

Review Article

CHARACTERISTICS and considerations in the medical treatment of COVID-19 in children

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It is rare for children to be in serious condition or die from coronavirus disease 2019 (COVID-19) caused by the 2019 novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) except for those with underlying diseases such as chronic lung disease (including asthma), cardiovascular disease, and immunosuppressive disease. Recently, patients with hyperinflammatory shock have been identified among children who are confirmed to have or are suspected of having SARS-CoV-2 infection. The presenting signs and symptoms are characterized by prolonged fever, abdominal pain, and cardiac involvement without any signs of pneumonia on chest computed tomography. However, it is uncertain at this time whether SARS-CoV-2 infection affects this syndrome. Compared with adults, quite a few children are asymptomatic even when infected with SARS-CoV-2, which could make these children serious sources of infection at home or in medical institutions. Considering these characteristics, it is important to take appropriate precautions during medical examinations and perform infection control in emergency departments to save the lives of both the children and adult patients. Most healthy children are suffering from huge stress due to restrictions against going outside and school closures as social means to control infection. It is possible that children are socially isolated when they come to the emergency department, and they might require mental or social support even if they are only complaining about their physical condition. Health-care providers are required to examine the children's circumstances carefully and cooperate with workers in other professions appropriately.

Key words: Abuse, asymptomatic, Kawasaki disease, nosocomial infection control, SARS-CoV-2

INTRODUCTION

IN DECEMBER 2019, an infection caused by a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China. The infection was named novel coronavirus disease 2019 (COVID-19). Later, SARS-CoV-2 infection spread throughout the world; early reports confirmed few infections in pediatric patients, whereas more than half of those infected were over 60 years of age. Therefore, it was pointed out that children may not be infected with SARS-CoV-2 or that they may experience very slight symptoms.¹ Since then, there have been reports of pathological conditions and epidemiology in children, and the characteristics of COVID-19 in children have become clear.

We summarized the characteristics of COVID-19 in children and the important points in pediatric emergency care during the COVID-19 pandemic based on literature and epidemiological data published as of June 10, 2020. We searched for papers on the PubMed web database as of June 10, 2020, using the search terms COVID-19, SARS-CoV-2, and children, and investigated survey reports, systematic reviews, and case reports that seemed to be clinically significant. For case reports, those with larger numbers of cases were prioritized and adopted. In addition, in view of the fact that social policies are changing over time, epidemiologic data published by public institutions such as the Japanese Ministry of Health, Labor and Welfare and the World Health Organization, and guidelines posted on the websites of related academic societies such as the Japanese Association for

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Acute Medicine and the Japan Pediatric Society were also examined.

CLINICAL FEATURES OF COVID-19 IN CHILDREN

Numbers of infected

ACCORDING TO REPORTS from each country, pediatric patients account for 0%–5% of COVID-19 patients diagnosed by polymerase chain reaction (PCR) and are considered to be rare.^{2–4} In Japan, 17,051 patients were confirmed to be COVID-19 positive by PCR, except for those returning by charter flights and those confirmed in airport quarantine or on the cruise ship Diamond Princess. Among these 17,501 patients, 284 (1.7%) are under the age of 10, and 418 are in their teens (Fig. 1).⁵ The rate of PCR testing for COVID-19 varies from one country to another, but the proportion of children with COVID-19 in Japan compared with that in other countries is not significantly different. Among children, patients have been reported in a wide range of age groups from 0 to late teens, and it appears that there is no difference in morbidity depending on age (Table 1).^{6–9}

Transmission route

From China, it was reported that in 28 pediatric patients (aged 1 month to 17 years) with confirmed COVID-19, all belonged to a family cluster of infections or had extensive contact with infected persons.¹⁰ By contrast, a follow-up report of 392 cofamily members who were in contact with 105 confirmed COVID-19 patients found a 16.3% incidence of secondary transmission within the family. The secondary attack rate was 4% in children younger than 18 years of age, significantly lower than that of adults at 17.1%.¹¹

It has been pointed out that the transmission route of SARS-CoV-2 may include aerosol transmission in addition to droplet/contact infection.^{12,13} Initially, the incubation period was reported to be about 5–6 days and that the amount of excreted virus was at its maximum immediately after the symptoms appeared.^{14,15} However, it was more recently reported that the excretion of virus increases over the 2–3 days before disease onset and peaks 0.7 days before onset.¹⁶ Even in children, it was reported that asymptomatic infants whose mother was diagnosed as having COVID-19 had nasopharyngeal excretion with a viral load similar to that of the mother.¹⁷ Children infected with SARS-CoV-2 have been shown to potentially excrete large amounts of

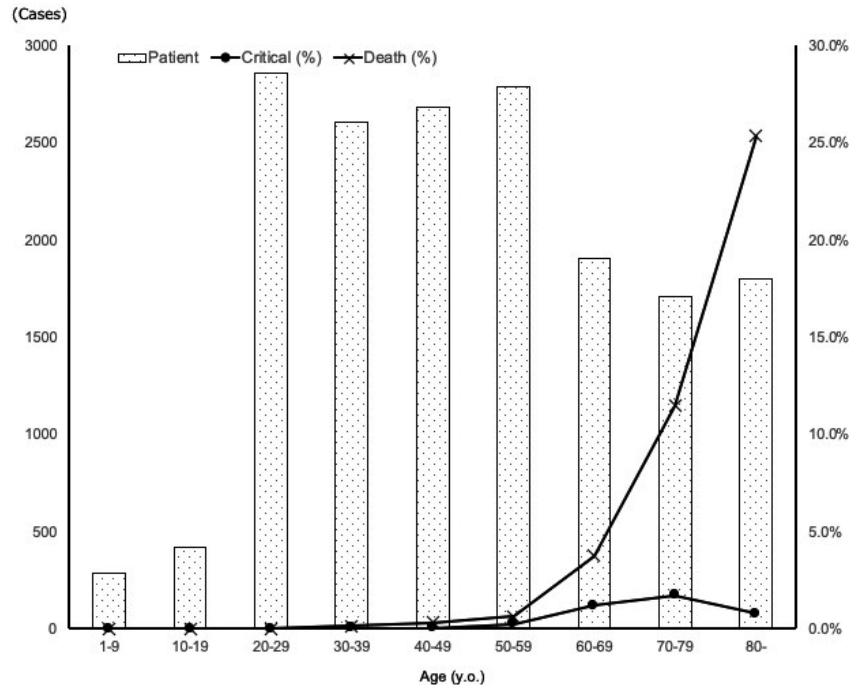


Fig. 1. Age distribution and percentage of critically ill and fatal cases of coronavirus disease 2019 (COVID-19) in Japan by age group (as of 6 p.m. on June 10, 2020).⁵Critical, patients requiring mechanical ventilation or who are in the intensive care unit. y.o., years old

Table 1. Age distribution of pediatric patients with laboratory-confirmed COVID-19

Country	United States ⁶		China ⁷		Italy ⁸		China ⁹	
Data collection	Data reported to the CDC		Children treated at Wuhan Children's Hospital		17 pediatric emergency departments		Data reported to the Chinese Center for Disease Control and Prevention	
Study period	Feb 12–Apr 2, 2020		Jan 28–Feb 26, 2020		Mar 3–Mar 27, 2020		Jan 16–Feb 8, 2020	
Number of patients [†]	2,572		171		100		731	
Median age (range), years	11 (0–17)		6.7 (1 day–15 years)		3.3 (0–17.5)		7 (n.d.)	
Age distribution, years, no. (%)	15–17	813 (32)	–	–	15–17	157 (21)	–	–
	10–14	682 (27)	11–15	42 (25)	11–17	24 (24)	11–15	180 (25)
	5–9	388 (15)	6–10	58 (34)	6–10	21 (21)	6–10	171 (23)
	1–4	291 (11)	1–5	40 (23)	1–5	35 (35)	1–5	137 (19)
	<1	398 (15)	<1	31 (18)	<1	40 (40)	<1	86 (12)

CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; n.d., not described.

[†]All cases were confirmed by laboratory testing.

virus in the long term, even when asymptomatic, and may be a potential source of infection.

Because of the effects of school closures worldwide, childhood infections are currently centered around secondary infections within the family. However, there is concern that the number of infected children may increase with the reopening of schools and that infection may also spread through asymptomatic children.

Clinical symptoms

In a meta-analysis of 3,600 patients with COVID-19, fever (83.3%), cough (60.3%), and malaise (38.0%) were the most common clinical symptoms.¹⁸ However, 5.8% of patients were also reported to be asymptomatic. Although there are no specific findings for COVID-19 in children, the incidence of individual symptoms tends to be lower than that in adults (Table 2).^{6–9} In addition, it was reported that among 171 pediatric patients with COVID-19, 27 (15.8%) were asymptomatic, and pneumonia could not be detected by radiological examination.⁷ Compared with adults, children are less likely to develop symptoms when infected with SARS-CoV-2, and the rate of asymptomatic passage may be higher than that of adults.

Blood test and imaging findings

It was reported that the sensitivities of PCR tests and computed tomography (CT) scans at the first visit in confirming COVID-19 infection in adults were 84.6% and 97.2%, respectively.¹⁹

CT examination findings are characterized by interstitial shadows called ground-glass opacification (GGO) that appears on the dorsal and peripheral sides of the lung field.^{20,21} In addition, as characteristic findings in children, GGO that appears as a lighter shadow in a more localized area that does not straddle a lung lobe²² and infiltrative shadows with a halo have been reported.²³ Among 15 patients under 15 years of age with confirmed COVID-19, 7 of 8 asymptomatic patients (4 at initial diagnosis, 3 during follow-up) had GGO.²⁴ From the above, it is possible that more sensitive diagnosis can be achieved in children by combining PCR with CT.

Hematological findings do not show any specific findings of COVID-19 in children but only nonspecific changes associated with viral infection.⁷ Therefore, it is difficult at present to diagnose SARS-CoV-2 infection from the results of blood tests alone.

Thus, tests with high sensitivity and specificity for SARS-CoV-2 infection are limited, disease severity in pediatric patients rarely increases, and there is no effective treatment at this time. Therefore, PCR testing should be performed in children only if there is a history of concentrated contact and symptomatic infection, mass infection, or pneumonia or respiratory distress of unspecified cause. Testing for asymptomatic and mild patients is not recommended.²⁵

Rates of disease severity and death

The mortality rate of patients of all ages due to COVID-19 is reported to be 5.6% worldwide.⁵ The severity of 44,672

Table 2. Signs and symptoms of adult and pediatric patients with COVID-19

Country	United States ⁶		China ⁷	Italy ⁸
Data collection	Data reported to CDC		Children treated at Wuhan Children's Hospital	17 Pediatric emergency departments
Study period	Feb 12–Apr 2, 2020		Jan 28–Feb 26, 2020	Mar 3–Mar 27, 2020
Median age (range), years	Adults n.d. (18–64)	Children 11 (0–17)	Children 6.7 (0–15)	Children 3.3 (0–17.5)
Number of patients [†]	10,944	291	171	100
Fever, %	71	56	42	54
Cough, %	80	54	49	44
Shortness of breath, %	43	13	n.d.	11
Myalgia, %	61	23	n.d.	n.d.
Runny nose, %	7	7	8	22
Sore throat, %	35	24	n.d.	4
Pharyngeal erythema, %	n.d.	n.d.	46	n.d.
Headache, %	58	28	n.d.	4
Nausea/Vomiting, %	16	11	6	10
Abdominal pain, %	12	6	n.d.	4
Diarrhea, %	31	13	9	9
Fatigue, %	n.d.	n.d.	8	9
Tachypnea on admission, %	n.d.	n.d.	29	n.d.
Tachycardia on admission, %	n.d.	n.d.	42	n.d.

CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; n.d., not described.

[†]Patients with signs and symptoms of COVID-19 confirmed by laboratory testing.

COVID-19 patients confirmed by PCR from China was reported previously; severe pneumonia with respiratory failure was present in 14%, respiratory failure/septic shock/organ failure occurred in 5%, and death in 2.3% (no deaths of patients under the age of 9).² In Japan, the total number of deaths was 920 (5.4%), and no deaths under the age of 19 were reported (Fig. 1).⁵

Table 3 shows the severity of pediatric patients confirmed to have COVID-19 by PCR and the number of deaths. From China, it was reported that of the 171 pediatric patients aged 15 or younger, 3 patients (1.8%) who had underlying disease required management in the intensive care unit (ICU), and 1 who had intussusception died.⁷ It was also reported that of the 731 children under the age of 18, 12.9% were

Table 3. Summary of studies on the severity of pediatric COVID-19

Country	Japan ⁵	United States ⁶	China ⁷	China ⁹
Number of patients	702	745	171	731
Age, years	≤19	≤17	≤15	≤17
Number of deaths	0	3 (0.4%)	1 (0.6%)	N.D.
Severity of disease				
Severe [†]	0 (0.0%)	15 (2.0%)	3 (1.8%)	21 (2.9%)
Moderate [‡]	702 (100%)	147 (19.7%)	140 (81.9%)	298 (41%)
Mild [§]		580 (77.9%)		314 (43.1%)
Asymptomatic			27 (15.8%)	94 (12.9%)

COVID-19, coronavirus disease 2019; n.d., not described.

[†]Severe: patients who were treated in the intensive care unit or required mechanical ventilation or extracorporeal membrane oxygenation.

[‡]Moderate: patients who were treated in a general ward.

[§]Mild: patients who had symptoms of acute respiratory tract infection but did not require hospitalization.

asymptomatic, 43.1% had respiratory symptoms, 41% had pneumonia, 2.5% had hypoxemia, and 0.4% had acute respiratory distress syndrome or organ failure.⁹ Furthermore, in the United States, it was reported that of the 745 children with COVID-19 under the age of 18, 147 (19.7%) were hospitalized, 15 (2.0%) were admitted to the ICU, and 3 (0.4%) died.⁶ Ninety-five infants under the age of 1 were included, with 59 hospitalized and 5 admitted to the ICU. Of these patients, the medical history and course of symptoms were available in 295. Thirty-seven children were hospitalized, of whom 28 (77%) had one or more underlying diseases such as chronic lung disease (including asthma), cardiovascular disease, and immunosuppression, but only 30 outpatients (12%) had underlying disease.

For severely ill children, a report of 48 admissions to pediatric ICUs in the United States and Canada (median age 13 years) found underlying disease in 40 cases (24 of 40 patients had two or more comorbidities).²⁶ The most common comorbidity was immunosuppression/malignancy (11 patients). As much as 19 of the 40 patients had a long-term dependence on technological support (including tracheostomy) associated with developmental delay and/or genetic anomalies. Of the 48 patients, 18 required a ventilator, and 1 required extracorporeal membrane oxygenation. Eleven patients suffered organ failure of two or more organs, and two died.

The rates of COVID-19-induced morbidity and mortality in children are very low compared with those in adults, but it should be noted that there are a certain number of pediatric patients who experience severe illness and require ICU management, especially in those with underlying diseases.

Systemic inflammatory syndrome associated with COVID-19

In the United Kingdom in April 2020, some children with confirmed or suspected COVID-19 showed rapid vasodilatory shock with fever, skin rash, conjunctivitis, peripheral edema, pain in the extremities, and prominent gastrointestinal symptoms despite the absence of pneumonia.²⁷ It was speculated that SARS-CoV-2 was associated with Kawasaki disease (KD), KD shock syndrome (KDSS), and toxic shock syndrome. As of June 2020, this disease state has been defined as multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) by the US Centers for Disease Control and Prevention (CDC) and pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIM-TS) by the European CDC.^{28,29} The accumulation of cases has begun.

According to a report comparing KD, KDSS, and toxic shock syndrome with 58 patients (male 48%) who met the

definition of PIM-TS, the median age of the children meeting the PIM-TS definition was significantly higher than that of those with KD/KDSS: PIM-TS, 9 years; KD, 2.7 years; and KDSS, 3.8 years.³⁰ SARS-CoV-2 was confirmed positive by PCR test in 15 of the 58 (26%), and 40 of 46 (87%) patients tested for antibody to coronavirus were positive for serum IgG antibody to SARS-CoV-2. Symptoms were mainly nonspecific, such as fever (100%), vomiting (45%), diarrhea (52%), skin rash (52%), and conjunctival hyperemia (45%). Only 12 (20%) had respiratory symptoms. Blood tests showed marked elevations of inflammatory markers such as C-reactive protein and ferritin, and 29 of the 58 (50%) were in cardiogenic shock accompanied by elevation of myocardial escape enzyme. Of the 58, 13 met the American Heart Association definition of KD, with 8 (14%) having dilated coronary arteries.

In a report of 35 people who met the MIS-C definition (median age, 10 years old), 88% had a confirmed SARS-CoV-2 infection by PCR or serology with a pharyngeal swab.³¹ Left ventricular ejection fraction decreased to less than 30% in 33% of cases, catecholamine administration was required in 80%, and induction of extracorporeal membrane oxygenation was required in 28%. Dilatation of the coronary arteries was observed in 17% of cases.

In the patients with this condition, the age at illness and the proportion of African, Hispanic, and Caribbean races are higher than those of patients with KD. In addition, few of the cases satisfy the classic KD symptoms mainly with regard to digestive symptoms, and the main pathological cardiac condition is deterioration of left ventricular function rather than changes in the coronary arteries. Thus, contrary to the initial consideration, characteristic differences from KD have been reported.³⁰⁻³² Many of the patients had an SARS-CoV-2 infection or a history of infection, but there are some who developed this condition a few weeks after the infection was confirmed by PCR, or who already had an elevated serum IgG level at the time of consultation.³³ Whether this condition is directly related to SARS-CoV-2 or is a secondary condition resulting from the immune reaction induced by SARS-CoV-2 infection remains unknown. It will be necessary to collect cases and analyze pathological conditions in the future.

POINTS TO NOTE IN PEDIATRIC EMERGENCY MEDICAL CARE DURING THE COVID-19 PANDEMIC

Nosocomial infection control

ACCORDING TO THE American Heart Association provisional guidelines, aerosol-generating procedures

in emergency medicine include chest compressions, manual ventilation, tracheal intubation and extubation, tracheal suction, high-flow nasal oxygen, noninvasive positive pressure ventilation, tracheostomy, and inhalation therapy with a nebulizer.³⁴ Especially, resuscitation is recommended to be performed in a negative-pressure private room.

The Japanese Society of Pediatric Allergy and Clinical Immunology recommends the use of a metered dose inhaler with a spacer in place of a nebulizer for the treatment of asthma, considering the potential transmission of aerosol-borne infections.³⁵ They also recommend that if severely ill children or young children have difficulty in inhaling with a metered dose inhaler and nebulizers are needed, adequate room ventilation should be taken into consideration due to the possibility of transmission of infection. However, on the basis of a systematic review of five cohort studies and five case-control studies,^{36,37} the US CDC says it is uncertain whether nebulizers and high-flow oxygen administration increase the risk of transmission.

When an infant infected with SARS-CoV-2 is hospitalized and a family member is also infected, the family member may need hospitalization/treatment depending on the medical condition. In many hospitals, even if the family is noninfected, the family cannot enter the infected ward where the child is hospitalized. Infants and children often require full-fledged life support, and it is difficult to control their behavior. Therefore, if family members cannot help, there is a high risk of causing infection or nosocomial infection in medical personnel who provide care.³⁸ For this reason, the Japanese Academy of Pediatrics provides specific guidelines for the practice of COVID-19 treatment in children.³⁸ For example, if the child's illness is mild, he/she will be treated at home. However, if the child needs to be hospitalized, the parents are allowed to take care of their child in the ward.

Consideration of the child's mental background and child abuse

There is a strong concern that in addition to restrictions on going out due to the spread of infection and restrictions on daily activities, the loss of social ties due to school closure changes the life rhythm of "healthy" children, which can have negative psychological and physical effects on them.³⁹ Children who are isolated from infection are reported to have a fourfold greater risk of post-traumatic stress syndrome than those who are not isolated.⁴⁰ It has also been pointed out that the mental and financial anxiety of parents who should be caring for their children may lead to domestic violence and child abuse.^{41,42} It is feared that restrictions on going out and school closure will keep these problems hidden in the home and isolate the affected children even more.

In pediatric emergency care, it is important not only to cure the illness of the child but also to encourage the family and society to advocate for and improve the environment for the child.⁴³ Health-care workers must consider that a child who is presenting with physical symptoms may need psychological support or may be socially isolated and that the visit to the emergency department may be the child's only social contact point. In addition, it is important to observe the behavior of the patient and his/her family at the time of medical examination and to deal with it by coordinating with multiple health-care professionals such as social workers as necessary.

CONCLUSION

WE HAVE SUMMARIZED the present characteristics of pediatric COVID-19 and the points to be noted in emergency care. Children with less severe disease but who have many subclinical infections may become a source of infection in families, communities, and medical institutions. However, restrictions on going out and school closures may have unexpected psychological and physical effects on healthy children. In the medical treatment of the emergency outpatient, it is important to take measures against COVID-19 and, if necessary, cooperate with various other professionals such as social workers to deal with them.

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