



Review Article

## Latest reviews regarding COVID-19 and its management

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### ABSTRACT

We discuss briefly regarding the origin of the SARS-CoV-2 virus, its structure, routes of transmission, and pathophysiology. Then, we go on to describe the symptomatology and clinical features based on different publications from different countries. Finally, we have summarized the variable guidelines available for the management and prevention of the COVID-19 disease.

**Keywords:** COVID-19, Corona, Corona in children, Management of Corona, Effect of corona in children

Coronavirus (CoV) is not a new virus. It is a large family of virus which has been causing different diseases such as common cold to Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV).

Almost all viruses causing common cold go through genetic mutation and form new strains. Same way, the current coronavirus called SARS-CoV2 is a new strain that causes COVID-19 disease and bat appears to be the reservoir but the intermediate host(s) is unknown.<sup>[1]</sup>

Coronaviruses are zoonotic. Detailed investigations found that SARS-CoV transmitted from civet cats to humans and MERS-CoV came from dromedary camels.<sup>[2]</sup> There are more coronaviruses which are circulating in animals that have not yet infected humans.

SARS-CoV-2 viruses like other coronaviruses, are spherical, containing single-stranded RNA and have protein spikes protruding from their surface called spike protein [Figure 1]. These spikes latch onto human cells and undergo a structural change that allows the viral membrane to fuse with the host's cell membrane. The viral genes can then enter the host cell to be copied, producing more viruses.<sup>[3]</sup>

Latest work shows that, like the virus that caused the 2002 SARS outbreak, SARS-CoV-2 spikes bind to angiotensin-converting enzyme 2 (ACE2).<sup>[3]</sup>

SARS-CoV-2 spike is 10–20 times more likely to bind ACE2 which might be the reason why they are more infectious than the previous strains of CoV.<sup>[3]</sup>

Even though the structure of latest strains of virus is similar to SARS-CoV, three known antibodies against SARS-CoV could not bind to SARS-CoV2, which indicates that the treatment with antibodies of SARS-CoV is unlikely to be successful.<sup>[3]</sup>

### ROUTES OF TRANSMISSION

- COVID-19 virus is transmitted through droplets and fomites, therefore, transmission can occur by direct contact with infected people and indirect contact with surfaces in the

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immediate environment or with objects used on the infected person (e.g., stethoscope or thermometer).<sup>[4]</sup>

- Airborne transmission may be possible during procedures or support treatments that generate aerosols; that is, endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, turning the patient to the prone position, disconnecting the patient from the ventilator, non-invasive positive pressure ventilation, tracheostomy, and cardiopulmonary resuscitation.<sup>[4]</sup>
- Prolonged (up to a month) fecal shedding of viable virus has been identified in a limited number of case reports, but feco-oral route of transmission has not been reported to date.<sup>[4,5]</sup>
- Vertical transmission of COVID-19 to infant during delivery or breastfeeding remains to be confirmed.<sup>[6]</sup>

## INCUBATION PERIOD

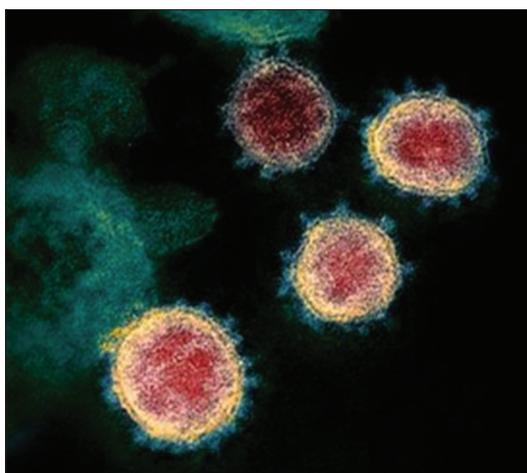
Incubation period varies from 1 to 14 days; mean period being 5–6 days.

## CHILDREN

Limited data available in India regarding COVID-19 in children show that the prevalence of the disease is around 2% which corresponds to reports from other countries.

According to Joint Commission by China and CDC, COVID-19 seems to be rare and mild in individuals aged <18 years (2.4%) and out of these patients, only 2.5% developed severe and 0.2% went on to have critical disease.<sup>[1]</sup>

According to CDC report of the U.S. cases, 2% were of pediatric age group.<sup>[5,7]</sup>



**Figure 1:** Transmission electron microscope image shows SARS-CoV-2.<sup>[3]</sup>

In Italy, 1.2% of COVID-19 cases were among the age group of <18 years.<sup>[8]</sup>

## PATHOPHYSIOLOGY

### ARDS

The primary pathology is characterized by diffuse alveolar damage through hyperinflammatory and direct effect of the virus activity.<sup>[9]</sup>

### Cytokine storm

New evidences suggest that some patients respond to SARS-CoV2 with cytokine storm-like sepsis and HLH.<sup>[10]</sup>

## THE SIGNS AND SYMPTOMS

Symptoms are non-specific and it can range from being asymptomatic to severe pneumonia and death [Table 1 and Figure 2].

Some children present in shock and with typical/atypical features of Kawasaki disease, which is a vascular inflammatory disease.

## SEVERITY OF DISEASE

- Asymptomatic
- Mild-to-moderate disease: It includes non-pneumonia and mild pneumonia cases.<sup>[1]</sup>
- Severe disease: Categorized by dyspnea, respiratory distress, blood oxygen saturation  $\leq 93\%$ , PaO<sub>2</sub>/FiO<sub>2</sub> ratio <300, and/or lung infiltrates >50% of the lung field within 24–48 h.<sup>[1]</sup>
- Critical: Respiratory failure, septic shock, and/or multiple organ dysfunction/failure.<sup>[1]</sup>

**Table 1:** 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, 2020.<sup>[7]</sup>

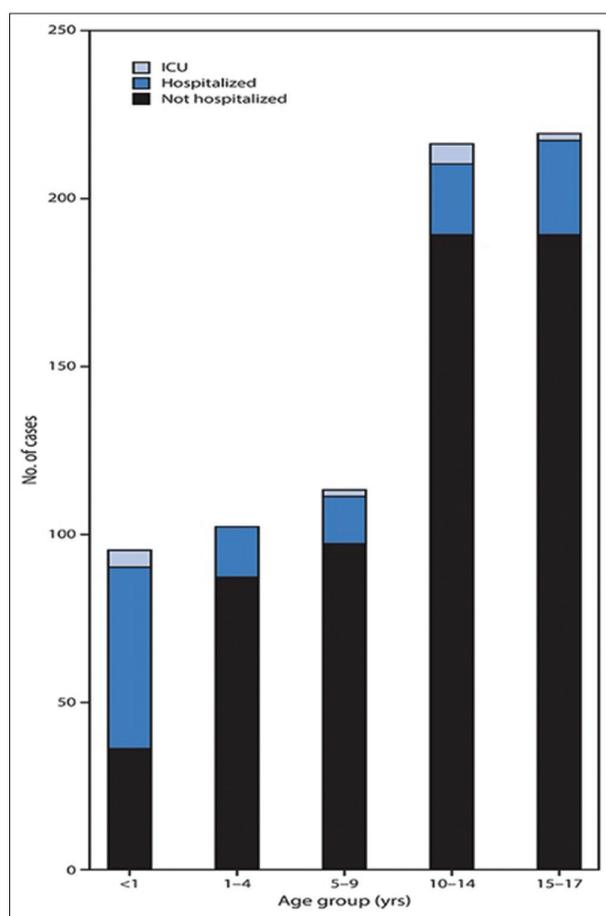
Sign/symptom	No. (%) with sign/symptom	
	Pediatric	Adult
Fever, cough, or shortness of breath	213 (73)	10,167 (93)
Fever	163 (56)	7794 (71)
Cough	158 (54)	8775 (80)
Headache	81 (28)	6,335 (58)
Sore throat	71 (24)	3,795 (35)
Myalgia	66 (23)	6713 (61)
Shortness of breath	39 (13)	4674 (43)
Diarrhea	37 (13)	3353 (31)
Nausea/vomiting	31 (11)	1746 (16)
Runny nose	21 (7.2)	757 (6.9)
Abdominal pain	17 (5.8)	1329 (12)

- High risk for severe and critical disease in younger age is underlying pulmonary pathology, immunocompromising conditions, obesity, and coinfection.<sup>[5]</sup>
- Pregnant women (8% had severe disease and 1% were critical): Risk of severity of the disease in pregnant and non-pregnant women of similar age appears to be equal.<sup>[1]</sup>

## APPROACH TO DIAGNOSIS AND TREATMENT

### History of epidemiology

1. Travel or residence history in containment zone and its surrounding areas or other communities with reported cases within 14 days before the onset of the disease.
2. History of contact with SARS-CoV2-positive patients within 14 days before the onset of the disease.

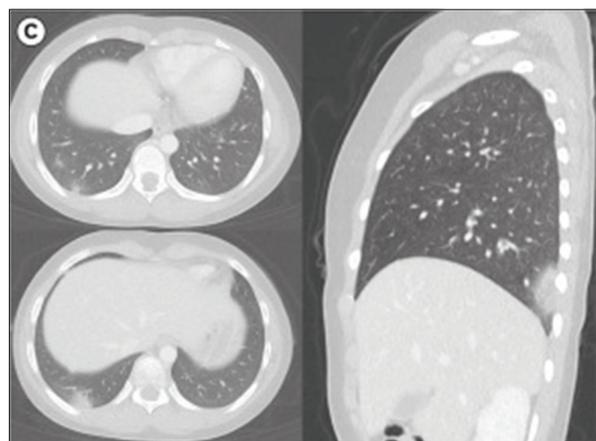


**Figure 2:** COVID-19 cases among children aged <18 years, among those with known hospitalization status (N = 745), <sup>†</sup>by age group and hospitalization status – United States, February 12–April 2, 2020.<sup>[7]</sup>  
<sup>†</sup>Number of children missing hospitalization status by age group: <1 year (303 of 398; 76%); 1–4 years (189 of 291; 65%); 5–9 years (275 of 388; 71%); 10–14 years (466 of 682; 68%); 15–17 years (594 of 813; 73%).

3. Contact with patients with fever or respiratory symptoms from containment zone and its surrounding areas or other communities with reported cases within 14 days before the onset of the disease.
4. Cluster infection: Within 2 weeks, 2 or more cases of fever, and/or respiratory symptoms occurred in small areas such as homes, offices, and school classes.

### Clinical manifestations and laboratory findings

1. Fever and/or respiratory symptoms
2. Having the imaging features of COVID-19:
  - a. Multiple patchy shadows and interstitial changes mostly in the lung periphery during the early stage of the disease.<sup>[10,11]</sup>
  - b. Multiple ground-glass opacities (GGOs) and infiltration shadows in the later stage of the disease [Figure 3].
  - c. Severe cases may develop consolidation of lung tissue.
  - d. Diagnosis of hydrothorax is rare.<sup>[10,11]</sup>
3. The total leukocyte count is normal or decreased, or the lymphocyte count is normal or decreased in the early stage of the disease.<sup>[10,11]</sup>
4. They can have normal platelet count or thrombocytosis.
5. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are elevated, while procalcitonin is normal in adults, it may be elevated in pediatric patients.<sup>[11]</sup>
6. Some patients have an increase in liver enzymes, lactate dehydrogenase (LDH), muscle enzymes, and myoglobin.
7. Elevated troponin is seen in some critically ill patients.
8. In severe cases, D-dimer increases and peripheral blood lymphocytes progressively decrease.
9. Severe and critically ill patients often have elevated inflammatory factors.



**Figure 3:** (C) Chest CT performed on the fourth day since symptom onset demonstrates patchy nodular consolidations with peripheral ground glass opacities in subpleural areas of the right lower lobe in axial and sagittal views of CT.<sup>[15]</sup>

10. Some present with multisystem inflammatory syndrome in children (MIS-C):<sup>[12]</sup>
- Defined by fever >24 h, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem ( $\geq 2$ ) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND
  - No alternative plausible diagnosis; AND
  - Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks before the onset of symptoms

Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C.

### Diagnosis of COVID-19

Is confirmed when suspected case with one of the following serological evidences:

- The result of RT-PCR for SARS-CoV2 is positive.<sup>[13,14]</sup>
- Serum IgM antibodies and IgG antibodies to SARS-CoV2 are positive; serum IgG antibodies to SARS-CoV2 turn from negative to positive or the IgG antibody titers of recovery period are 4 times or more higher than that of acute phase.<sup>[13,14]</sup>
- The result of virus gene sequencing analysis is highly homologous with the known SARS-CoV2.<sup>[13,14]</sup>

### PREVENTION

- Practice good personal hygiene:
  - Cover mouth and nose with a tissue when coughing or sneezing.
  - Wash hands frequently.
  - Do not touch mouth, eyes, and nose with dirty hands, and do not spit on the ground.
- Avoid family gatherings and eat separately, as during meal everyone, are in close contact.
- Avoid public places as much as possible.
- Keep house well ventilated and sunlit.
- Wear a mask if you have cold, cough, or fever. Consult a doctor and mention about travel history or if you have come across any individual who is suspected to have COVID-19 or diagnosed with COVID-19 in the past 14 days.<sup>[13]</sup>

### TREATMENT

- Confirmed and suspected cases should be isolated and treated in designated hospitals with effective isolation and protective conditions, and suspected cases should be isolated in separate rooms.

- Self-isolation in pediatric age group is difficult. Considering the circumstances, the Korean Centers for Disease Control and Prevention and the Korean Society of Pediatric Infectious Diseases recommend one of the family members to be assigned as a caregiver for infants and young children who are suspected or confirmed with COVID-19, and the caregiver should take adequate measures to avoid being exposed to the virus. Thus, further pediatric-specific guidelines on the isolation and adequate personal protective equipment for caregivers should be prepared.<sup>[15]</sup>
- Multiple confirmed cases can be admitted in the same ward, and critical cases should be shifted to ICU as soon as possible.
- General treatments: Patients should be on bed rest, monitor vitals, connect them to pulse oximeter to monitor oxygen saturation, keep them well hydrated without causing fluid overload, prevent electrolyte imbalance, hourly visits to look out for respiratory distress and importantly, should receive adequate nutrition.
- Complete blood count, urinalysis, CRP, biochemical indicators (liver enzyme, myocardial enzyme, renal function, etc.), blood coagulation function, arterial blood gas analysis, and chest imaging should be investigated according to the conditions of the patients.
- Cytokines testing can be done if available.
- Effective oxygen therapy measures should be provided in time, using nasal cannula, oxygen masks, and high-flow nasal cannula oxygen therapy.
- Early intubation and protective mechanical ventilation are recommended and make sure closed tracheal aspiration systems are used.<sup>[16]</sup>
- NIV to be avoided due to high risk of aerosol dispersion.<sup>[16]</sup>
- Treatment with nitric oxide and/or sildenafil (0.5–2 mg/kg/dose Q4–6 h with a maximum of 20 mg/dose Q8 hours) for patients with persistent hypoxemia.<sup>[16]</sup>
- ECMO

### ANTI-VIRUS TREATMENT

- Hydroxychloroquine/chloroquine (5–10 mg/kg/day of basic chloroquine for 10 days) and azithromycin (10 mg/kg on the 1<sup>st</sup> day, followed by 5 mg/kg/day for 4 days with a maximum dose of 30 mg/kg or 1500 mg).<sup>[16]</sup>
- Antiviral agents, such as oseltamivir, ribavirin, ganciclovir, remdesivir, lopinavir, and ritonavir, have been used to reduce the viral load to prevent potential respiratory complications without any success.<sup>[16]</sup>

### IMMUNOMODULATORY TREATMENT IN CHILDREN WITH COVID-19

- Glucocorticoids to be considered in patients with COVID-19 and hyperinflammation.<sup>[17]</sup>

- Anakinra at >4 mg/kg/day I.V/S.C is found to be safe in severe infection and maybe be beneficial if administered before invasive ventilation.
- Tocilizumab (<30 kg: 12 mg/kg IV; >30 kg: 8 mg/kg IV, max: 800 mg) may be effective in reducing the mortality. It may increase risk of bacterial and fungal infection.<sup>[17,18]</sup>

### ANTIPLATELET AND ANTICOAGULATION THERAPY IN MIS-C

- Low-dose aspirin (3–5 mg/kg/day; max 81 mg/day) in MIS-C and KD-like features and/or thrombocytosis (platelet count  $\geq 450,000/\mu\text{L}$ ) and continued until normalization of platelet count and confirmed normal coronary arteries at  $\geq 4$  weeks after diagnosis. Contraindicated in patients with a platelet count  $\leq 80,000/\mu\text{L}$ .<sup>[17]</sup>
- Children with dilated coronary artery are recommended to receive enoxaparin at therapeutic dose along with low dose of aspirin.<sup>[17]</sup>
- For MIS-C patients who do not meet the mentioned criteria should have a tailored antiplatelet and anticoagulation therapy based on risk for thrombosis.<sup>[17]</sup>

### IMMUNOMODULATORY TREATMENT IN MIS-C

- High-dose IVIG (typically 1–2 g/kg) is recommended for the treatment of MIS-C. Cardiac function and hydration status should be checked before IVIG administration. IVIG to be administered when cardiac function is restored.<sup>[17]</sup>
- Low-moderate-dose glucocorticoids to be considered for the treatment of MIS-C. High-dose, IV pulse glucocorticoids may be considered to treat patients with life-threatening complications, such as shock, especially refractory shock.<sup>[17]</sup>
- Anakinra (IV or SQ) can be considered for the treatment of MIS-C refractory to IVIG and glucocorticoids or in patients with contraindications to these treatments.<sup>[17]</sup>

### DISCHARGE CRITERIA

- Clinical recovery:
  - Afebrile >3 days,
  - Resolution of symptoms and radiologic improvement.
- Two negative PCR tests taken 24 h apart.<sup>[14]</sup>

### PROGRESSION OF DISEASE

- From the data available, the average time taken from the onset of disease to clinical recovery for mild cases is approximately 2 weeks, while it is 3–6 weeks for patients with severe or critical disease.<sup>[14]</sup>

- Onset of severe disease from initial symptoms, including hypoxia, is 1 week.<sup>[14]</sup>
- Among patients who have died, the duration of the disease ranges from 2 to 8 weeks.<sup>[14]</sup>

Early identification of cases and contacts allows for earlier treatment and better recovery.

### PROGNOSIS

- Symptoms in infected children are relatively mild.
- According to the cases currently treated, most of the patients have a good prognosis and a few are in severe condition.
- The prognosis of the elderly and patients with chronic underlying diseases is relatively poor.
- Prognosis of COVID-19 in pregnant and non-pregnant women of similar age appears to be equal.<sup>[14]</sup>

### RECOMMENDATIONS AFTER DISCHARGE

- After discharge, it is advised to continue to monitor self-health for 2 weeks, wear mask, and if possible, live in a single room with adequate ventilation.
- Avoid close contact with family members, eat separately, keep hands clean, and avoid outdoor activities.
- Go to the hospital for a follow-up visit at the 2<sup>nd</sup> and 4<sup>th</sup> weeks after discharge or at the onset of recurrence of any symptoms.<sup>[14]</sup>

### Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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