

COVID - 19**CLINICAL FEATURES AND DISEASE STRATIFICATION OF COVID-19 IN CHILDREN**

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Abstract: *We are in the midst of a pandemic caused by novel virus SARS-Cov-2 with no sign of abating. The clinical features have been ranging from asymptomatic to severe respiratory distress leading to death. Fortunately, children have been less affected in terms of both morbidity and mortality. Although the signs and symptoms are similar to adults, a smaller number of children tend to be symptomatic. Some children however have been reported with unusual skin lesions or vasculitis like syndrome and also recently an overlap of Kawasaki and toxic shock like syndrome named as Pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2. The common presentations in children and their difference from adults are discussed.*

Keywords: *Covid-19, SARS-CoV-2, Clinical features, Children.*

In the later part of 2019, a novel coronavirus infection emerged in Wuhan, Hubei province, China. It was linked to animal-to-human transmission in local wet markets. Subsequently, human-to-human transmission of the virus commenced, resulting in widespread respiratory illness in Wuhan and other areas of the Province.¹ The virus then spread across China and then to other nations across the globe. On February 11, the World Health Organization named the virus SARS-CoV-2 and the syndrome was named COVID-19, or coronavirus disease 2019.² Although not as lethal as the severe acute respiratory syndrome (SARS) outbreak in 2003, COVID-19 is still characterized by severe respiratory illness and significant mortality, especially among the elderly and individuals with underlying co-morbid conditions such as cardiac and respiratory diseases, diabetes and hypertension.¹ As of 28th May 2020, more than 5.69 million cases have been reported

across 188 countries and territories, resulting in more than 3,55,000 deaths and 1.56 million people have recovered too.³

As COVID-19 is a new disease, many aspects such as to how it spreads is not proved conclusively.⁴ The infection is spread during close contact, often by small droplets produced during coughing, sneezing, or talking.⁴ The droplets are transmitted and cause new infection, when inhaled by people in close contact (1 to 2 meters / 3-6 feet). They are also produced during breathing out, but as these droplets are relatively heavy, they usually fall to the ground or surfaces.⁴ Loud talking releases more droplets than normal talking.⁵ Although not proven crying in children has also been postulated to release droplets.⁶

After the droplets fall on floor or surfaces, they can still infect other people, if they touch these contaminated surfaces and then touch their eyes, nose or mouth with unwashed hands.⁴ On surfaces, the amount of active virus decreases over a period of time until it can no longer cause infection. However, the virus has been found to survive on various surfaces for some time - for example copper or cardboard for a few hours, and plastic or steel for a few days.⁷

Sputum and saliva carry large amounts of virus.^{4,7} Some medical procedures which produce aerosol like dental procedures may result in the virus being transmitted easier than normal.^{4,7} Although COVID-19 is not a sexually transmitted infection, kissing, intimate contact and fecal oral routes are suspected to transmit the virus.⁸

The incubation period for COVID-19 is from 2 to 14 days, with an average of 4-6 days. 97.5% of people who develop symptoms, do so within 11.5 days of infection.⁹ The virus is most contagious during the first three days after onset of symptoms, spread can occur even two days before symptoms appear (pre-symptomatic transmission) and in later stages of the disease. A section of infected people do not develop noticeable symptoms at any point of time. These asymptomatic carriers tend not to get tested, and their role in transmission is not yet fully known.¹⁰ However, preliminary evidence suggests they may contribute to the spread of the disease.

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Symptoms and signs - adults

Fever is the most common symptom, although some older people and those with other health problems experience fever later in the disease. In one study, 44% of people had fever when they presented to the hospital, while 89% went on to develop fever at some point during their hospitalization.¹¹

Other common symptoms include cough, loss of appetite, fatigue, shortness of breath, sputum production, and muscle and joint pains.¹¹ Symptoms such as nausea, vomiting, and diarrhea have been observed in varying proportions.¹² Less common symptoms include sneezing, runny nose or sore throat¹³ (Table I). Some patients in China initially presented with only chest tightness and palpitations.¹⁴ A decreased sense of smell (hyposmia) or disturbances in taste (hypogeusia) may occur.¹⁵ Severity of symptoms tend to be more in patients with underlying medical conditions.

According to Centre for disease control (CDC), Atlanta, USA, people with these symptoms or combinations of symptoms may have COVID-19: Cough with shortness of breath or difficulty in breathing: Or at least two of the following symptoms: Fever, chills, repeated shaking with chills, muscle pain, headache, sore throat, new loss of taste or smell.¹⁶

Risk scoring

In collaboration with the National Health Commission of China, and based on a retrospective cohort of 1590 patients with COVID-19 from 575 hospitals, a high-risk score has been developed for adults.¹⁷ The score provides an estimate of the risk that a hospitalized patient with COVID-19 will develop critical illness. Critical illness was defined as the composite measure of admission to the intensive care unit, invasive ventilation or death. The mean

Table I. Symptoms in adults¹¹

Symptoms	Range
Fever	83–99%
Cough	59–82%
Loss of appetite	40–84%
Fatigue	44–70%
Shortness of breath	31–40%
Coughing up sputum	28–33%
Muscle aches and pains	11–35%

age of patients in the cohort was 48.9 years (57.3%) were men. 72 potential predictors were evaluated, ten variables were found to be independent predictive factors and were included in the risk score: chest radiographic abnormality, older age, hemoptysis, dyspnea, unconsciousness, more number of comorbidities, cancer history, increased neutrophil-to-lymphocyte ratio, elevated lactate dehydrogenase and direct bilirubin. The score has been translated into an online risk calculator that is freely available to the public (<http://118.126.104.170/>).

Covid-19 in children

Pediatric cases of COVID-19 have been reported but there are relatively fewer cases among children compared to adult patients. It was 2% in the United States, 2.2% in China, 1.2% in Italy and 0.8% in Spain of confirmed cases who were below 18 years of age.¹⁸ Most of the children had exposure to household members with confirmed COVID-19.

The predominant signs and symptoms of COVID-19 reported to date among all patients are similar to other viral respiratory infections, including fever, cough and shortness of breath. Although these signs and symptoms may occur at any time during the overall disease course, children with COVID-19 may not initially present with fever and cough as often as adult patients.¹⁸ Data from China suggest that pediatric COVID-19 cases might be less severe than adults and that children might experience different symptoms than do adults.^{19,20} These findings are largely consistent with a report on pediatric COVID-19 patients aged <16 years in China, which found that only 41.5% of pediatric patients had fever, 48.5% had cough and 1.8% were admitted to an ICU.¹⁸ A second report suggested that although pediatric COVID-19 patients infrequently have severe outcomes, the infection might be more severe among infants. The same report detected no substantial difference in the number of cases among males and females.²⁰

Age distribution

Data from 1,49,760 laboratory-confirmed COVID-19 cases in the United States occurring during February 12-April 2, 2020 were analyzed. Among 1,49,082 (99.6%) reported cases for which age was known, 2,572 (1.7%) were among children aged <18 years (the median age being 11 years).²¹ Nearly one third of reported pediatric cases (32%) occurred in children aged 15-17 years, followed by those in children aged 10-14 years (27%). Among younger children, 15% occurred in children aged <1 year, 11% in children aged 1-4 years and 15% in children aged 5-9 years. Among 2,490 pediatric COVID-19 cases

for which sex was known, 57% occurred in males; among cases in adults aged ≥ 18 years for which sex was known, 53% were males.

Symptoms and signs

In the same US study, complete data on signs and symptoms of COVID-19 were available for 291 of 2,572 (11%) pediatric cases and 9.6% cases among adults aged 18-64 years. Among the children with available information, 73% only had symptoms of fever, cough, or shortness of breath compared with 93% of adults aged 18-64 years. Among those with known information on each symptom, 56% of pediatric patients reported fever, 54% reported cough, and 13% reported shortness of breath, compared with 71%, 80%, and 43% respectively, reporting these signs and symptoms among patients aged 18-64 years (Table II). Myalgia, sore throat, headache and diarrhea were also less commonly reported by pediatric patients.²¹ These data support previous findings that children with COVID-19 might not have reported fever or cough as often as adults.¹⁸

Hospitalization in children

Information on hospitalization status was available for 29% (745 of 2572) cases in children aged < 18 years and 31% cases in adults aged 18-64 years. Among children

Table II. Signs and symptoms among 291 pediatric (age < 18 years) and 10,944 adult (age 18-64 years) patients with laboratory-confirmed COVID-19 - United States, February 12-April 2, 2020²¹

Sign/Symptom	No. (%) Pediatric	with sign/symptom Adult
Fever, cough, or shortness of breath	213 (73)	10,167 (93)
Fever	163 (56)	7,794 (71)
Cough	158 (54)	8,775 (80)
Shortness of breath	39 (13)	4,674 (43)
Myalgia	66 (23)	6,713 (61)
Runny nose	21 (7.2)	757 (6.9)
Sore throat	71 (24)	3,795 (35)
Headache	81 (28)	6,335 (58)
Nausea/Vomiting	31 (11)	1,746 (16)
Abdominal pain	17 (5.8)	1,329 (12)
Diarrhea	37 (13)	3,353 (31)

with COVID-19, 147 (estimated range = 5.7%–20%) were reported to be hospitalized, with 15 (0.58%–2.0%) admitted to an ICU. Among adults aged 18-64 years, the percentages of patients who were hospitalized (10%–33%), including those admitted to an ICU (1.4%–4.5%), were higher. Whereas most COVID-19 cases in children are not severe, serious COVID-19 illness resulting in hospitalization still occurs in this age group. Children aged < 1 year accounted for the highest percentage (15%–62%) of hospitalization among pediatric patients with COVID-19. Among 95 children aged < 1 year with known hospitalization status, 59 (62%) were hospitalized, including five who were admitted to an ICU. The percentage of patients hospitalized among those aged 1-17 years was lower (estimated range = 4.1%–14%), with little variation among age groups.²¹

Among 345 pediatric cases with an underlying condition, 80 (23%) had at least one underlying condition. The most common underlying conditions were chronic lung disease including asthma 40(50%), cardiovascular disease 25(31%) and immunosuppression 10(13%). Among the 295 pediatric cases for which information on both hospitalization status and underlying medical conditions was available, 28 of 37 (77%) hospitalized patients, including all six patients admitted to an ICU, had one or more underlying medical condition; among 258 patients who were not hospitalized, 30 (12%) patients had underlying conditions.²¹ Three deaths were reported among the pediatric cases included in this analysis; however, review of these cases is ongoing to confirm COVID-19 as the likely cause of death. In the present analysis, the predominance of males in all pediatric age groups, including patients aged < 1 year, suggests that biologic factors might play a role in any differences in COVID-19 susceptibility by sex.

In a study of 20 children admitted in Wuhan children's hospital during the early part of the pandemic, 7 had a previous history of congenital or acquired diseases, which may indicate that children with underlying diseases may be more susceptible to COVID-19 infection.²² It was noted that the procalcitonin (PCT) was elevated in 80% cases in this study, with or without coinfection, which was not common in adult patients. Co infection was however noted in 8/20 (40%) indicating it is probably more common in pediatric patients.²³

Relevance of Pediatric COVID presentation

This preliminary examination of characteristics of COVID-19 disease among children in the United States and China suggests that children do not always have fever or cough as reported signs and symptoms. Although most

cases reported among children to date have not been severe, clinicians should maintain a high index of suspicion for COVID-19 infection in children and monitor for progression of illness, particularly among infants and children with underlying conditions. As persons with asymptomatic and mild disease, including children, are likely playing a role in transmission and spread of COVID-19 in the community, social distancing and everyday preventive behaviors are recommended for persons of all ages to slow the spread of the virus, protect the health care system from being overloaded and protect older adults and persons of any age with serious underlying medical conditions.^{11,22}

Dermatological manifestations

Five skin conditions associated with coronavirus have been identified by dermatologists and deserve special mention. A research carried out on 375 patients in Spain²⁴, aimed to build a picture of how the disease might manifest with skin symptoms. The Spanish dermatologists were asked to identify patients who had an unexplained skin “eruption” in the last two weeks and who had suspected or confirmed Covid-19. Five different lesions were identified. Lesions were classified as acral areas of erythema with vesicles or pustules (Pseudo-chilblain, 9%), other vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%) and livedo or necrosis (6%). Vesicular eruptions appear early in the course of the disease (15% before other symptoms). The pseudo-chilblain pattern frequently appears late in the evolution of the COVID-19 disease (59% after other symptoms), while the rest tend to appear with other symptoms of COVID-19. Severity of COVID-19 shows a gradient from less severe disease in acral lesions to most severe in the other groups. Results are similar for confirmed and suspected cases. Alternative diagnoses were discussed but seem unlikely for the most specific patterns (pseudo-chilblain and vesicular). These may help clinicians approach patients with the disease and recognize pauci-symptomatic cases.²⁴

Course of the disease

The disease can have a very variable course, from asymptomatic to life threatening. All the various determinants of this variability have not been worked out yet. A typical course can be described as below.²⁵ Symptom onset is preceded by an incubation period from the day of contact which ranges from 1 to 14 days with median estimates of 5 to 6 days.

Day 1: Patients start having fever. They may also experience fatigue, muscle pain, and a dry cough. A small

minority of them may have had diarrhea or nausea one or two days before the onset of symptoms.

Day 5: Patients may have difficulty breathing specially if they are older or they have a preexisting health condition.

Day 7 is the average time the patients are admitted.

Day 8. At this point patients with severe illness develop ARDS. If the disease worsens patients are generally admitted to the ICU by day 10.

Day 14-17 is the usual time the patient is discharged from the hospital.

The child has to be restricted from mixing with other family members, especially the elderly, during the course of the disease and even later. The duration of quarantine can be time based, symptom based or test based.²⁶ The patient should be quarantined for 14 days after recovery. Recovery is when 3 days (72 hours) have passed after resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (e.g., cough, shortness of breath) and at least 10 days have passed since symptoms first appeared. In test-based strategy, resolution of fever without the use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath) and negative results of at least two consecutive respiratory specimens collected more than 24 hours apart are considered as indicators of recovery.

Disease stratification

The decision to manage a pediatric patient with mild to moderate COVID-19 in the outpatient or inpatient setting should be decided on a case-by-case basis. Pediatric healthcare providers should consider the patient’s clinical presentation, requirement for supportive care, underlying conditions and the ability for parents or guardians to care for the child at home.¹¹

Severe COVID-19 in children is rare. The largest review of children with COVID-19 included 2143 children in China. Only 112 (5.6%) of 2143 children had severe disease (defined as hypoxia) and 13 (0.6%) children developed respiratory or multiorgan failure or ARDS.³³ Emergency signs and symptoms include difficulty in breathing, persistent chest pain or pressure, new confusion, blue lips or face. If there are any of these signs or symptoms the child should be admitted immediately. Any child without these symptoms but has a chronic medical condition such as heart disease, lung disease or on chemotherapy should also be admitted.¹¹ Classification based on the severity of illness is summarized in Box 1.

Box.1 Definitions of clinical types of COVID-19 in pediatric patients³⁸**Mild disease**

- Upper respiratory symptoms (eg, pharyngeal congestion, sore throat and fever) for a short duration or asymptomatic infection
- Positive RT-PCR test for SARS-CoV-2
- No abnormal radiographic and septic presentation

Moderate disease

- Mild pneumonia
- Symptoms such as fever, cough, fatigue, headache, and myalgia
- No complications and manifestations related to severe conditions

Severe disease

Mild or moderate clinical features, plus any manifestations that suggest disease progression:

- Rapid breath (≥ 70 breaths per min for infants aged <1 year; ≥ 50 breaths per min for children aged >1 year)
- Hypoxia
- Loss of consciousness, depression, coma, convulsions
- Dehydration, difficulty feeding, gastrointestinal dysfunction
- Myocardial injury
- Elevated liver enzymes
- Coagulation dysfunction, rhabdomyolysis and any other manifestations suggesting injuries to vital organs

Critical illness

Rapid disease progression, plus any other conditions:

- Respiratory failure with need for mechanical ventilation (eg, ARDS, persistent hypoxia that cannot be alleviated by inhalation through nasal catheters or masks)
- Septic shock
- Organ failure that needs monitoring in the ICU

In the absence of studies involving large number of children and considering the fact that the incidence and as well as proportion of critically ill children is too little, assessment of physiological status will give a guidance on disease stratification as given in Box 1 .

Complications**Respiratory**

In some people, COVID-19 may cause viral pneumonia. In those most severely affected, COVID-19 may rapidly progress to acute respiratory distress syndrome (ARDS) causing respiratory failure, septic shock, or multi-organ failure and death.²⁹ Complications associated with COVID-19 include sepsis, abnormal clotting and damage to the heart, kidney and liver. Approximately 20-30% of people who present with COVID-19 demonstrate elevated liver enzymes more frequently seen in severe cases.³⁰ Neurological manifestations include seizures, stroke, encephalitis and Guillain-Barré syndrome.³¹ Cardiovascular related complications may include heart failure, arrhythmias, thrombosis and myocarditis.³²

Inflammatory syndrome

A growing number of hospitals in the U.S. and U.K. have reported cases with presentation similar to Kawasaki Disease.³³ Symptoms of these children include fever, rash, eye irritation, swollen lymph nodes and/or swelling of the hands and feet. The link between Kawasaki syndrome and COVID-19 is still not well established. The UK Kawasaki Disease Foundation released a statement saying that many children with the disease tested negative for COVID-19 and there is no current evidence of any increased incidence or greater susceptibility to COVID-19 infection for children who had Kawasaki Disease in the past.³⁴

Though COVID in children presents with milder symptoms and less complications, the hospitalization and ICU admission are relatively more in infants and those with existing health conditions within the pediatric age group. The pediatrician has to be aware of certain atypical manifestations such as dermatological lesions and inflammatory syndromes which may be related to SARS-CoV-19 infection.

Points to Remember

- *Children are less often involved compared to adults.*
- *The pediatric patients may be asymptomatic or show mild non-specific viral symptoms like fever, cough and cold.*

- *Some may present with skin lesions or vasculitis.*
- *High index of suspicion is required in view of non-specific mild illness in pediatric age group.*
- *Children less than three years should be carefully monitored for deterioration as they may not be able to communicate worsening.*

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CLIPPINGS

Consensus statement on chest imaging in pediatric COVID-19 patient management: Imaging findings and imaging study recommendations.

CXR: In the clinical experience of this expert panel of pediatric chest radiologists, both unilateral and bilateral opacities have been observed in pediatric COVID-19, although bilateral opacities are more typical and may show patchy opacities with peripheries and lower lung zone predominance. Bilateral peripheral and/or subpleural ground-glass opacities and/or consolidation are suggestive of COVID-19 pneumonia. However, other viral or atypical pneumonia would also be differential considerations. Less sensitive than CT in detecting lung parenchymal opacities. CXR is considered the most appropriate first step in imaging evaluation

CT chest: Bilateral and subpleural ground-glass and/or consolidative opacities often in the lower lobes of lungs. The "halo" sign, which describes a focal consolidation with a rim of surrounding ground-glass opacity, has been reported in up to 50% (10/20) of cases. The "halo" sign is generally observed early in the disease course (early phase) and progresses to ground-glass (progressive phase) and eventually develops into consolidative opacities (developed phase). Peribronchial thickening and inflammation along the bronchovascular bundle are observed more frequently in the pediatric population compared to adults. Fine mesh reticulations and crazy paving sign have also been reported. These CT findings are not pathognomonic. Thus the American College of Radiology currently recommends against using CT as a first line screening test to diagnose COVID-19 because of the risk of radiation and states that chest CT should be reserved for symptomatic hospitalized patients with specific clinical indications.

Foust AM, Phillips GS, Chu WC, Daltro P, Das KM, Peña PG, et al. International Expert Consensus Statement on Chest Imaging in Pediatric COVID-19 Patient Management: Imaging Findings, Imagings study reporting and imaging study recommendations. Radiology: Cardiothoracic Imaging Vol. 2, No. 2. Published Online: Apr 23 2020 <https://doi.org/10.1148/ryct.2020200214>.