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Review Article

Children in Coronaviruses' Wonderland: What Clinicians Need to Know

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Abstract. Human coronaviruses (HCoVs) commonly cause mild upper-respiratory tract illnesses but can lead to more severe and diffusive diseases. A variety of signs and symptoms may be present, and infections can range in severity from the common cold and sore throat to more serious laryngeal or tracheal infections, bronchitis, and pneumonia. Among the seven coronaviruses that affect humans (SARS)-CoV, the Middle East respiratory syndrome (MERS)-CoV, and the most recent coronavirus disease 2019 (COVID-19) represent potential life-threatening diseases worldwide. In adults, they may cause severe pneumonia that evolves in respiratory distress syndrome and multiorgan failure with a high mortality rate. Children appear to be less susceptible to develop severe clinical disease and present usually with mild and aspecific symptoms similar to other respiratory infections typical of childhood. However, some children, such as infants, adolescents, or those with underlying diseases may be more at-risk categories and require greater caution from clinicians. Available data on pediatric coronavirus infections are rare and scattered in the literature. The purpose of this review is to provide to clinicians a complete and updated panel useful to recognize and characterize the broad spectrum of clinical manifestations of coronavirus infections in the pediatric age.

Keywords: Children, Coronavirus, SARS, MERS, COVID-19.

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Introduction. Human coronaviruses (HCoVs) are a large group of viruses that commonly causes mild upper-respiratory tract illnesses but can lead to more severe and diffusive diseases. A variety of signs and symptoms may be present, and infections can range in severity from the common cold and sore throat to more serious laryngeal or tracheal infections, bronchitis, and pneumonia. Coronaviruses are known to circulate in many different animal species such as mammals and birds that can represent intermediate hosts and animal reservoirs for human infections. Coronaviruses, belonging to the family Coronaviridae, are enveloped, positive-sense, single-stranded RNA (ribonucleic acid) viruses so-called for their corona- or crown-like surface projections. They are further classified into four genera: Alpha- and Betacoronavirus (typical in bats, rodents, civets, and humans), Delta- and Gammacoronavirus (mainly detected in birds). Their typical sizes range from 80 to 120 nm. The genome encodes for two nonstructural replicase polyproteins and four or five

structural proteins, including the spike (S), envelope (E), membrane (M), nucleocapsid (N), and sometimes a hemagglutinin-esterase protein (HE). The HE protein binds to specific receptors and guides membrane fusion; the S protein is responsible for cell entry, the M and E proteins mediate viral assembly process, the inner N protein develops ribonucleoprotein complexes binding to viral RNA.[1-5]

To date, seven coronaviruses affect humans: in 1960s HCoV-229E and HCoV-OC43 were firstly reported;[6,7] HCoV-NL63 and HCoV-HKU1 were discovered subsequently in 2004 and 2005, respectively.[8,9] Additionally, three HCoVs responsible for outbreaks involving high case fatality rates have been detected in humans in the last two decades: the severe acute respiratory syndrome (SARS)-CoV, the Middle East respiratory syndrome (MERS)-CoV and the new coronavirus disease 2019 (COVID-19) (**Table 1**).

Table 1. Principal features of severe acute respiratory syndrome (SARS)-CoV, the Middle East respiratory syndrome (MERS)-CoV and the most recent coronavirus disease 2019 (COVID-19).

	SARS-CoV	**MERS-CoV**	**COVID-19**
Classification	beta-CoV	beta-CoV	beta-CoV
Incubation period	2-11 days	2-15 days	4-5 days
General mortality rate	10%	34%	2-3%
Mortality rate in children	0%	4 cases reported overall	2 cases reported overall
Symptoms in children	- Asymptomatic - Fever - Cough - Sore throat - Rhinorrhea - Malaise - Myalgia - Headache - Dyspnea - Tachypnea - Febrile seizures - Abdominal pain - Lack of appetite - Vomiting - Diarrhea - Respiratory distress	- Asymptomatic - Fever - Cough - Shortness of breath - Abdominal pain - Vomiting - Diarrhea - Dyspnea - Tachypnea - Respiratory distress - Multiorgan failure	- Asymptomatic - Fever - Cough - Nasal congestion - Runny nose - Conjunctivitis - Wheezing - Myalgia - Pharyngitis Expectoration - Nausea - Vomiting - Diarrhea - Dyspnea - Cyanosis - Poor feeding - Irritability - Decreased response - Respiratory distress - Multiorgan failure
Clinical examination	- Crackles - Signs of lung consolidation	- Bilateral rhonchi - Crackles	- Mostly negative for pulmonary signs - Rales - Thoracic retractions
Laboratory findings	- Lymphopenia - Elevation of transaminases - Elevation of lactic dehydrogenase - Elevation of creatine phosphokinase - Leucopoenia Thrombocytopenia - Elevation of D-dimer levels - Prolonged activated partial thromboplastin times	- Thrombocytopenia - Leukopenia - Elevation of creatinine - Prolonged prothrombin time	- Leukopenia - Lymphopenia - Thrombocytopenia - Elevation of transaminases Elevation of myoglobin - Elevation of muscle enzymes - Elevation of D-dimers
Children at-risk categories	- Younger than 1 year - Older than 12 years	With underlying comorbidities	- Younger than 1 year with underlying diseases

HCoV-OC43, HCoV-HKU1, SARS, MERS, and COVID-19 belong to beta coronaviruses while HCoV-229E, HCoV-NL63 belong to alphacoronaviruses.[10-12] HCoVs can infect all age groups. Generally, children appear to be less susceptible to coronavirus infections with milder symptoms and a more favorable clinical course than the adult population. In addition, coronavirus infections in children often have peculiar clinical features that differentiate them from those of adults. Available data on pediatric coronavirus infections are scattered in the literature. The purpose of this review is to provide to clinicians a complete and updated panel useful to recognize and characterize the broad spectrum of clinical manifestations of coronavirus infections in the pediatric age.

Endemic Coronavirus in Children. Before SARS and MERS epidemics and the recent COVID-19 pandemic, coronaviruses used to be considered commonly responsible for mild respiratory diseases as the common cold. Generally, their median incubation period is three days. Respiratory droplets are the usual route of transmission. Hand contamination and transferal from surfaces and objects are also implicated.[13]Children under the age of 3 years or with cardiac disease appear most frequently affected.[14-16]

The most common symptoms are rhinorrhea, sore throat, fever, and dry cough, but there is increasing evidence that coronaviruses are also important causes of more severe respiratory diseases including bronchitis, bronchiolitis, asthma exacerbations and pneumonia in children.[17]

About the detection frequency, the most common strains in alternate seasons are HCoV-OC43 and HCoV-229E followed by HCoV-NL63, and HCoV-HKU1.[18] Common circulating HCoVs can be isolated from 5% to 13% of children hospitalized for acute respiratory tract infections.[19-22]

Frequently, respiratory pediatric coronavirus infections are associated with multiple infections caused by other common viruses, but the clinical significance of these coinfections is unclear. Coinfections between coronaviruses and other respiratory viruses such as respiratory syncytial virus, human metapneumovirus, adenovirus, and influenza or parainfluenza viruses have been reported in up to 40% of cases.[23-30]

Especially in younger children, the virus most frequently associated with human coronaviruses infections is a respiratory syncytial virus (RSV) probably because of a season overlapping.[31,32] Among the respiratory infections caused by coronaviruses in children, a strong association between HCoV-NL63 and croup is also highlighted[33,] whereas HCoV-NL63 and HCoV- HKU1 appear associated with bronchiolitis and wheezing.[34,35] Although the possible pathogenic role of coronaviruses in pediatric respiratory infections has been hypothesized, and this has not yet been confirmed. In several studies a similar prevalence in the detection of HCoVs in patients with respiratory symptoms compared to healthy children has been found.[36-39]Moreover, patients with other underlying medical conditions or immunocompromised appear more susceptible to developing severe infections than healthy patients.[40-43] Additionally, human coronaviruses are responsible for other common childhood diseases such as acute otitis media[44-47], asthma exacerbations[48,] and conjunctivitis[8]. They have also been involved in nosocomial infections, especially in the neonatal intensive care units (NICU). Gagneur et al. in a prospective study determined the incidence of HCoV-related respiratory infections in newborns hospitalized in a NICU. Among 64 neonates, seven positive nasal samples for HCoVs (11%) were detected. All children were symptomatic. Oxygen and ventilatory support were frequently needed.[49] Sizun et al. evaluated the clinical role of coronaviruses respiratory infections in premature newborns. All premature infants infected had severe respiratory symptoms, including bradycardia, apnea, and hypoxemia, while chest X-ray revealed diffuse infiltrates.[50] It has also been shown that coronavirus infections are not only responsible for respiratory symptoms but can also affect other organs and systems in children. Several studies have also reported that respiratory symptoms caused by coronavirus infection may be associated with central nervous system (CNS) involvement. HCoVs have an intrinsic capacity to affect neurons and diffuse centrifugally from CNS via the transneuronal route.[51,52]

Among neurological symptoms, febrile seizures, convulsions, loss of consciousness, encephalomyelitis, and encephalitis have been reported.[53-55] Primarily in 1980, the viral genome was detected post-mortem in the cerebrospinal fluid of two patients with multiple sclerosis (MS).[56] Subsequently, the HCoVs neuroinvasion capacity was confirmed in a large panel of human brain autopsy samples affected by MS and other neurological diseases.[57] In 2004, Yeah et al. reported a case of a child with acute disseminated encephalomyelitis in which the genome of HCoV-OC43 in cerebrospinal fluid was detected.[55] In 2016, Li et al. demonstrated the presence of anti-CoV IgM (immunoglobulin M) in 22 (12%) of 183 children with acute encephalitis.[58] In 2017, a prospective study on 192 children with febrile seizures demonstrated that coronaviruses were frequently detected.[59]

Additionally, HCoVs have been implicated as possible causes of many gastrointestinal disorders in children, and gastrointestinal symptoms have been reported in several studies in more than 50% of pediatric patients[28,60,61]. Firstly, HCoVs could be associated with neonatal necrotizing enterocolitis[62]. Furthermore, diarrhea, vomiting or other gastrointestinal symptoms have been associated with coronavirus infections.[63-65] Besides the demonstrated finding in respiratory swabs,

all HCoVs can also be detected in stool samples of patients affected by gastroenteritis.[60,66] Moreover, most of the HCoVs found were coinfections with well-known gastroenteric viruses, including norovirus and rotavirus. HCoVs may also be found occasionally in healthy children's stool samples.[67] Although HCoVs have always been associated with respiratory symptoms, these findings suggest that other systems may also be involved in children. The absence of serious symptoms may not be coupled with serological negativity. Therefore, these viruses should be considered in the differential diagnoses of most of the common diseases of childhood.

SARS in Children. The 2002–2004 severe acute respiratory syndrome outbreak was a viral respiratory illness caused by SARS-CoV. The outbreak firstly emerged in the southern Chinese province of Guangdong in November 2002 and[68] then spread to 29 countries with 8,096 people infected and 774 died.[69]

The SARS global outbreak was contained in July 2003. Since 2004, there have not been any known cases of SARS reported anywhere in the world.[70] Probably, civet cats or bats could be the initial step of the transmission to humans. Humans to humans infection occurs by respiratory droplets or direct contact. Healthcare or household contacts are critical routes of transmission.[71,72]

SARS-CoV infection cases were classified by the World Health Organization (WHO) into suspected, probable, and confirmed (**Table 2**).[73]

The median incubation period ranges between 2-11 days. SARS causes atypical pneumonia, which may progress to respiratory failure. Symptoms include fever, malaise, myalgia, headache, diarrhea, and rigors. Adults are more likely to develop severe illness characterized by dyspnea, lymphopenia, acute respiratory distress syndrome (ARDS), and a fatal clinical course in 10% of cases. The exact number of children affected by SARS worldwide is unknown. However, children appear to be less susceptible to SARS with a lower incidence of the disease and no reported mortality. The majority of children had documented exposure to adults with SARS, usually a family member. Most infected children had previously attended school, but the spread of the infection in the school environment has not been demonstrated, and this could probably be linked to lower infectiousness of the virus among children.[74,75] Children have less severe symptoms than adults, and they rarely need intensive care. However, subclinical and asymptomatic infections appear uncommon. Most children reported worldwide were healthy, previously and underlying conditions were infrequently reported.[75-77] Usually, children require hospitalization after 3–4 days the onset of symptoms: fever (90-100%), dry cough (43-80%), sore throat (5-30%), rhinorrhea (33-60%), malaise and myalgia (10-40%), headache (14-40%) are common. Dyspnea, tachypnea, and febrile seizures are infrequent. Aspecific gastrointestinal symptoms, including abdominal pain, appetite lack, vomiting, and diarrhea, have been reported. Physical examination at presentation is negative in the majority of children, and chest auscultation does not reveal significant findings. Moreover, sometimes crackles or signs of lung consolidation can be detected. As well as the clinical examination, laboratory findings are not specific in children with SARS and can be confused with those of other respiratory infections typical of childhood. Commonly lymphopenia, the elevation of transaminases, lactic dehydrogenase, and creatine phosphokinase are detected. Other hematological abnormalities such as leukopenia, thrombocytopenia, the elevation of D-dimer levels and mildly prolonged activated partial thromboplastin times are also observed.[78-80] Circulating interleukin (IL)-1β levels might be increased, resulting in caspase-1-dependent pathway activation responsible for an exaggerated and persistent inflammatory response and the consequent respiratory failure in severe cases.[81] In children, radiological findings are nonspecific and similar to other viral respiratory abnormalities.

Table 2. World Health Organization (WHO) Case Definitions for Surveillance of Severe Acute Respiratory Syndrome (SARS).

Suspect case
1) A person presenting after November 1 2002 with history of: - high fever (>38 °C) **AND** - cough or breathing difficulty **AND** one or more of the following exposures during the 10 days prior to onset of symptoms: - close contact with a person who is a suspect or probable case of SARS cough or breathing difficulty - history of travel, to an area with recent local transmission of SARS - residing in an area with recent local transmission of SARS
Probable case
1) A suspect case with radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome (RDS) on chest X-ray (CXR). 2) A suspect case of SARS that is positive for SARS coronavirus by one or more assays. See Use of laboratory methods for SARS diagnosis. 3) A suspect case with autopsy findings consistent with the pathology of RDS without an identifiable cause.

Commonly, the chest X-ray shows ground-glass opacity or focal consolidation. Linear atelectasis and peribronchial thickening have also been reported. Computed tomography (CT) shows more extensive airspace consolidation and ground-glass attenuation than chest X-ray, but it is performed in selective cases in pediatric age.[78-80,82] Usually, the clinical course is less severe in children compared to adults, and few patients require oxygen supplementation and assisted ventilation but preterm newborns, children younger than one year and older than 12 years of age have more severe symptoms and are likely to develop respiratory distress.[78-80] In pediatric age, SARS infection commonly has a "biphasic" pattern. The first stage of the disease is characterized by virus replication and clinically by the onset of symptoms. The second phase is characterized by pulmonary involvement, which is typically less severe in children than in adults. Most children will become afebrile within seven days, and they usually do not progress to respiratory distress, the adult third phase, that is only reported in a minimal number of cases, commonly among teenagers.[83,84]

In pregnant women, SARS infection is associated with a high incidence of spontaneous miscarriage, prematurity, and intrauterine growth retardation (IUGR). The increased morbidities during pregnancy are likely to be due to the hypoxic state and circulatory insufficiency that worsen placental blood flow and cause miscarriage or IUGR. Significantly, among pregnant women, mortality is 25%.[85] However, perinatal SARS infections have not been documented. In none infants born from pregnant women affected, real-time PCR (RT-PCR) assays and viral cultures conducted on neonatal blood, body secretions and amniotic fluid were positive for SARS. In infants, no congenital malformations have been reported. However, in premature newborns, severe gastrointestinal complications such as jejunal perforation and necrotizing enterocolitis have been described[86]. However, it is not known if these neonatal morbidities are related to prematurity or if maternal infection is a factor that increases their incidence.

It is unclear why children develop a less serious disease than adults. Recurrent viral respiratory infections typical of the pediatric age could be helpful to the immune system in promptly recognizing and defeating new viral pathogens. Furthermore, the immaturity of the immune system could be protective because the inflammatory cascade that causes respiratory failure in adults is more difficult to activate. Additionally, children generally have fewer comorbidities than adults.

Children recovered quickly from SARS. Li et al. assessed the radiological and clinical outcomes of forty-seven children with SARS after 6 months from diagnosis. All children were asymptomatic while mild pulmonary abnormalities including ground-glass opacities and air trappings were found at CT in sixteen patients.[87]

Although clinical and laboratory findings of SARS are aspecific in children, certain features can be useful to distinguish SARS from other respiratory viral infections. Children with SARS have a lower incidence of rhinorrhea and productive cough and higher incidence of monocytopenia than children with influenza.[88] Additionally, serum lactate dehydrogenase in the presence of a low neutrophil count and low serum creatine phosphokinase could be suggestive of SARS infection.[89]

SARS infections in children appear to be a relatively mild and aspecific disease, and the diagnosis should be accompanied by laboratory assessment. Although infants and teenagers are more likely to have a worse clinical course, usually, all pediatric patients recover entirely without significant long-term sequelae.

MERS in Children. The Middle East respiratory syndrome (MERS) is a viral respiratory infection caused by the MERS-coronavirus (MERS-CoV). The first identified case occurred in 2012 in Saudi Arabia.[11,90] Subsequently, a total of 2494 confirmed cases of MERS, including 858 associated deaths with a case–fatality rate of 34% were reported globally; the majority of these cases were reported from Arabian Peninsula, and in the Middle East.[91] Currently, MERS is an extremely rare disease: in the last year MERS was signaled only in Saudi Arabia.[92]

MERS-CoV is a zoonotic virus: dromedary camels are the primary reservoir hosts. Humans are infected through contact with infected dromedary camels, animal products, or humans, especially among close contact between family members and health care workers. MERS-CoV infection cases were classified by the WHO into suspected, probable, and confirmed (**Table 3**).[93] Usually, the mean incubation period ranges from 2 to 15 days. Clinical severity of the disease varies from asymptomatic to fatal forms, and the impact of asymptomatic spread is unclear. The infection can cause severe pneumonia, which may progress to ARDS, respiratory failure, and death, particularly in older people, immunocompromised patients, and those with chronic diseases. Common symptoms include fever, cough, and shortness of breath. Gastrointestinal symptoms (including diarrhea, vomiting, abdominal pain), pericarditis, septic shock and disseminated intravascular coagulation have been reported.[94-97] Children appear to be less susceptible to MERS-CoV infection, and pediatric cases described in the literature are rare with a low proportion (0.1%–4%) of infected children.[98-102] Fagbo et al. demonstrated in a study conducted on 2235 hospitalized children with respiratory infections that all patients tested were harmful to MERS-CoV.[102] Khuri-Bulos et al. confirmed the low incidence of MERS-CoV infection in childhood in a prospective study conducted in children <2 years of

Table 3. World Health Organization (WHO) Case Definitions for Surveillance of Middle East respiratory syndrome (MERS).

Confirmed case
A person with laboratory confirmation of MERS-CoV infection irrespective of clinical signs and symptoms.
Probable case
- A febrile acute respiratory illness with: - Clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome) **AND** - Direct epidemiologic link with a laboratory-confirmed MERS-CoV case **AND** - Testing for MERS-CoV is unavailable, negative on a single inadequate specimen or inconclusive - A febrile acute respiratory illness with: - Clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome) that cannot be explained fully by any other etiology **AND** - The person resides or travelled in the Middle East, or in countries where MERS-CoV is known to be circulating in dromedary camels or where human infections have recently occurred **AND** - Testing for MERS-CoV is inconclusive - An acute febrile respiratory illness of any severity: **AND** - Direct epidemiologic link with a confirmed MERS-CoV case **AND** - Testing for MERS-CoV is inconclusive.

age hospitalized with acute respiratory symptoms and/or fever. Among these, none of 474 children tested resulted positive for MERS-CoV.

[103] In pediatric age, few cases of MERS CoV infection have been described. Most of the children were asymptomatic and positive during routine screening of MERS-CoV. Al-Tawfiq et al. reported a total of 31 pediatric MERS-CoV cases with a mean age of 10 years. Overall, 42% were asymptomatic, while in symptomatic cases, fever and mild respiratory symptoms were common.[104] Subsequently, Alfaraj et al. reported a total of 7 pediatric MERS-CoV cases with a mean age of 8 years. In this case series, common symptoms were fever (57%), cough (14%), shortness of breath (14%), and gastrointestinal symptoms (28%). Two (28.6%) patients had abnormal chest radiographic findings with bilateral infiltration, one (14.3%) required ventilatory support, and two (28.6%) required supplemental oxygen.[99] Four with underlying conditions (cystic fibrosis, nephrotic syndrome, craniopharyngioma, and a right ventricular tumor) had a fatal outcome. These children developed a critical form of MERS infection complicated by respiratory and multiorgan failure. Frequently, clinical examination revealed bilateral rhonchi and crackles while chest X-ray showed diffuse bilateral infiltrates, ground-glass opacification and pleural effusion.[105-109] Thrombocytopenia, leukopenia, increased creatinine and prolonged prothrombin time were the only laboratory findings reported in literature.[99,105,106]

MERS-CoV in children is less frequent than adults and appears to be associated with low mortality unless the patients have underlying comorbidities. Few cases of MERS-CoV have been reported during pregnancy. A pregnant woman, aged 39 years, had a stillbirth at approximately five months of gestation[110] and another woman gave birth to a healthy term baby, but she died after delivery.[107]

In conclusion, although MERS-CoV represents a clinical concern for the adult population with a high fatality rate, it remains a sporadic disease in childhood. Clinicians should learn to recognize and suspect MERS-CoV infection, as the symptoms and signs are nonspecific, based on epidemiological criteria to avoid the spread of the disease in patients at higher risk of worse clinical course.

COVID-19 in Children. The outbreak of COVID-19 infection (coronavirus disease 2019; previously 2019-nCoV) began in Wuhan, Hubei, China, in December 2019, which then spread rapidly to other provinces of China and around the world.[111] On January 30, 2020, the WHO declared the outbreak of a Public Health Emergency of International Concern and, on March 11, 2020, a pandemic.[112] As of June 5, 2020, 188 other countries and regions, with more than 6.669.358 confirmed cases, are declared. Among the confirmed cases, 2.904.828 are recovered, and 393.205 died.[113] Recent genetic analysis suggests the COVID-19 emerged from an animal source. The full genome sequences showed high homology between COVID-19, bat coronavirus, and pangolin coronavirus, but further genetic study is required.

Moreover, according to current evidence, the principal route of transmission of COVID-19 is from

human to human.[114,115] COVID-19 spread between people through respiratory droplets and contact routes. Droplet transmission occurs when there is close contact with a person with respiratory symptoms such as coughing or sneezing, who may spread potentially infectious droplets. Transmission may also occur by direct contact with infected persons and indirect contact with infected surfaces or objects. COVID-19 can persist on inanimate objects for days but can be efficiently inactivated by common disinfectants. Airborne transmission may be possible when a high risk of aerosolization procedures are performed, such as endotracheal intubation and bronchoscopy. The virus is also detected in stool specimens, and consequently, the feco-oral transmission is also hypothesized.[116-119] The high transmissibility of COVID-19 may be explained by its demonstrated presence in the upper respiratory tract of asymptomatic or presymptomatic subjects with viral loads comparable to those detected from symptomatic patients. The real proportion of asymptomatic cases is unclear, ranging from 1% to 78% in different studies. Transmission from asymptomatic patients infected with COVID-19 most likely contributed to the rapid and extensive spread of pandemic but further studies are needed to more accurately estimate the proportion of genuinely asymptomatic cases and their risk of transmission.[120-126]

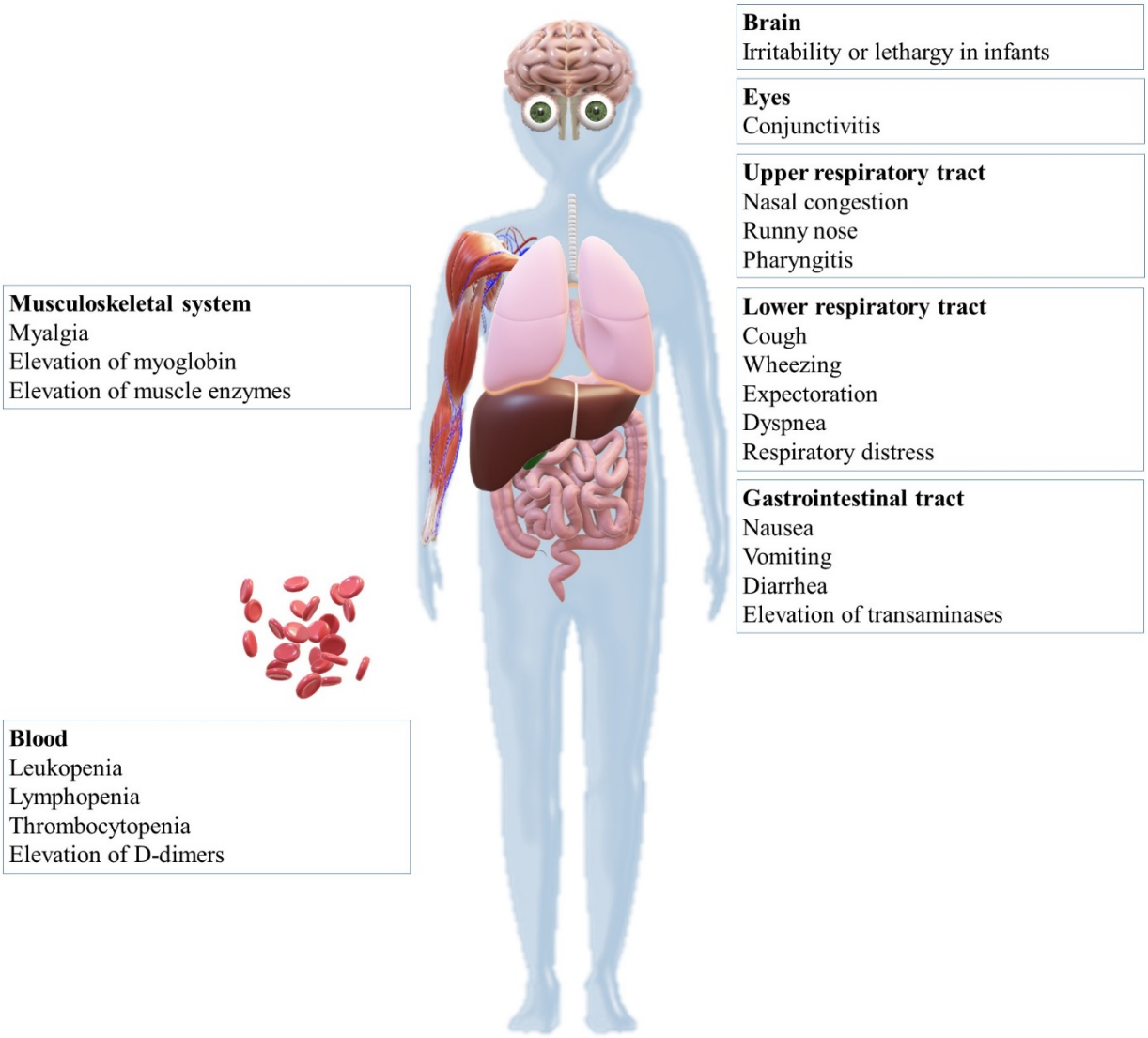
COVID-19 has been reported among all age groups. The median incubation period of COVID-19 infection is 4-5 days with a range up to 24 days.[119,127]
COVID-19 infection case is classified by the WHO into suspected, probable, and confirmed (**Table 4**).[128] Clinical severity of the infection varies, ranging from asymptomatic forms to critical diseases. Common symptoms are fever, dry cough, malaise, lethargy, shortness of breath, sore throat, and myalgia. Headache, conjunctivitis, productive cough, and diarrhea are also described. Mild forms present as a common cold, and severe cases may worsen in pneumonia that may evolve to ARDS, shock, and multiple organ dysfunction. More severe clinical pictures are associated with stronger immune response and with the production of proinflammatory cytokines, including IL-2, IL-7, IL-10, and tumor necrosis factor- α (TNF-α). Adverse outcomes are common in elderly patients and those with underlying diseases. The need for intensive care admission is in 25–30% of patients. The fatality rate is estimated to range between 2 and 3%.[129-133] About 2% of COVID-19 confirmed cases are children.[124-134,135]

Generally, children appear to be less likely to develop a severe form of COVID-19 infection, and commonly they have a mild clinical course with a good prognosis. Few children may evolve into lower respiratory infections. Probable reasons include having an immune system still immature, healthier respiratory tract, and less underlying conditions than adults.[136] Most of them have an infected contact history with family members. Moreover, children, especially those with asymptomatic or milder form, may represent significant spreaders. Pediatric patients appear to be likely as adults to become infected but are less likely to develop symptoms. However, future studies are needed to understand the role of children in the transmission of the virus.[137-139] Current researches show that the median age of infection in pediatric cases is 6-7 years. In symptomatic cases, symptoms are typical of acute

Table 4. World Health Organization (WHO) Case Definitions for Surveillance of COVID-19.

Confirmed case
A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.
Suspect case - A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath) **AND** - a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset **OR** - A patient with any acute respiratory illness **AND** - having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset **OR** - patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath) **AND** - requiring hospitalization **AND** - In the absence of an alternative diagnosis that fully explains the clinical presentation
Probable case - A suspect case for whom testing for the COVID-19 virus is inconclusive **OR** - A suspect case for whom testing could not be performed for any reason

Figure 1. Symptoms of COVID-19 infection in pediatric age.



respiratory infections and frequently included fever (59%) and cough (46%), which may be accompanied by nasal congestion, runny nose, conjunctivitis, pharyngitis, wheezing, myalgia, and expectoration. Few children have an atypical presentation with gastrointestinal manifestations, including nausea, vomiting, and diarrhea. Low oxygen saturation of less than 92%, dyspnea, cyanosis, and poor feeding, are less common than adults. Among infants, symptoms such as irritability, reduced response, and poor feeding could be the main signs of infection. Family clustering occurred for all infected infants. Rarely infants require intensive care or mechanical ventilation or have any severe complications. Common symptoms of pediatric age are summarized in **figure 1**. The majority of children recovers 1–2 weeks after the onset of the disease.

Regarding biochemical results, leukopenia and lymphopenia are frequent in children. Elevation of transaminases, myoglobin, muscle enzymes, and D-dimers might be seen in severe cases.[140-146] Dong et al. reported that 94% of 2143 pediatric patients affected by COVID-19 developed an asymptomatic, mild, or moderate form of infection. A severe disease characterized by dyspnea, central cyanosis, and oxygen saturation of less than 92% was reported in 5% of cases. A critical disease characterized by ARDS and multiple organs failure was reported in less than 1% of cases.[141] The prevalence of severe and critical disease appears higher in younger children, particularly in children aged <1-year-old and in children with underlying diseases. To date, death was an uncommon event reported in one 10-month-old infant with intussusception and multiorgan failure and in one 14-year-old boy.[145,147]

Other systemic symptoms appear to be related to the infection, but their link has not yet been demonstrated. Since the outbreak of the pandemic, a large number of rashes, urticaria, and vasculitis affecting hands and feet of healthy children and adolescents have been reported

as well as itching, burning, difficulty in joint movements and pain.[142]

Recently, the relationship between COVID-19 infection and the development of cardiac diseases in children has been hypothesized. Belhadjer et al. have reported a large number of febrile children resulted positive for COVID-19 admitted in intensive care units for acute heart failure associated with a multisystem inflammatory state. In most of the children, clinical features appeared similar to those of Kawasaki syndrome: lasting fever, cutaneous rash, lymphadenopathy, persistent activation of systemic inflammation and positive response to intravenous immunoglobulin.[148] Similar clinical features have subsequently been reported in children with COVID-19 positive serology.[149,150]

As in COVID-19 infection, Kawasaki syndrome is triggered by proinflammatory cascade activated primarily by innate immunity response. However, further studies are needed to establish the real pathogenetic relationship between emerging COVID-19 and Kawasaki-like syndromes.[151]

Dufort et al. [152] have recently reported the emergence of a multisystem inflammatory syndrome in children in New York State coincidental with widespread SARS-CoV-2 transmission, which can better clarify the relationship between Kawasaki Disease and COVID-19. Among 191 children admitted to the New York hospitals for multisystem inflammatory syndrome in children (MIS-C), 95 patients had a laboratory-confirmed acute or recent severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection. This hyperinflammatory syndrome manifested with dermatologic, mucocutaneous, and gastrointestinal features associated with cardiac dysfunction. Of these 95 patients, a total of 36 patients (37%) received a diagnosis of Kawasaki's disease or atypical (or incomplete) Kawasaki's disease; 7 of the 9 patients with coronary-artery aneurysms also received a diagnosis of Kawasaki's disease.[152]

COVID-19 infection may also trigger the onset of other immune-mediated diseases such as immune thrombocytopenia,[153-156] Evans syndrome,[157] and autoimmune hemolytic anemia.[158]

Among radiological findings, ground-glass opacity, mono or bilateral infiltrates, mesh shadows, and tiny nodules are frequently detected. In severe cases, radiological alterations are diffused, presenting as a "white lung." However, radiologic evidence of pneumonia might be absent in 15-20% of children.[139,140, 159-163] In selected cases, lung ultrasound might be useful in the managing and follow-up of COVID-19 infection. This radiological technique can precociously identify abnormalities including small pleural effusion and subpleural consolidation and appear more available then X-ray and CT.[164-165]

Clinical examination appears mostly negative for pulmonary signs, and in rare cases, rales and thoracic retractions have been reported.[161] Whether pregnant women and children born to affected mothers are more likely to have a worse outcome is currently unclear. Maternal-infant vertical transmission has not been documented. Amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples from newborns delivered by infected women were tested for COVID-19, and all samples tested negative.[166] Data on the maternal and perinatal outcomes of pregnant women infected with COVID-19 is limited. Most pregnant women with COVID-19 present with fever and coughing. Severe and critical maternal symptomatology have also been reported, but no women died. The most common adverse pregnancy outcome is preterm birth, occurring in 41% of cases while the rate of perinatal death is 7%, including one case of stillbirth and one neonatal death. There is no data on miscarriage for COVID-19 occurring during the first trimester. In more than a third of cases, fetal distress and frequent admission neonatal intensive care units have been reported.[166,167] Rarely, cases of COVID-19 positivity in newborns have been reported. Common symptoms are fever, cough, lethargy, and vomiting milk. Mottled skin and moderate respiratory distress presented with tachycardia, tachypnoea, subcostal retractions, and low oxygen saturation are also described in newborn babies.[169-173] Although it can be severe in some cases, compared with SARS-CoV and MERS-CoV, COVID-19 causes less severe disease in children. A recent meta-analysis shows that children infected with COVID-19 have less fever than that other epidemic HCoVs.[174]

Despite the rapid worldwide spread of COVID-19 infection, additional data are needed to define the severity of the disease in children. The severity of the symptoms and the mortality rate will be better assessed in the future.

Diagnosis and Treatment of HCoVs Infections. Differential diagnosis with common viral respiratory infections of childhood, such as influenza virus, adenovirus, respiratory syncytial virus, and metapneumovirus, should be considered. In the diagnosis of suspected cases, epidemiological and clinical criteria must be assessed.[73,93,138]

RT-PCR represents the gold standard to confirm the diagnosis of HCoVs infections performed on samples of respiratory secretions.[175-181] The viral load is higher in lower respiratory tract secretion samples than in upper respiratory tract samples.

Therefore, suspected cases resulted in firstly negative could be re-tested with a second swab, better if with a low respiratory sampling is performed as proved for SARS and MERS infection.[182,183]

Currently, few data have been published about the sensitivity and specificity of RT-PCR nasopharyngeal swabs for COVID-19. In vitro analyses suggest that the RT-PCR test is highly specific and sensitive.[184] In vivo,

sensitivity is estimated to be higher than 70% but seems to be lower for "mild" cases while specificity is close to 100%.[185,186]

Accuracy of RT-PCR swabs in clinical practice differs depending on the site and quality of the sample. Taking swabs from children may be more difficult given the intrusive nature of the procedure and further reduce the specificity and sensitivity of the test. RT-PCR of bronchoalveolar lavage fluid appears the most accurate technique of virologic confirmation, but it may not always be easily collected in all patients, especially in pediatric age. Although a negative test cannot currently rule out the disease, further studies are needed to define the exact specificity and sensitivity of RT-PCR nasopharyngeal swabs.[187,188]

Moreover, RT-PCR appears to be useful in virus detection on stool samples.[116] To date, serology is not considered a diagnostic method. Although most patients with COVID-19 appear positive for immunoglobulin-G (IgG) within 19 days while IgM reaches a peak 20–22 days after symptom onset, the serological response is not useful for early individuation of positive patients.[189] Additionally, numerous cross-reactions occur between COVID-19 and common HCoVs[190,] and protective immunity against COVID-19 is not proved. Despite its potential role in supporting RT-PCR in the diagnosis of COVID-19, the clinical and immunological meaning of serology is still unclear.[191]

The spread of the infection can be prevented if children and family members were educated about proper hygienic practices and infection control measures, including regular hand washing, cover the mouth with napkin or towel when coughing or sneezing, avoid crowded places and contact with sick people. Children with HCoVs should receive early supportive therapy and continuous monitoring. Additional oxygen, caloric, and hydro electrolytic support should be performed if necessary. Frequent checks of oxygen saturation and hematological, urinary, and biochemical parameters, including liver, kidney, myocardial enzymes, and coagulation parameters should be analyzed. Finally, blood gas analysis and radiological diagnostics of the chest should be done when necessary. This strategy could be useful in the prevention of ARDS, multiorgan failure, and other nosocomial infections possibly treated, if bacterial, with appropriate antibiotics. In critical cases, mechanical ventilation with endotracheal intubation and other more invasive interventions, such as blood purification and extracorporeal membrane oxygenation (EMCO), should be adopted. Additionally, the use of antiviral drugs in children with severe HCoVs infections may help to reduce viral load and the duration of symptoms. However, their safety and real effectiveness have not yet been proven. Interferon alfa and beta, corticosteroids, lopinavir/ritonavir, and ribavirin, were used in the treatment of SARS-CoV and MERS- CoV in adults and children.[75, 76, 78, 192] However, ribavirin can cause hemolytic anemia and liver dysfunction, as well as corticosteroids, increase the risk of iatrogenic immune immunosuppression.[193] To date, there is no evidence regarding the management and treatment of COVID-19 infection in children. In addition to supportive therapy, the use of nebulized interferon-alpha-2b and oral lopinavir/ritonavir together with corticosteroids for complications and hydroxychloroquine or intravenous immunoglobulin for severe cases have been suggested.[145, 194,] Recently, a position paper of the Italian Society of Pediatric Infectious Disease on the treatment of children with COVID-19 infection has been published.[195] In asymptomatic or mild cases, only antipyretic therapy is recommended. In severe or critical cases, the use of hydroxychloroquine ± azithromycin or lopinavir/ritonavir must be considered. Immunomodulating therapy with methylprednisolone or tocilizumab or anakinra must be considered in case of the simultaneous presence of ARDS or progressive deterioration of respiratory function, the elevation of proinflammatory biomarkers and an interval of at least seven days from symptoms onset. Supportive therapy should include antipyretic therapy, inhalation therapy with topical steroids and/or bronchodilators and venous thromboembolism prophylaxis therapy.[196-203]

Discharge from the hospital is recommended when the patient is without fever for almost three days, respiratory symptoms have improved, and RT-PCR samples are negative.[195]

Conclusions. Most cases of HCoVs infection in children have clinically mild symptoms and a relatively short time to resolution. Children seem to have a better prognosis compared to adults, and death is a sporadic event. However, some children, such as infants, adolescents, or those with underlying diseases may be more at-risk categories and require greater caution from clinicians. Learning to recognize pediatric clinical presentations often indefinite or similar to other typical infections of this age, allows clinicians to perform a correct and early diagnosis and prevent the spread of infections in the general population. Furthermore, the psychological and social impact of the pandemic outbreak should be considered, especially in the pediatric age. Moreover, we think it is necessary to implement innovative clinical tools, such as narrative medicine, to recognize the burden of disease in children and caregivers. [201-204]

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