



A Review of COVID-19 in Children

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Abstract

Since the outbreak of COVID-19, global concern emerged inspiring scientists to dedicate more attention to this pandemic. The disease caused by a novel coronavirus requires urgent striking action to probe the disease phases and find a proper cure. In this regard, the necessity of brief and thorough explanations comes into view. In this study, we gathered useful information about the virology, pathogenesis, epidemiology, manifestations, diagnosis, and treatment with special consideration of pediatric patients. This review article helps medical caregivers to receive a quick and effective approach to deal with this disease in their practice.

Keywords: COVID-19, Children, Pediatrics, SARS-CoV-2

1. Context

The outbreak of novel coronavirus infection in Wuhan, China, in 2019 has led to a large pandemic of severe acute respiratory syndrome, designated as Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO). By April 24, 2020, there were more than 2.6 million confirmed cases and more than 181,900 deaths due to COVID-19 worldwide and 87,026 cases with 5,481 deaths in Iran (1). Of 149,760 reported cases by the United States Centers for Disease Control and Prevention [US CDC] by April 2, 2020, 1.7% were younger than 18 years while children aged < 18 years comprise 22% of the US population (2). People should be involved in health and social programs to prevent further spreading of the disease and overcome this condition. This review study helps medical practitioners to have a quick, practical approach to the disease to use in different scopes, especially pediatric medicine.

2. Virology

2.1. Viral Characteristics

Coronaviruses are a group of large, enveloped positive-sense RNA viruses that have four genera: α , β (infecting mammals) γ , and δ (mostly infecting birds) (3). SARS-CoV-2 is the seventh coronavirus that attacks the human respiratory system. It belongs to the *orthocoronavirinae* subfamily and is classified as a new beta coronavirus of group 2B

(4, 5). The virus is pleomorphic, spherical, and elliptic with 60 - 140 nm in diameter, sensitive to ultraviolet, heat, and lipid solutions such as sodium hypochlorite and ethanol (6, 7). Although the primary source remains to be investigated, it has been proposed that COVID-19 is zoonotic with a bat origin (3, 8). The virus genome has 6-11 open reading frames (ORF). In the genome, ORF 1a/b encodes 16 non-structural proteins. Four essential structural proteins, including S, N, M, and E proteins are encoded by the rest of the genome. spike (S) glycoprotein binds to host cell ACE2 receptors. The N and E proteins interfere with host immune response, and the M protein transports transmembrane nutrients (9). The S protein is classified into S1 and S2 subunits. The S1 subunit interacts with ACE2 receptors and is critical for host cell entry with the receptor-binding domain (RBD), while S2 mediates membrane fusion through heptad repeat 1 (HR1) and HR2 (5, 9).

2.2. Viral Replication

The viral invasion starts with the attachment of a capsid surface protein, called spike glycoprotein (S protein), to angiotensin-converting enzyme 2 (ACE2) receptors of pulmonary epithelial cells; it is similar to what happens in SARS coronavirus infection. The epithelial surfaces of vessels, lungs, and intestine are replete with ACE2 receptors (10). The affinity of SARS-CoV-2 to ACE2 is very high (4, 5). When the virus is fused, the RNA genome is released and translated into two polyproteins ppla and pplab. These

proteins establish the replication-transcription complex (RTC) in a vesicle. Repeated replication of RTC leads to the formation of a nested set of subgenomic RNAs that encode accessory and structural proteins. Viral particle buds contain genomic RNA, nucleocapsid proteins, and envelope glycoproteins. The exact mechanisms of endocytosis and pathogenesis of SARS-CoV-2 remain to be clarified (9).

3. Pathogenesis

The pathogenesis of COVID-19 can be classified into two phases. The first phase consists of the illness caused by the virus itself, and the second phase is due to the immunological host response. A three-stage classification system is proposed to explain the pathogenesis of the disease.

The first stage consists of the inoculation period for the establishment and multiplication of the virus in the host. Mild early nonspecific upper respiratory tract symptoms (fever, malaise, and dry cough) may be seen in this stage. Positive pharyngeal PCR, chest imaging, lymphopenia, neutrophilia, serology, and liver function tests (LFTs) may occur (10). The second stage comprises viral pneumonia, which can be divided into two stages (IIa and IIb) based on the presence of hypoxia. The manifestations of this stage include fever, cough, and possibly hypoxia. Positive chest imaging, increased lymphopenia, positive LFTs, and elevated systemic inflammatory markers can also be identified (10).

As the most severe stage, stage III consists of the systemic hyperinflammatory syndrome (10). It is theorized that the elevation of IL-6 causes “cytokine storm”, an increased immune reaction in the host (11). The clinical manifestations of this phase comprise multi-organ failure, shock, myocarditis, respiratory failure, and renal failure, somehow similar to hemophagocytic lymphohistiocytosis. Decreased T helper, cytotoxic lymphocytes, and regulatory lymphocytes, as well as increased inflammatory cytokines and biomarkers, can be found in this stage (10).

4. Epidemiology

4.1. Epidemiologic Data

The novel coronavirus (SARS-CoV-2) arose when several inexplicable pneumonia cases were reported in Wuhan, China, in December 2019 (12). The WHO was concerned about the early epidemics in China, Italy, and Iran (13). While China seems to be on the comeback trail, almost all other countries are tackling with copious pressure on their health and medical systems (14). Regarding the recent emergence of the virus and the unavailability of vaccines,

the whole population is naive and susceptible to SARS-CoV-2 (15).

At present, COVID-19 is extremely infectious but less fatal than SARS and MERS (9, 16). The fatality rates of SARS-CoV-1 and MERS-CoV were estimated at 10 % and 37%, respectively. Since we are in a pandemic phase of COVID-19 infection, its total fatality rate is determined in the future. Based on the Chinese Center for Disease Control and Prevention (CDC), the survival rate of SARS-CoV-2 depends on multiple factors including the phase of the outbreak, gender (2.8% for males vs. 1.7% for females), age, and underlying health conditions (especially cardiovascular disease) (14). However, the reported fatality rate in China was less than 4% (17, 18). The cumulated attack rate (CAA) of SARS-CoV-2 was 0.11% in Hubei, China, which is 50 times higher than that of influenza virus pH1N1; as a result, social distancing and self-quarantine are emphasized (19).

The epidemiologic data of age and sex have been studied in many reviews. Dong et al., investigating 2,135 pediatric patients with COVID-19 in China, showed all age groups were susceptible to the disease, and there was no sex difference among patients. The median age was seven years (range 2 - 13 years), and 56.6% were boys (20). Based on the US CDC, the median age of pediatric patients was 11 years, and 57% were males (2). However, in a systematic review, of 2,228 children suspected to COVID-19, the age ranged from one day to 16 years, and 70.32% were boys (21). The male susceptibility to disease may be due to biologic factors (2).

4.2. Children Vulnerability

Similar to the previous SARS and MERS outbreaks, the current epidemiological data suggest a low incidence in children (22-24). This may be due to their imperfect function and development of the ACE2 protein and lower intracellular response of alveolar ACE2 receptors than in adults. The low level of adaptive immune response caused by the immature immune system of children may play a role in their low vulnerability to this disease. Children often present mild symptoms due to low inflammatory responses related to their immature immune systems (25). In addition, the use of certain vaccines, such as Bacille Calmette-Guerin (BCG), has been proven to have beneficial effects on generating immune memory. Studies support the idea that the inoculation of BCG can be a reason for a benign version of the disease in children (16). Different incidences among particular ages may be related to the variation in the arrangement, development, and function of viral receptors. Moreover, children have a healthier respiratory system without underlying disease than have adults (26). Further studies are needed to verify these issues.

4.3. Transmission

SARS-CoV-2 can be transmitted in several ways. Animal-to-human transmission is considered the first route of transmission. Recent studies assumed a spike mutation in late November 2019 to be responsible for the initial transmission to humans (11, 27). The most common transmission way is the person-to-person transmission via direct contact and droplets (4, 19), especially during unprotected, prolonged exposure to a symptomatic patient (28). Moreover, 91% of US pediatric patients were infected by household or community contact, and 9% by traveling (2). It is noteworthy that children have an important role in viral transmission in the community (29).

There has been no evidence for transmission during cesarean sections (4) and vertical transmission in pregnant women who were infected with COVID-19 in their third trimester (30). However, a report of an infected mother stated that the neonate had a positive test result in a pharyngeal swab (19, 31). In a study of nine pregnant women with COVID-19 undergoing cesarean section, SARS-CoV-2 was examined in neonatal throat swab, cord blood, amniotic fluid, and breast milk specimen of six patients. No positive result was obtained (30). Reports from the previous SARS outbreak confirms that infected pregnant mothers may have unfavorable pregnancy outcomes such as intrauterine growth restriction, intrauterine death, and preterm birth (32). Since the novel coronavirus characteristics are still under investigation and its possible neonatal sequelae are unknown, vigorous screening programs should be considered. Long-term follow-up of both mothers and newborns can be helpful (33).

Evidence supports the presence of the virus in the gastrointestinal tract, blood sample, tear sample, and rectal swab, implying the possibility of transmission. Still, transmission through aerosols and contaminated food needs further investigations (19, 34-36). A variety of routes contributing to the transmission may vindicate the rapid spread of the disease (36). Due to evidence of feco-oral transmission even several weeks after disease, children who are not potty trained play an important role in spreading the virus in households and day-care centers (29).

5. Clinical Manifestations

5.1. General Considerations

SARS-CoV-2 shows a wide clinical presentation from asymptomatic to mild, moderate, severe, and critically ill (fulminant) disease (19, 31). The mean incubation period is three days (range 0 to 24 days) (19, 37, 38). Based on different studies, the most common symptoms are fever, cough, myalgia/fatigue, and atypical symptoms, including

abdominal pain, headache, hemoptysis, vomiting, and diarrhea (19, 31, 38). Unusual clinical symptoms such as taste and olfactory alteration and cutaneous manifestations like a rash, urticarial, and chickenpox-like vesicles have been reported, as well (39, 40). Most patients were 30-79-years-old, and less than 2% were under 19 (19, 41). As reported by the US CDC, the age range of pediatric patients was 0 - 17 years, with the median age of 11 years, and 15% of pediatric COVID-19 patients were below one-year-old. Moreover, 5.7% of all pediatric patients were hospitalized compared to 10% in adults, and 0.58% needed ICU care. Most of the pediatric hospitalized patients had the underlying disease or were younger than one year (2).

Patients older than 60 years were at a higher risk of disease. Besides, 25% of patients had at least one risk factor like hypertension and chronic obstructive pulmonary disease, including asthma (2, 19, 42). Some other risk factors include male gender, diabetes, coronary artery disease, cancer, recent chemotherapy, and immunodeficiency diseases (41-44). Acute respiratory distress syndrome, acute heart injury, secondary infections, and ICU admission mostly occur in high-risk patients (19, 41).

5.2. Children Manifestations

The early diagnosis and treatment of children with COVID-19 are better accomplished by greater attention to the history of close family contact (21). Although COVID-19 is not severe in children, infants with underlying conditions should be monitored for the progression of the disease (2). The clinical manifestations may be milder in children than in adults with a few upper respiratory symptoms such as nasal congestion and rhinorrhea (19, 31, 38). Prognosis is good in children, and most of them recover after one to two weeks (19). In a severe form, children may show tachypnea with a respiratory rate of ≥ 30 times/min, oxygen saturation of less than 93% in the resting situation, and arterial partial pressure of oxygen (PaO₂)/oxygen concentration (FiO₂) ≤ 300 mmHg. Critically ill or fulminant disease in children is defined as respiratory failure, septic shock, and other organ failures (45). It lasts 11 days from the onset of the symptoms to the need for invasive mechanical ventilation. Death might occur within 23.7 days after the symptom onset (19).

A systematic review of children's clinical manifestations reported that fever (96%), dry cough (91%), and fatigue (45%) were more common in symptomatic patients. Other manifestations include mild upper respiratory tract symptoms that were seen in 66% of patients, abdominal pain with 23% prevalence, and gastrointestinal symptoms such as vomiting and diarrhea with lower incidence. Besides, 72% of children had mild symptoms characterized by upper respiratory tract symptoms, a positive PCR test,

and a normal chest X-ray. Moreover, 22% had moderate symptoms consisting of mild pneumonia, fever, cough, fatigue, headache, and myalgia; 6% had severe disease identified by the presentation of mild or moderate disease plus manifestations of disease progression (21). Underlying diseases such as diabetes, hypertension, chronic respiratory disease, cardiac disease, aplastic anemia, and prematurity with low Apgar scores are among the prognostic risk factors (21, 46). Malnutrition, congenital heart disease, and hydronephrosis may also be important in prognosis (47). According to the US CDC, 73% of pediatric patients complained of fever, cough, and dyspnea and 5.7% were hospitalized (2).

5.3. Neonatal Manifestations

Infection with SARS-CoV-2 has been reported in newborn infants in China. It seems that the transmission is through close contact, and there is no evidence of vertical (intrauterine) transmission at present. Infection with SARS-CoV-2 should be considered in a neonate with a history of close contact with a confirmed case of COVID-19 in the family or caregivers who present with at least one clinical symptom like unstable body temperature, low activity, poor feeding, or shortness of breath, especially when chest x-ray shows unilateral or bilateral ground-glass opacities (31). Case reports have stated fever, cough, vomiting, lethargy, cutaneous mottling, and respiratory distress in neonates (47, 48).

6. Diagnosis

6.1. Etiological Diagnosis

Real-time reverse transcription polymerase chain reaction (rRT-PCR) is the recommended diagnostic method for COVID-19, as it confirms the viral RNA genome in oropharyngeal and nasopharyngeal specimens. It is necessary to consider that there is still no proven relationship between viral load, clinical manifestations, and the severity of disease (49). Serology for COVID-19 is not yet clinically approved, although some data can be found in studies (50). On the other hand, laboratory data can be used as evidence beyond etiological diagnosis and disease inspection (49).

6.2. Lab Abnormalities

In most studies, no abnormal neutrophil counts or leukocyte indices were found in children. This contradicts evidence perceived from adult labs stating leukocytosis and neutrophilia in severe cases. Indeed, the severity of the disease can be associated with lymphopenia. The limited number of severe cases in children may explain the rarity of reported lymphopenia in this group (51, 52). In the

precedent SARS and MERS outbreaks, the decreased lymphocyte count was known to be a primary feature. This was explained by cytoplasmic damage made via viral components and cell apoptosis (53-55). Similar to COVID-19, this finding is not common in young children due to their immature immune systems (56, 57). The increase in C-reactive protein (CRP) and procalcitonin (PCT) may be found. Procalcitonin in adults is correlated with unfavorable progression and severe disease, while in children, bacterial coinfection should be considered. A high level of interleukin-6 was reported in viral respiratory infections, and it was associated with the severity and mortality of the disease. Thus, it is proposed to use CRP and lymphocyte counts for measuring disease severity. Interleukin-6 and PCT can be known as benchmarks for prognosis and bacterial coinfection, respectively (58). In addition, biochemical test results illustrated abnormalities in severe cases, including decreased albumin and increased levels of cardiac troponin I, lactate dehydrogenase (LDH), liver enzymes (ALT and AST), bilirubin, creatinine, D-dimer, creatine kinase, serum ferritin, erythrocyte sedimentation rate (ESR), and prothrombin time (51, 59-61). Regarding the limited data, more studies are needed to analyze the lab results in children.

6.3. Imaging Studies

The results of imaging tests are different upon cases regarding the variety of disease stage, age, immunity status, and drug effectiveness (19). The X-ray examination and chest CT scan, if necessary, should be done for all suspected or confirmed patients (62). Imaging results of COVID-19 resemble the reports of SARS and MERS (19). The early phase is diagnosed by peripheral multiple small plaques and interstitial changes. As time passes, bilateral multiple ground-glass opacities and/or infiltrating shadows may appear. While lung consolidation may appear in serious cases, pleural effusion seems to be uncommon (62).

It is proposed that a chest CT can provide a better and clearer view of lesions than does a chest X-ray. Although CT scan and chest X-ray are useful tests for confirming COVID-19, in a study, 21% of patients with SARS-CoV-2 had normal CT scan results. Multiple lobar lesions may exist in seriously infected children (19). A four-year-old male was reported with spots in two upper lobes, right lower lobes, and left lower lobes. Another case showed bilaterally bronchovascular bundles on chest CT (25). In a review of chest CT scans of children with COVID-19 in China, moderate lung abnormalities with peripheral ground-glass lesions were reported. Children's CT findings were similar to those of adults but more modest (63).

7. Treatment

Mild cases could be symptomatically treated at home. They should be isolated to prevent transmission and monitored for clinical deterioration. The patient should have enough calorie and water intake and be assessed for vital signs and oxygen saturation. Moreover, CBC, CRP, blood biochemistry, myocardial and liver enzymes, kidney function, and coagulation test results should be assessed if needed. Physical cooling and antipyretics such as acetaminophen are recommended in case of fever and discomfort. In hypoxic patients, oxygen should be given by masks or nasal catheters, but severe cases must be admitted to the ICU (3).

Interferon- α and Interferon- α 2b have been proposed for the treatment of viral infections in the early stages of the disease. The efficacy of lopinavir/ritonavir is not fully confirmed in children (3). Other antiviral agents such as oseltamivir, peramivir, zanamivir, ganciclovir, acyclovir, and ribavirin are not recommended (9). Remdesivir has been used in COVID-19 because of its effects on SARS-CoV-2 in vitro and animal studies (64, 65). It has been reported to successfully treat the first US case of COVID-19 (66); however, many trials are ongoing to confirm its effectiveness (67). Chloroquine can inhibit replication and spread of viruses, mainly SARS-CoV. It also has an immunomodulatory effect, suppressing IL-6 and TNF- α and interfering with glycosylation of receptors. Therefore, it is used for the treatment of COVID-19 (9). Tocilizumab is an IL-6 inhibitor and may be effective in seriously ill patients with elevated IL-6, but its effect is still under investigation in many clinical trials (68). Antibiotics should be administered when bacterial co-infection is suspected. Oseltamivir can be used when co-infection occurs with other influenza viruses (3). Glucocorticoids should not be routinely used in COVID-19 pneumonia (9). Immunoglobulins and glucocorticoids are recommended for seriously ill patients (3, 10). Trials with melatonin, thalidomide, and stem cell therapy are ongoing in adults (69-72), which may be a glimmer of hope in the future.

In a recent case report from Iran, nine children with COVID-19 were treated with antiviral agents (oseltamivir), chloroquine, and antibiotics without the need for ventilatory support or use of lopinavir/ritonavir (38). In China, three children with underlying diseases needed invasive mechanical ventilation (73). In another study, eight children who were severely ill and had cytokine storm were admitted to the ICU and two of them underwent invasive mechanical ventilation (45). If respiratory support is needed and non-invasive ventilation is not effective or cannot be tolerated, one should consider invasive mechanical ventilation with a lung-protective ventilation strategy. Extra-

corporeal membrane oxygenation (ECMO) can be used in special conditions with refractory hypoxia (3). Most studies recommend supportive care, oxygen therapy, and antibiotics for superinfections. The efficacy of antiviral treatment should be confirmed in children in further studies (37). Hopefully, most case reports in children show a benign clinical course with little mortality (16, 37, 38, 73, 74).

8. Conclusion

Because of the benign course in most affected children, it is believed that supportive care, oxygen therapy, and antibiotics, if indicated, are adequate. According to disease staging, antivirals may be beneficial at the beginning of the disease, but they are not routinely recommended in children and should be used in severe cases along with corticosteroids, immunoglobulins, and tocilizumab.

Footnotes

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