cough, sore throat) Absence of pneumonia signs Gastrointestinal symptoms (nausea, vomiting, abdominal pain and diarrhoea)
Moderate	Fever and cough, dry and productive Wheezing without hypoxia or shortness of breathe, dry and/or wet rales Chest imaging shows pneumonia Some children can be asymptomatic but with positive chest imaging
Severe	Children show at least one of the following symtpoms: 1. Increased respiratory rate accoding to the age 2. Blood oxygen saturation at rest <92% 3. Symptoms of hypoxia: assisted breathing (groaning, wing flaps, sags), cyanosis, intermittent apnea 4. Unconsciousness: lethargy, coma, convulsions 5. Difficulty in feeding
Critical	The disease progresses quickly and at least one of the following symptoms is present: 1. Respiratory failure requiring mechainical ventilation 2. Shock 3. Combined with other organ failure, require intensive care unit

were reported in Italy (1). On May 1st, 2020, 3 pediatric deaths were reported in China and 3 in the US (10); a death was reported in a 12-years-old boy dies in Belgium; a death was reported in a 13-years-old boy in the United Kingdom (UK); a death was reported in 16-years-old girl and death was reported in 10-years-old girl in France (20-22). However, the contribution of COVID-19 to the cause of death in all these cases has not been well clarified (23).

Risk factors for developing severe forms of SARS-CoV-2 infection in the pediatric population

At present, few data are available on the role of age and comorbidities on the severity of pediatric COVID-19 (12). Although a large study showed that children of all ages were susceptible to the COVID-19 (16), the reported proportion of severe and critical cases was 10.6% for children younger than 1 year; 62% of children requiring hospitalization were also younger than 1 year; 4-14% of children aged 1-17 years was

admitted to the hospital. However, data analysis of children admitted to PICU revealed no significant difference based on age (8% of children younger than 1 year *vs.* 11% of children older than 1 year), suggesting that age does not affect the illness severity (3, 24).

Taking into account data generated in adults, it is assumed that some clusters of pediatric patients could be at higher risk of severe illness including children affected by congenital or acquired cardiovascular and pulmonary diseases, diabetes mellitus, neoplasia, obesity, congenital or acquired immunodeficiencies, hemoglobinopathies (10, 12). Recent data suggest a higher risk for children with complex diseases, obese children (10, 12).

Clinical symptoms of SARS-CoV-2 infection in the pediatric population: data from the literature

The prevalence of clinical symptoms in the pediatric population ranges widely among studies because it is influenced by differences in case definition and

diagnostic criteria. Recently, in their systematic review including 18 studies and 1065 children, Castagnoli et al. highlighted that the most common symptoms were dry cough, fever, pharyngitis, and rhinorrhea (12). Vomiting, diarrhoea, difficulty feeding, headache, myalgias, syncope episodes have also been reported. In a US study,93% of adult patients reported at least one of the following symptoms fever, cough, and shortness of breath, while one of these symptoms was described in 73% among children. Specifically, 71% of adult cases reported fever compared with 56% of pediatric cases, 80% of adult cases reported cough compared with 54% of pediatric cases, and 43% of adult cases reported dyspnoea compared 13% of children with confirmed infection (10).

In Wuhan, in 171 infected children younger than 16 years of age, the most common signs and symptoms included cough (48.5%), pharyngeal erythema (46.2%), and fever >37.5°C in the 41.5% of cases, and > 38°C in 32% of cases. Diarrhea was also present in 6-15% of the cases (27). In this regard, 8 pediatric patients with confirmed COVID-19 and also reporting diarrhoea, showed a real-time RT–PCR-positive rectal swabs. Moreover, all of them demonstrated persistently positive real-time RT–PCR tests of rectal swabs also after their nasopharyngeal testing become negative. Therefore, potential fecal-oral transmission has been hypothesized (28).

Fever in the absence of other signs and/or symptoms can be an uncommon manifestation of COVID-19 in infants; suggesting routine RT-PCR-based testing for SARS-CoV-2 use in infants, showing only fever in an outbreak setting (28).

32% adult patients with severe COVID-19 had ocular manifestations, such as conjunctival congestion, epiphora, and chemosis; only 1 case has been described in the pediatric population (29). Myocarditis has also been reported in patients with COVID-19, and a possible causative link between COVID-19 and Kawasaki-like disease has been hypothesized (30-32).

This new form has been denominated SARS-CoV-2–Related Inflammatory Multisystem Syndrome in Children and show peculiar clinical features with respect to Kawasaki disease. It may have a different racial/ethnic predilection, affecting primarily people of African American, Caribbean, and Hispanic ancestry, whereas KD affects primarily those of East Asian ancestry. It also appears to affect an older age group than KD and has a higher prevalence of gastrointestinal symptoms and lower prevalence of classic KD clinical signs. With respect to children with KD or KD shock syndrome these children had higher white blood cell count, neutrophil count, and CRP more profound lymphopenia and anemia lower platelet counts higher fibrinogen levels greater elevation of troponin. Some children developed shock, often associated with evidence of left ventricular dysfunction on echocardiography, elevation of troponin, NT-proBNP, and arrhythmia, and some need for adjunctive steroid treatment (30-32).

The dysregulated immune response occurring in COVID-19, especially in the late stages of the disease, can lead to endothelial dysfunction with impaired microvascular permeability and thrombosis. These events could explain the acute self-healing acroischemic lesions manifesting with cyanosis, blisters, and gangrene of fingers and toes detected in patients with severe COVID-19 (33).

Due to the affinity of SARS-CoV-2 for angiotensin-converting enzyme (ACE)-2, the virus can interfere with the renin–angiotensin–aldosterone system (RAAS) and affects podocytes and tubular epithelial cells, resulting in kidney injury. Renal involvement in children with COVID-19 is rare compared to adults (34).

Thanks to its neuroinvasive capabilities, SARS-CoV-2 can spread from the respiratory tract to the central nervous system (CNS), causing neurological manifestations such as febrile seizures, convulsions, change in mental status, and encephalitis, Guillain-Barrè syndrome, and acute necrotizing encephalopathy (35). Moreover, following nasal infection, SARS-CoV-2 enters the CNS through the olfactory bulb, causing inflammation and demyelination, and resulting in ageusia and anosmia (36, 37). At present, these symptoms have not been described in children.

Disseminated intravascular coagulation, macrophage activation syndrome, sepsis, and multi-organ dysfunction have been reported in the adult population; data on the pediatric population are still awaited.

Laboratory findings in the pediatric population with SARS-CoV-2 infection

The abnormal laboratory findings commonly detected in the adult population are less frequently reported in the pediatric population. 25% of children with confirmed COVID-19 showed leucopenia (white cells <5.500/µL), 3.5% of the cases reported lymphocytopenia (1.200/uL), 4.6% neutropenia or neutrophilia (3, 38). Because of COVID-19 is able to cause a CD8 T-cell depletion and eosinophil consumption, eosinopenia has been frequently detected in patients with SARS-CoV-2 infection (39).

Increased C-reactive protein (C-RP) and interleukin (IL)-6 values were detected in 13.6%-20% of the cases, especially in severe forms (3, 38). High levels of procalcitonin were significantly associated with severity of COVID-19, suggesting bacterial superinfection (3, 38). High levels of C-RP (> 10 mg/dL), leucopenia, increased lactic dehydrogenase creatine kinase, D-dimers, and ferritin values are also significantly associated with the severity of COVID-19 (10, 40).

SARS-CoV-2 infection is confirmed by RT-PCR of samples taken from upper nasopharyngeal swabs (Table 2). The sensitivity and specificity of COVID-19 diagnostics and serology testing, as well as their performance, change widely across different populations. In a study collecting 1070 specimens from 205 patients with confirmed COVID-19, bronchoalveolar lavage fluid specimens showed the highest positive rates (14 of 15; 93%), followed by sputum (72 of 104; 72%), nasal swabs (5 of 8; 63%), fiber bronchoscope brush biopsy (6 of 13; 46%), pharyngeal swabs (126 of 398; 32%), feces (44 of 153; 29%), and blood (3 of 307; 1%). All 72 urine specimens tested negative (37). There are no data on serological tests in children (38, 41, 42).

Instrumental findings in the pediatric population with SARS-CoV-2 infection

Data on radiographic features associated with severe/critical COVID-19 pneumonia are sparse. In the pediatric population, chest radiography is typically normal and not correlating with illness severity. Cases of interstitial pneumonia have been detected in asymptomatic children as well as normal chest radiography has been reported in children with COVID-19-caused pneumonia. Bronchial thickening and ground-glass opacities are the most common radiologic features reported in children (12). In a case series involving 10 children, unilateral patchy opacities were observed in 4/10 (40%) of the cases (43). Other authors described unilateral and bilateral opacities in children with COVID-19, and bilateral opacities appeared to be more typical in the pediatric population (44). Bilateral peripheral and/or subpleural ground-glass and/or consolidative opacities in the lower lobes of the lungs are the most common abnormalities found on CT. The "halo" sign, generally observed in the early phase of the disease and defined as a focal consolidation with a rim of surrounding ground-glass opacity, has been reported in up to 50% of cases. Successively, it progresses to ground-glass (progressive phase) and can develop into consolidative opacities (developed phase). Fine mesh reticulations and "crazy paving" signs have also been reported, even if less frequency in the pediatric population compared to adults. Pleural effusion and lymphadenopathy have been rarely described (44).

Lung imaging can also be considered in the diagnostic management of children with COVID-19 (45).

Therapy

Currently, there is no approved specific treatment or vaccine against COVID-19. Patients can require supportive care and oxygen supplementation through non-invasive ventilation or *via* mechanical ventilation (46).

In critically ill adult patients, tocilizumab, convalescent plasma, low-molecular-weight heparin, antioxidant agents, and antiviral drugs have been used as potential treatments against the inflammatory status, cytokine storm, microangiopathic thrombotic inflammation, disseminated intravascular coagulation, and viral replication cycle (16, 47-54, table 3).

There is no validated evidence on the treatment and prevention in children infected with SARS-CoV-2. A multicenter initial guidance on the use of antivirals for children with SARS-CoV-2 infection has been recently published (8). Authors highlighted

Table 3. List of drugs in treating SARS-CoV-2 infection and mechanism of action

Drugs	Therapeutical tools
Virus entry	
Camostat Mesylate	TMPRSS2 inhibition
Anti-S (RBD) protein	Monoclonal antibody
Convalescent plasma	Neutralizing action
Arbidol	Inhibits S-protein-ACE2 interaction
Cloroquine/Hydroxicloroquine	Inhibits endocytosis
Low molecular weight-Heparin	Inhibits the 3'Chymotrypsin-like protease
Proteolysis of viral polypeptides	
Lopinavir/Ritonavir	Inhibits the 3'Chymotrypsin-like protease
Virus repilcation-transcription complex	
Remdesevir, Ribavirin, Favipiravir	Inhibits RNA -dependent RNA polymerase
Host immunomodulatory and overinflammatory response	
Cloroquine/Hydroxicloroquine	Inhibits RNA sensors in infected cells
Tocilizumab/Sarilumab	Anti-IL-6 receptor
Nebulized INF-1ß	
Corticosteroids	Inhibits several cytokines and chemokines
Omalizumab	Increases regulatory mechanisms, reduces type 2 response
Low molecular weight-Heparin	Inhibits hypercouagulation-FXa
Opportunistic Pathogens	
Azytromicin	

that, although COVID-19 in most children is of mild or moderate severity, there is a cluster at higher risk for developing a severe form of COVID-19 (8). Supportive treatment, including sufficient fluid intake and additional oxygen supplementation, is the only treatment recommended in children with COVID-19. The use of antivirals should be evaluated for severely or critically ill children in accordance with an individual risks-benefits ratio (8).

Evidence on the role of specific risk factors for the development of severe COVID-19 are not still available; however, underlying medical conditions such as lower respiratory tract disease, viral superinfection (*Influenza, Parainfluenza, Respiratory Syncytial Virus,* and other *Coronaviruses*), obesity, diabetes mellitus, immunodeficiencies, comorbidities, and respiratory support requirement should be taken into account (6, 8, 55-58). In particular, because of obesity is associated with

a chronic low-grade inflammation and adipose tissue may be a reservoir for viral spread, obesity can represent a risk factor for severe SARS-CoV2 infection (54). Conversely, allergy and asthma might be "protective" factors for disease severity from COVID-19. Although allergic diseases are the most prevalent chronic disorders in the pediatric population, at present, patients affected by allergy are less suffering from SARS-CoV2 infection, both as incidence and severity. These findings could be explained by the evidence that allergic sensitization seems to be inversely related to ACE2 expression (55, 56, 59).

Conversely, younger age does not seem to be associated with an increased risk of severe disease. Drug toxicity and drug-drug-interactions should be evaluated before any eventual antiviral treatment (8). Generally, children with mild-to-moderate COVID-19 should be treated with supportive therapy, while antiviral treatment should be reserved only to hospitalized children with severe forms. Among several proposed antiviral agents, remdesivir, a nucleoside analog, is the drug-of-choice (8, 16). It is available for children through an FDA Emergency Use Authorization or through a compassionate use program (60). When remdesivir is not available, or patients are not candidates for remdesivir, hydroxychloroquine, with a loading dose on day 1 and a total duration of no more than five days, might be considered. Given that a short duration of therapy is rarely associated with dose-dependent toxicities, G6PD screening is not routinely recommended before initiation of hydroxychloroquine (8, 16). Conversely, the hydroxychloroquine in combination with azithromycin is not supported due to safety concerns such as a higher risk of arrhythmia and death. Data on the lopinavir-ritonavir use are controversial. Strongly discouraged is lopinavir-ritonavir-ribavirin combination therapy (8). In summary, for all the agents above-mentioned, there are insufficient data to recommend for or against the use of specific antivirals or immunomodulatory agents for the treatment of COVID-19 in pediatric population. Clinical conditions, underlying comorbidities, disease severity, and potential for drug toxicity or interactions may guide the management decisions on a case-by-case basis (60). The suggested dose and duration of treatment in the pediatric

population are summarized in table 4. The reported information is derived from data on the use of these drugs and biologic products for FDA-approved indications or from clinical trials, and, where available, it is supplemented with data from patients affected by COVID-19. Although the doses listed in the table 4 are primarily derived from FDA-approved indications or from RCTs investigating therapies for SARS-CoV-2 infection, currently, the effective dosing of these agents as well as dose modifications for critically ill patients are still unknown. In regard to treatment-related adverse events (AEs) in patients with COVID-19, the reported AEs of these drugs are commonly associated with long-term therapy, however, they are not well defined. Accordingly, conclusive safety data are not available (60). In summary, all antiviral agents should be preferably administered as part of a clinical trial, when available.

Conclusion

COVID-19 is an emerging disease with a significant impact on children's psycho-physical health (61). SARS-CoV-2 infection affects the pediatric population less commonly and less severely as compared with the adult population. However, physicians should maintain a high index of suspicion for COVID-19 in children as well as monitor strictly for progression of the disease, especially in children affected by underlying conditions. In this regard, author reported a critical reduction (>70%) in pediatric emergency department visits that could represent a tremendous scenario for children's health during the pandemic. The severity of health status, especially in children suffering for underlying conditions, could be underestimated and quickly evolve into life-threatening situations (62). On the other hand, although children are less likely to be symptomatic or develop severe symptoms, they could represent a critical source of transmission, especially since a new fecal-oral transmission has been recently suggested. There are no significant laboratory findings, but the disease progression is associated with increased serum levels of lactic dehydrogenase creatine kinase, D-dimers, and ferritin, and leucopenia. Although any correlation between imaging and the course of the

Table 4. Approved antiviral drugs in treating SARS-CoV-2 infection in the pediatric population

Drug	Dose treatment	Note
Remdesivir	**<40 kg:** 5 mg/kg IV* loading dose on day 1; followed by 2.5 mg/kg IV q24h **≥40 kg:** 200 mg IV loading dose on day 1; followed by 100 mg IV q24h Up to 10 days, with 5-day duration favored for fast responders	**For Patients with Severe COVID-19:** The Panel recommends Remdesivir for treatment of COVID-19 in hospitalized patients with SpO2 ≤94% on ambient air or those who require supplemental oxygen, and in patients on mechanical ventilation or ECMO*. **For Patients with Mild to Moderate COVID-19:** There are insufficient data to recommend for or against Remdesivir for the treatment of patients with mild or moderate COVID-19. **Availability:** Remdesivir is available for the treatment of hospitalized adults and children with severe COVID-19. Remdesivir is also available for other patient populations through compassionate use
Chloroquine	**Adolescents Weighing ≥50 kg:** 1 gm PO* once on Day 1, then 500 mg po once daily for 4–7 days of total treatment based on clinical evaluation	The Panel recommends **against** the use of CQ for the treatment of COVID-19.
Hydroxychloroquine	13 mg/kg (maximum: 800 mg) PO* followed by 6.5 mg/kg (maximum: 400 mg) PO at 6, 24, and 48 hours after initial dose **OR** 6.5 mg/kg/dose (maximum: 400 mg/dose) PO BID* on day 1, followed by 3.25 mg/kg/dose (maximum: 200 mg/dose) PO BID **Newborns:** dosing not established Duration could be extended for up to 5 days on a case-by-case basis	The Panel recommends **against** the use of CQ for the treatment of COVID-19.
Lopinavir-ritonavir	**Newborns ≥14 days and postmenstrual age ≥42 weeks** to **children <18 years of age:** Lopinavir 300 mg/m2 (maximum 400 mg/dose) PO BID Up to 7-14 days	The Panel recommends **against** the use of CQ for the treatment of COVID-19.
Azithromycin (when Used with Hydroxychloroquine)	500 mg PO once on day 1, then 250 mg PO daily on days 2–5	The Panel recommends **against** the use of azithromycin plus hydroxychloroquine for the treatment of COVID-19

*IV: intravenous; PO: per os; BID: bis in die; ECMO: extracorporeal membrane oxygenation.

disease has been reported, bilateral peripheral and/or subpleural ground-glass and/or consolidative opacities in the lower lobes of the lungs are the most common abnormalities found on CT. There is no validated evidence on the treatment and prevention in children infected with SARS-CoV-2. Supportive treatment is the only therapy recommended in children with COVID-19. The use of antivirals should be evaluated for severely or critically ill children balancing an individual risks-benefits ratio.

Further systematic data collection on pediatric patients with confirmed COVID-19 would be helpful better to understand the clinical course of the disease in children and intercept risk factors for severe COVID-19 illness.

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