Review Article

COVID-19 in Children

Pornumpa Bunjoungmanee[1], Detchvijitr Suwanpakdee[2]

Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a pandemic in many countries necessitating the employment of massive public health responses. Clinical manifestations of children with COVID-19 are typically less severe than adult patients. Most children with COVID-19 remain asymptomatic or become mildly symptomatic. However, children can also get severely ill from COVID-19. Infants who are under the age of one year and children with preexisting comorbidities may be more likely to develop severe illness and are at an increased risk for hospitalization and critical care. Rarely, COVID-19 may result in multisystem inflammatory syndrome in children (MIS-C). The pathogenesis involves post-infectious immune dysregulation which can result in potentially serious illness in children. Currently, there are no antiviral treatment options or immunomodulatory drugs with proven efficacy for children with acute SARS-CoV-2 infection. Supportive care is the mainstay of therapy for all pediatric patients.

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

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[1] Department of Pediatrics, Faculty of Medicine, Thammasat University, Pathum Thani 12120, Thailand
[2] Pediatric Infectious Unit, Department of Pediatric, Phramongkutklao Hospital, Bangkok 10400, Thailand
Corresponding author: Pornumpa Bunjoungmanee, Department of Pediatrics, Faculty of Medicine, Thammasat University, Pathum Thani 12120, Thailand Tel. +66 2926 9514 Fax. +66 2926 9513 Email: pornumpa@staff.tu.ac.th

Introduction

Coronavirus disease 2019 (COVID-19) is defined as illness caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus first emerged in China during late December 2019 and subsequently spread worldwide resulting in a major burden on the world's public health system. Acute SARS-CoV-2 infection tends to be asymptomatic or mildly symptomatic in most children. However, some children with preexisting comorbidities may suffer from severe disease requiring hospitalization. Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious condition associated with COVID-19. MIS-C usually develops 2 to 4 weeks after acute SARS-CoV-2 infection with severe cardiac complications.

Transmission among children

Children likely have similar SARS-CoV-2 viral loads in the nasopharynx to that of adults and can transmit virus to others, but the rate of viral dissemination by young children is uncertain.[1-3] A major mode of transmission to children is infection via close household contacts. Limited evidence suggests transmission from children to household contact can occurs. In studies of pediatric COVID-19 patients in China and Switzerland, only 4.0 - 8.0% of infected children were suspected to be index cases.[4, 5] A study in Greece reported on observations of 43 SARS-Cov2-infected children; median age 11 years old (range; 6 days to 18.4 years). The study found no significant difference in initial viral loads in the nasopharyngeal sample between children with symptomatic infection and children with asymptomatic infection (mean; 9.8×10^5 copies/mL versus 8.2×10^5 copies/mL; $P = 0.787$).[6]

Studies in many countries have shown relatively few reports of school outbreaks when mitigation strategies (e.g., mask-wearing, physical distancing, and smaller class sizes) were in place. In many studies of SARS-CoV-2 transmission in educational settings from Australia, Norway, Switzerland, and the United States, the overall child to child transmission rate was 6.0% and the attack rate for child to staff member was 4.0%. After all schools implemented infection prevention and control measures, the attack rate decreased by 60.0% for child to child and 70.0% for child to staff members.[7-10] Based on current available data, SARS-CoV-2 transmission in schools may be ancillary rather than central in regards to community spread when effective case-contact testing and epidemic control strategies are implemented.

Clinical manifestation

Children of all ages can be affected by COVID-19. Current data suggests that incidence increases with increasing age. The United States Centers for Disease Control and Prevention researchers in December of 2020 observed based on electronic laboratory reporting data that incidence increased with increasing age. Of the five age groups ranging from 0 - 24 years, the age group with the highest rate of positive SARS-CoV2 test results was adults aged 18 - 24 years with a rate of 57.4%. This was followed by adolescents aged 14 - 17 years with a rate of 16.3%, children age 5 - 10 years with 10.9%, children age 11 - 13 years with 7.9%, and children aged 0 - 4 years with 7.4%.[11]

The incubation period of SARS-CoV-2 in children is the same as that of adults, ranging from 2 to 14 days with an average of 6 days. Children often experience milder disease than adults. However, a small minority of children with underlying comorbidities or those coinfected with other respiratory pathogens can have severe manifestations and require hospitalization. Approximately one-third of hospitalized children require intensive care and 5.0% of cases receive invasive mechanical ventilation, similar to the proportions seen in adults.[12, 13]

The clinical symptoms of children infected with SARS-CoV-2 are typically mild and often cold-like. Fever, chills, and cough are the most common reported symptoms. Other symptoms include fatigue, headache, myalgia, nasal congestion, rhinorrhea, a loss or change to sense of smell (anosmia) or taste (ageusia), pharyngeal erythema, sore throat, shortness of breath, abdominal pain, diarrhea, nausea, vomiting, and anorexia. Notably, gastrointestinal involvement is twice as common in children as in adults.[14] In many aspects, the clinical findings of COVID-19 overlap with those of other infectious and noninfectious processes, including influenza, amongst other respiratory pathogens, enteric viral infections, group A streptococcal pharyngitis, and allergic rhinitis. Disease as a result of acute SARS-CoV-2 infection usually follows a predictable course

with most patients usually recovering within one to two weeks of disease onset.

There is limited evidence about which underlying medical conditions in children might increase the risk for severe illness. The extensive list of suspected predisposing conditions includes infancy, diabetes, asthma, chronic lung disease, genetic, neurologic, metabolic conditions, sickle cell disease, congenital heart disease, medical complexity, immunodeficiency, and obesity.[15]

In a study conducted in China comprised of 2,597 cases of children with COVID-19 from 2019 to 2020, the proportions of cases were 25.2%, 23.8%, 19.7%, 17.9%, and 13.4% among the age groups 6 - 10, 1 - 5, 11 - 15, less than 1 and more than 15 years, respectively. Most common symptoms reported were cough (43.4%), fever (43.1%), sore throat (20.4%), rhinorrhea (16.4%), and nasal congestion (15.3%). Less common symptoms include tachypnea (12.6%), diarrhea (6.6%), vomiting (5.8%), myalgia or fatigue (5.1%), hypoxemia (1.8%), and chest pain (0.4%). Of the involved cases, most were diagnosed as mild illness (45.5%) and moderate illness (41.5%). Only 4.4 % were assessed as severe and 0.9% as critical illness which predominantly occurred in infants under 1 year of age. Among 23 critical cases, only 26.1% of cases were complicated by underlying diseases, most notably acute lymphoblastic leukemia, congenital heart diseases and prematurity.[16]

In a multicenter cohort study involving 82 participating health-care institutions across 25 European countries, the study comprised 582 cases of children with COVID-19. The median age was 5 years old (interquartile range [IQR]: 0.5 to 12.0 years). Significant risk factors for severe disease include age younger than 1 month (odds ratio [OR]: 5.06, 95%CI: 1.72 - 14.87; $P < 0.01$), pre-existing medical conditions (OR: 3.27, 95%CI: 1.67 - 6.42; $P < 0.01$) and presence of respiratory signs and symptoms of lower respiratory tract infection (OR: 10.46, 95%CI: 5.16 - 21.23; $P < 0.01$).[17]

Coinfection

Bacterial and viral co-infections and secondary infections commonly occur in influenza and other respiratory viruses, which leads to increased mortality and morbidity. In many studies of SARS-CoV-2 infected children from China, Europe, and the United States, co-infection was found in 4.0 - 6.0% of cases overall. Multiple common respiratory pathogens include chiefly rhinovirus, enterovirus, respiratory syncytial virus, influenza virus, and human metapneumovirus. However, the clinical significance of the presence of these coinfections is still unclear.[17-19] Meanwhile, bacterial coinfections are rare. Of the cases reported in current literature, *Mycoplasma pneumoniae* is the predominant pathogen.[18, 19] Similarly, a systematic review suggests that 6.0% of children with COVID-19 also had a concurrent bacterial or viral co-infection.[20]

Multisystem inflammatory syndrome in children/pediatric inflammatory multisystem syndrome temporally related to SARS-CoV-2 (MIS-C/PIMS-TS)

MIS-C is a serious condition in children that results from delayed immunologic responses to SARS-CoV-2 infection. Evidence indicates that many of these children were infected with the virus causing COVID-19 in the past, as shown by positive antibody test results, suggesting that the pathogenesis involves post-infectious immune dysregulation. MIS-C seems to be a relatively rare complication which has been found in less than 1% of children with confirmed SARS-CoV-2 infection, with the incidence of 316 persons per 1 million COVID-19 infections in persons under 21 years. The incidence was higher among black, Hispanic or Latino, and Asian or Pacific Islander ethnicities.[21]

In Europe and North America, it was reported clusters of children and adolescents with a multisystem inflammatory condition that leads to multiorgan failure and shock, requiring admission to intensive care units. Many children can have symptoms resembling diseases that require prompt treatment, such as sepsis, toxic shock syndrome, myocarditis, or Kawasaki disease. The condition has been recognized as multisystem inflammatory syndrome in children (MIS-C), and also called pediatric inflammatory multisystem syndrome temporally related to SARS-CoV-2 (PIMS-TS). The case definition by the United States Centers for Disease Control and Prevention, the World Health Organization and the Royal College of Pediatrics and Child Health in United Kingdom are summarized in Table 1.[22-24]

Table 1 definition of MIS-C and PIMS-TS[22-24]

MIS-C definition of CDC	MIS-C definition of WHO	PIMS-TS definition of the RCPCH
Required: all six criteria 1. Age < 21 years 2. Fever: documented ≥ 38.0°C ≥ 24 hours or reported subjective fever lasting ≥ 24 hours 3. Clinical presentation consistent with MIS-C, including all of the following: a. evidence of clinically severe illness requiring hospitalization, with multisystem (≥ 2) organ involvement : cardiovascular, renal, neurologic, hematologic, gastrointestinal, or dermatologic system b. severe illness requiring hospitalization 4. Laboratory evidence of inflammation including, but not limited to any of the following: a. elevated: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), interleukin 6 (IL-6), neutrophils b. reduced lymphocytes, low albumin 5. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms 6. No alternative plausible diagnoses.	Required: all four criteria 1. Age < 19 years 2. Fever for ≥ 3 days 3. Clinical signs of multisystem involvement (at least 2 of the following) a. rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet) b. hypotension or shock c. cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP) d. evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer) e. acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain) 4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin) 5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes 6. Evidence of SARS-CoV-2 infection (any one of the following) a. positive SARS-CoV-2 RT-PCR b. positive serology c. positive antigen test d. contact with an individual with COVID-19	Required: all four criteria 1. Fever > 38°C 2. C-reactive protein > 100 mg/L 3. One or more of the following: a. cardiac involvement (any one of the following) : myocarditis/pericarditis/valvulitis : coronary artery involvement (echo) : cardiac failure/arrest b. gastrointestinal involvement (any one of the following) : vomiting/diarrhea : an acute abdomen : abnormal liver function (LFTs/clotting) c. respiratory failure (requiring any one of the following) : high flow and humidified oxygen (HFHO) : continuous positive airway pressure (CPAP) : ventilation. d. raised ferritin (> 500 ug/L) +/- raised D-dimers (> 2 times the upper limit of normal) 4. No pathogen (except SARS-CoV-2) or diagnosis (e.g., confirmed appendicitis)

MIS-C = multisystem inflammatory syndrome in children
PIMS-TS = pediatric inflammatory multisystem syndrome temporally associated with COVID-19
CDC = the Centers for Disease Control and Prevention
WHO = the World Health Organization
RCPCH = the Royal College of Pediatrics and Child Health
SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2
RT-PCR = reverse transcriptase polymerase chain reaction
COVID-19 = coronavirus disease 2019

MIS-C usually develops approximately 2 to 6 weeks after SARS-CoV-2 infection. Children may have been infected from an asymptomatic contact. Sixty percent of children had a positive SARS-CoV-2 serologic testing with negative PCR, 35% were positive on both tests, and 5% had both negative results. Approximately two-thirds of patients in the United States with MIS-C required admission to intensive care.[25, 26]

Children with MIS-C usually present with persistent fever (100.0%), gastrointestinal symptoms (87.0%) (e.g., vomiting, abdominal pain, diarrhea), mucocutaneous lesions (50.0%) (e.g., rash, conjunctivitis), and may experience neurological symptoms (29.0%) (e.g., headache, meningism). Approximately one-thirds of hospitalized children developed cardiac dysfunction, hypotension and shock. A minority of children (16.0%) were placed on extracorporeal membrane oxygen (ECMO) support.[25-28]

Laboratory abnormalities often include elevated inflammatory markers (e.g., CRP, ferritin, Interleukin-6) that have been shown to correlate with disease severity. Laboratory markers of myocardial injury (e.g., troponin, B-type natriuretic peptide; BNP or proBNP) have been observed in moderate to severe patients. The clinical features of MIS-C can be closely compared with that of severe acute COVID-19. Differences in the clinical features and laboratory results of MIS-C and severe acute COVID-19 are as shown in Table 2.[25-28]

Table 2 comparison of clinical and laboratory features of severe acute COVID-19 and MIS-C or PIMS-TS[25-28]

Characteristic	Severe acute COVID-19	MIS-C or PIMS-TS
Pre-existing medical conditions	+++	+
History of previous SARS-CoV-2 infection within 2 to 4 weeks	-	+++
Severe pulmonary involvement (pneumonia, ARDS)	+++	+
Shock and/or impaired cardiac function	+	+++
Abdominal pain	+	+++
Mucocutaneous involvement	+	+++
Neutrophilia	+	+++
Lymphopenia	++	+++
Thrombocytopenia	+	+++
Elevated CRP	++	+++
Elevated D-dimer	++	+++
Elevated ferritin	++	+++
SARS-CoV-2 antibody titers	+/-	+++
A positive RT-PCR for SARS-CoV-2	+++	+

+++ = very common, ++ = common, + = uncommon, +/- = rare, - = never, MIS-C = multisystem inflammatory syndrome in children, PIMS-TS = pediatric inflammatory multisystem syndrome temporally associated with COVID-19, SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2, COVID-19 = coronavirus disease 2019, ARDS = acute respiratory distress syndrome, CRP = C-reactive protein, RT-PCR= reverse transcriptase polymerase chain reaction.

Laboratory findings and imaging studies

Laboratory findings of children with COVID-19 are variable. Early in the course of the disease, the white blood cell count is often normal or decreased, the lymphocyte count is decreased, neutrophil counts are normal, inflammatory markers (including procalcitonin) are mildly elevated, and liver enzymes are slightly increased. Severe or critical cases of acute SARS-CoV-2 infection may be accompanied by an elevation in hepatic and muscular enzyme levels and high D-dimer levels. In particular, elevated inflammatory markers, neutrophilia, and lymphocytopenia may indicate MIS-C rather than acute SARS-CoV-2 infection.[25-28]

Chest imaging is not generally recommended for the diagnosis of COVID-19 in children unless they are at risk for disease progression, have clinical findings suggestive of lower respiratory tract involvement, or suffer from worsening respiratory function. Radiologic findings are variable and may be present before symptom development. Such findings include unilateral or bilateral infiltrates that are distributed towards the periphery of the lungs, subpleural ground-glass opacities, and consolidation on chest radiograph.

In a number of patients with COVID-19 pneumonia at the Pediatric Care Unit at Thammasat University Hospital, Thailand, the author found bilateral pneumonia in 100% (Figure 1) and ground-glass opacities in about 30% of chest radiographic images (Figure 2).

The American College of Radiology (ACR) recommends against using computed tomography (CT) for screening or a first-line test to diagnose COVID-19. It is recommended that CT should be reserved for the management of hospitalized patients. Findings on CT of the chest include ground-glass opacities/nodules, consolidation with a surrounding halo sign, bilateral or local patchy shadowing, and interstitial abnormalities.

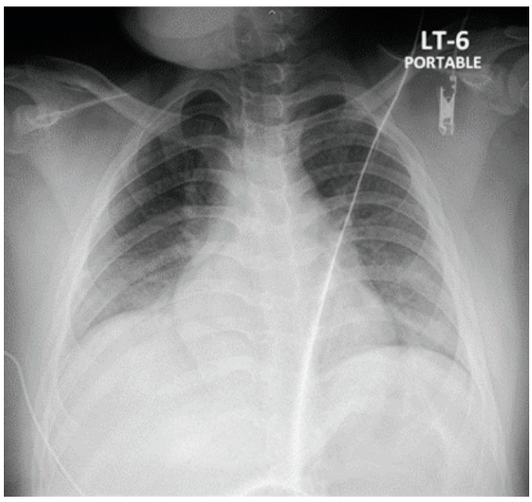

Figure 1 Chest X-ray shows bilateral infiltrates with ground-glass opacities and right lower lung atelectasis of a 12-year-old boy with COVID-19 pneumonia in a cohort ward at Thammasat University Hospital, Thailand (day 3 after onset of illness).

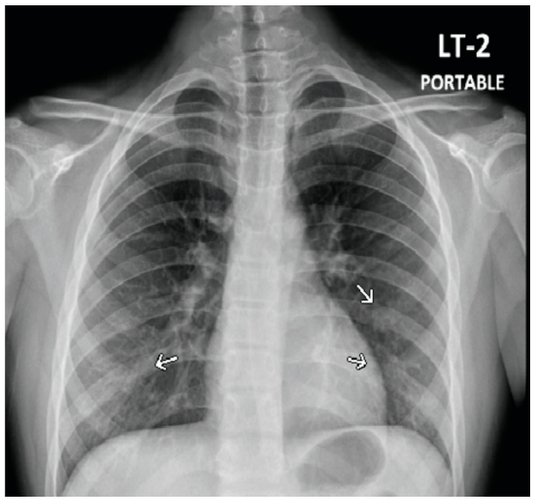

Figure 2 Chest X-ray shows faint ground-glass opacities both lower lungs of an 11-year -old boy with pneumonia in a cohort ward at Thammasat University Hospital, Thailand (day 2 after onset of illness).

Treatment

Currently, as of 21 April 2021, there are no antiviral agents which are approved by the United States Food and Drug Administration for treatment of COVID-19 in pediatric patients aged less than 12 years or weighing less than 40 kg. Supportive care is the mainstay of therapy for all pediatric patients with COVID-19. Oxygen therapy is recommended for patients with hypoxia. Antibiotics should generally be reserved for children with suspected or confirmed bacterial co-infections. The information about treatment regimens and the safety or efficacy of antiviral therapy in children with COVID-19 is extremely limited. A careful consideration of the risks and benefits of therapy should be assessed based on illness severity, age, and the presence of risk factors.

Remdesivir is a prodrug of an adenosine nucleotide analogue which binds to the viral RNA-dependent RNA polymerase and inhibits viral replication through premature termination of RNA transcription. Remdesivir is recommended for hospitalized pediatric patients (aged ≥ 16 years or age ≥ 12 years with risk factors for severe disease) who have an emergent or increasing need for oxygen supplementation. The safety and effectiveness of using remdesivir to treat COVID-19 have not been evaluated in pediatric patients aged < 12 years or weighing < 40 kg. The emergency use authorization (EUA) allows remdesivir therapy for hospitalized pediatric patients with a bodyweight ≥ 3.5 kg. A clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (Clinical Trials.gov Identifier NCT04431453).[29]

Remdesivir can cause gastrointestinal symptoms (e.g., nausea), elevated transaminase levels, an increase in prothrombin time, and hypersensitivity reactions. Liver function tests and prothrombin time should be obtained in all patients before and during administration of remdesivir as clinically indicated.[29]

Corticosteroids may prevent or mitigate a systemic inflammatory response that can potentially lead to lung injury and multisystem organ dysfunction. The safety and effectiveness of dexamethasone or other corticosteroids for treatment of pediatric patients have not been sufficiently evaluated in the setting of current or previous SARS-CoV-2 infection. Dexamethasone is believed to be an effective treatment for hospitalized pediatric patients who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[29]

There is limited data on the use of anti-SARS-CoV-2 monoclonal antibodies in pediatric patients. Based on studies on adults, bamlanivimab plus etesevimab or casirivimab plus imdevimab may be considered for non-hospitalized high-risk pediatric patients as defined by the EUA and should be used strictly with the approval of a pediatric infectious disease specialist on a case-by-case basis. There is insufficient data for baricitinib in combination with remdesivir or tocilizumab for use in the treatment of hospitalized pediatric patients. The use of COVID-19 convalescent plasma is also recommended against for pediatric patients with COVID-19 who are undergoing mechanical ventilation.[29]

Currently, there are only observational studies available to guide treatment for MIS-C. Treatment usually involves general supportive care and measures to reduce inflammation with the goal of protecting vital organs from permanent or life-threatening damage. Intravenous immunoglobulin (IVIG) and/or corticosteroids are recommended for the treatment MIS-C.[29] Other immunomodulatory agents (interleukin-1 and interleukin-6 inhibitors) are recommended as the second options. Low dose aspirin is recommended to decrease the risk of blood clots.[29]

In an observational study across 32 countries worldwide from June 2020 through February 2021, the study comprised 614 cases of children with MIS-C. The median age was 9.4 years old (IQR: 3.7 to 15.0 years). There was no evidence that recovery outcomes from MIS-C differed between primary treatment with IVIG alone, IVIG plus glucocorticoids, or glucocorticoids alone.[30] Therefore, randomized trials are needed to establish the most effective treatment of MIS-C.

Discussion

To date, data on COVID-19 in children and adolescents remain limited and the majority of children are either asymptomatic or have mild form of disease. Most pediatric COVID-19 patients in Thailand are a result of household exposure, usually with an adult index case. The role that children and adolescents play in transmission of this virus

remains unclear. Similar to adults, children with pre-existing medical conditions, as well as infants younger than 1 year of age, might be at increased risk for severe illness from COVID-19. The most common symptoms of COVID-19 in children are fever and cough. Gastrointestinal involvement (vomiting, diarrhea, etc.) is notably more common in children than in adults. Most cases of pediatric SARS-CoV-2 infections have mild abnormalities in white blood cell counts, with mildly elevated inflammatory markers and liver enzymes.

There is no evidence for the safety and efficacy of antiviral therapy for treatment of children with acute SARS-CoV-2 infection. The mainstay of treatment for all pediatric patients with acute COVID-19 is supportive care. Consideration of the risks and benefits of therapy with antiviral drugs, systemic glucocorticoids, anti-SARS-CoV-2 monoclonal antibodies, and immunomodulatory agents should be assessed based on illness severity, age, and the presence of risk factors. Antibiotics should not be used for children with COVID-19 if there is no evidence of bacterial coinfection.

The clinical features of MIS-C and severe acute COVID-19 often overlap. The difference in the patterns of clinical presentation and organ system involvement may help differentiate MIS-C from severe acute COVID-19. Most children with MIS-C are treated initially with both IVIG and glucocorticoids. The role of immunomodulatory agents (e.g., interleukin-1 and interleukin-6 inhibitors) in the treatment of MIS-C is limited and should be considered as the second line according to disease severity and markers of inflammation. Researchers around the world are working to find the best possible ways to understand, treat and prevent illness from SARS-CoV-2 infection.

In conclusion, most children infected with SARS-CoV-2 virus experience asymptomatic to mild illness and usually recover without special treatments. However, a small proportion develop severe disease. Currently, there are no antiviral treatment options or immunomodulatory drugs with proven efficacy for children. Future research is needed in order to establish reliable best practice guidelines on the treatment and prevention of COVID-19 in children.

Conflict of interest

The author declares that there are no conflict of interest.

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