

Mysterious Side of COVID-19 Pandemic: Children

COVID-19 Pandemisinin Gizemli Yanı: Çocuklar

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ABSTRACT

As of December 31, 2019, the Severe Acute Respiratory syndrome Coronavirus-2 (SARS-CoV-2) was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei province of China and has been responsible for over 40,000 deaths worldwide. Data on the epidemiologic characteristics and clinical features, diagnosis and management of infected children are limited. Despite the high mortality rate of Middle East Respiratory syndrome and SARS in adults, the morbidity and mortality rates in children are low. Understanding the role of paediatric population in the transmission dynamics of the outbreak is important and critical for effective disease containment with respect to the public health. The aetiology of the milder disease form caused by the CoVs, including SARS-CoV-2, remains unknown in children. Infected children may be asymptomatic or have fever, dry cough, and fatigue and rarely have severe disease. Asymptomatic children may be driving the transmission of CoV more than we realise. Early diagnoses and treatment along with careful isolation can limit the outbreak. Children may help in future development of immunotherapy and vaccines for SARS-CoV-2. This review aimed to summarise current data available on SARS-CoV-2 pandemic to manage the diagnosis, treatment, and prevention of CoV disease 2019 in the paediatric population.

Keywords: Coronavirus, COVID-19, SARS-CoV-2, newborn, children

ÖZ

31 Aralık 2019'dan itibaren dünya çapında 40,000'den fazla ölümden sorumlu olan 2019'un yeni koronavirüsü [Şiddetli Akut Solunum sendromu - Koronavirüs-2 (SARS-CoV-2)], Çin'in Hubei eyaletindeki bir şehir olan Wuhan'da pnömoni olgularının nedeni olarak tanımlanmıştır. Enfekte çocukların epidemiyolojik özellikleri ve klinik özellikleri tanı, tedavisi ile ilgili veriler sınırlıdır. Orta Doğu Solunum sendromu ve SARS'da yetişkinlerde yüksek mortalite oranına rağmen, çocuklarda ölüm ve morbidite oranları azdır. Salgının bulaşma dinamiklerinde pediatrik popülasyonun rolünün anlaşılması, halk sağlığı kontrolünün etkili olması için önemli ve kritiktir. Çocukların SARS-CoV-2 de dahil olmak üzere koronavirüslerin neden olduğu hastalıkları neden daha hafif atlattıkları bilinmemektedir. Enfekte çocukta semptom olmayabileceği gibi ateş, kuru öksürük ve yorgunluk olabilir ya da nadiren kritik seyredebilir. Asemptomatik çocuklar virüsün farkettiğimizden daha fazla yayılmasına neden olabilir. Erken teşhis ve tedavi ve dikkatli izolasyon salgını sınırlandırabilir. Çocuklar SARS-CoV-2 için immünoterapi ve aşıların gelecekteki gelişimine yardımcı olabilir. Bu derlemede pediatrik popülasyonda COVID-19'un tanısı, tedavisi ve önlenmesine rehberlik etmek için SARS-CoV-2 pandemisi hakkındaki mevcut veriler özetlenmiştir.

Anahtar Kelimeler: Koronavirüs, COVID-19, SARS-CoV-2, yenidoğan, çocuk

Introduction

On 31 December 2019, unknown pneumonia cases were reported in people associated with the Huanan Seafood Wholesale Market in Wuhan, Hubei Province, China. On January 7, 2020, the Chinese health authorities confirmed that this case community was associated with a new type of coronavirus (1). Later, this clinical picture was named Coronavirus disease 2019 (COVID-19), and its factor was reported as "Severe Acute Respiratory syndrome Coronavirus 2 (SARS-CoV-2)" (2).

COVID-19, which has been declared a pandemic with current data, continues to spread by increasing the number of infected cases and mortality day by day. SARS-CoV, an epidemic with viruses from the same family, appeared in 2002-2003, while 8,000 cases and 800 deaths occurred; Middle East Respiratory syndrome (MERS)-CoV appeared in 2012, causing 2,500 cases and 800 deaths (3). On March 11, 2020, the World Health Organization (WHO) classified the COVID-19 infection as a pandemic. As of March 31, 2020, more than 825,000 confirmed cases and more than 40,000 deaths (an approximate fatality rate of 4.8%) have



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been reported. Comparison of the characteristics of SARS, MERS and COVID-19 diseases are shown in Table 1 (3,4).

For now, the main source for the disease is patients infected with COVID-19. Contagion is known to be through droplets or contact from the respiratory tract, but there is no clear information about the fecal-oral or vertical transition. One of the key differences of the coronavirus 2019 pandemic is that most of the information is generated by adult patient data. MERS-CoV infection, which is from the same family as COVID-19 disease factor, also affects children less and has less mortality if the affected patient does not have any underlying comorbid disease (5). As discussed in detail below, information about infected children and infants is limited and scattered.

The first pediatric case was reported on January 20 in Shenzhen. On February 10, 398 confirmed cases of children were reported in China outside the Hubei region. Hubei region was excluded because children were screened less in there (6,7). Numbers reported from Italy on 18 March were that 1.2% of 22,512 cases were children and it did not cause death in children (8). On March 16, the United States announced that 5% of 4,226 COVID-19 cases were children (9). In a report from China, only 2% of COVID-19 infections were in people under 20 (10). Similarly, only 6.3% of the nearly 8,000 infections in South Korea have been seen in those under the age of 20 (11). Like MERS-CoV, there may be different reasons why SARS-CoV-2 is rarely seen in children. As discussed below, children surviving with asymptomatic or mild symptoms may be due to low exposure to the virus, immature immune systems and a number

of factors that are not yet identified. The more screening is done, the higher the rate may appear in children and adolescents.

This article is compiled in order to make earlier diagnosis of asymptomatic children which are considered as a hidden source rather than the patient in infectious and epidemic prevention studies and to review the innovations in treatment, with the differences in diagnosis, stimulant clinical findings and laboratory data.

Etiopathogenesis

Coronavirus was first isolated in the tissue culture of a patient with a cold in 1965. Culture durations are 4 days in human airway epithelial cells and 6 days in Vero E6/Huh - 7 cells. CoVs are single-chain, enveloped, ribonucleic acid (RNA) viruses that can be isolated from different animals in diameters of about 60 to 140 nm (12). SARS-CoV-2 has low resistance to external environment, it is easily deactivated at 56 °C in 30 minutes or with 60-80% ethanol and chlorinated disinfectants, chloroform (excluding chlorhexidine) and peracetic acid (13).

The Coronaviridae family is part of the Nidovirales team, consists of the Coronavirinae and Torovirinae subfamilies, causing various diseases in the respiratory, enteric, neurological and hepatic system by infecting mammals and birds (3). The virus family can be examined in 4 groups. Alpha and beta groups infect mostly mammals, gamma and delta mostly birds. The most known subgroup is the genus Alpha-coronavirus, which causes classic cold symptoms in human. SARS-CoV and MERS-CoV are in genus Beta-coronavirus. It is known that both

Table 1. Comparison of the characteristics of SARS, MERS and COVID-19 diseases (3,4,9)

Properties	SARS	MERS	COVID-19
The first reported patient	Guangdong, China November 2002	Zarga, Jordan April 2012 Saudi Arabia June 2010	Wuhan, China December 2019
Virus	SARS-CoV	MERS-CoV	SARS-CoV-2
Subgroup of the virus	Beta-coronavirus	Beta-coronavirus	Beta-coronavirus
Host cell receptor	ACE-2	Dipeptidil peptidaz 4	ACE-2 (possibly)
Animal host	Bat (natural carrier) Musk cat and raccoon (intermediate host)	Bat (natural carrier) Single humped camel (intermediate host)	The bat (possible natural carrier) can be the intermediate host in the seafood market (pagolin?)
Incubation period	2-14 days	2-13 days	2-14 days
The period from the start of the disease until the hospital application	2-8 days	0-16 days	0-9.1-12.5 (data incomplete)
Contagion rate	2-3	>1	2.2
Number of patients	8098	2506	825,000 (31 March 2020)
Adult	93%	98%	90%?
Child	5-7%	2%	2.5-10%?
Age range	1-91 years	1-94 years	36 hours-89 years
Gender M/F	43-57%	64.5-35.5%	56-44%
Number of deaths	774	862	41000 (31 March 2020)
Mortality	9.6%	35-40%	4.8% (31 March 2020)
Effects in pregnancy	3/12 pregnancy death No vertical transition	No vertical transition	No vertical transition? (In 36 hour newborn SARS-CoV-2 PCR +)

SARS: Severe acute respiratory syndrome, MERS: Middle East respiratory syndrome, COVID-19: Coronavirus disease 2019, M/F: male/female, PCR: polymerase chain reaction, ACE-2: angiotensin converting enzyme-2

viruses tend to infect intrapulmonary epithelial cells instead of upper respiratory epithelial cells (14). SARS-CoV-2 virus, which has a cytopathic effect in cell culture and is in beta group, has been shown to have a 86.9% nucleotide sequence similarity with bat-derived SARS-like CoV (bat-SL-CoVZC45, MG772933.1) in phylogenetic analysis. The SARS-CoV-2 chain is 79% similar to SARS-CoV and 50% similar to MERS-CoV (15). Its phylogenetically similar features shed light on the treatments developed.

Differences in Sensitivity of Children and Adults to COVID-19

There are some studies investigating why the disease is transmitted in children with a milder clinic picture. Due to the immature immune system in children, there are some data supporting the rarely occurrence or slight affect of some infections. For example; It has been shown that immature mice do not have poliovirus-induced paralysis due to maturational changes of the axonal transport system (16). Another thesis is that children have a more active natural immune response. Unlike adults, less exposure to air pollution and cigarette smoke, and other factors such as underlying diseases are thought to be the reason for the healthier airways of children. In addition, acute respiratory distress syndrome (ARDS) was associated with a much stronger immune response reaction in adults. One of the most remarkable reasons among these is that the distribution, maturation and functional differences of viral receptors vary depending on age. SARS-CoV, SARS-CoV-2 and human coronavirus NL63 use the SARS-CoV receptor, namely angiotensin converting enzyme-2 (ACE-2) as a cell receptor to enter the host cells in humans. As a result, these and similar effects can be cited as the reason why children are more resistant to COVID-19 infections (17).

Expression of ACE-2 in the lungs of mice has been found to be significantly reduced with increasing age. Although this is not consistent with children's low sensitivity to SARS-CoV-2, it has also been noted that ACE-2 functions as the protective mechanism of the lungs. It has been demonstrated in experimental mouse studies and pediatric patients that ACE-2 plays a protective role from severe lung damage caused by virus infections involving the respiratory tract. ACE-2 also protects against acute severe lung damage triggered by sepsis, respiratory syncytial virus (RSV), acid aspiration, SARS, and terminal bird flu H5N1 virus infection. In addition, administration of the recombinant ACE-2 protein has been shown to reduce the severity of lung damage caused by RSV. Even decrease in ACE-2 protein levels in the lungs of mice was detected during RSV infection (18).

In a different study, it was reported that the main reason for children to be less affected is that ACE-2 protein actually acts as a receptor for virus entry, but is related to the development and function of ACE-2 protein, such as low sensitivity, low binding ability or differences of ACE-2 in children. Thus, the fact that ACE-2-induced intracellular response in alveolar epithelial cells in children lower than in adults is considered as the reason of that children are less affected by the disease (19).

ACE-2 is a surface molecule and is also expressed in the upper esophageal epithelial cells and in the absorptive parts of enterocytes in the ileum and colon, and mostly in AT-2 cells located in the lungs. This explains how COVID-19 affects the digestive system, like the lungs, as a potential pathway. The ACE-2 expression level in Asian populations is significantly

higher than in European and American populations. ACE-2 expression in men's cells is higher than in women's. The high incidence of coronavirus in Asian men can explain the pneumonia rates (19).

In adults infected with the SARS-CoV-2 virus, there is a markable or progressive decrease in the number of peripheral absolute lymphocytes at an early stage. Both the CD4+ and CD8+ lymphocyte count decrease, and the neutrophil/lymphocyte ratio increases as SARS-CoV-2 consumes lymphocytes as an early and prominent sign (20). This proves that the virus used lymphocytes to reproduce and spread in the early stages. Adult cases become severe within 7-10 days from the onset of the disease. As a result of rapid virus replication, inflammatory cell infiltration, proinflammatory cytokines, and chemokine response increase, transition to ARDS, which is fatal lung injury occurs (20). The fact that the number of leukocytes and absolute lymphocytes is quite normal and there is no decrease in lymphocytes after the SARS-CoV-2 infection in children suggests that there is fewer immune dysfunction.

On the other hand, mild COVID-19 disease in children may be associated with trained immunity/active immunization. The creation of a trained immune system is a new immune model. Some designated vaccines, such as Bacillus Calmette Guerin (BCG), create immune memory by training natural immunity. In a study in mice, nonspecific protection against influenza virus has been demonstrated by stimulating trained immunity depending on BCG vaccine administration. Most of the children in China and Asia are regularly vaccinated according to the routine scheme, which also includes BCG. In the light of this information, it should be investigated in more detail in terms of educating the immune system with vaccination, which may be one of the reasons why children have less ARDS than adults (21).

Infectiousness

Although the incubation period of the virus is known as 5-6 days, it can be extended up to 14 days. Contagion begins 1-2 days before symptoms begin. The infection was initially seen among the adults, and then the elderly and children become infected by spreading around the family and creating a "cluster". SARS-CoV-2 is transmitted from human to human by droplet, contact and aerosol. Infection occurs when these droplets are inhaled or touched on the surfaces contaminated by the virus and then brought to the nose, mouth and eyes. Although it is known that it cannot travel more than 2 meters in the air and cannot remain suspended for a long time, it has been shown in an article that SARS-CoV-2 aerosols can remain active for at least 3 hours under experimental conditions (22). Therefore, attention should be paid to aerosol-forming conditions and processes to reduce spread in this way (Table 2) (23).

Vaginal birth is considered as a transmission route due to close mother-baby contact. Although it is thought that the possibility of transmission in vaginal birth is high, there is no evidence of this. SARS-CoV-2 was found to be negative in all babies born with cesarean from 9 symptomatic pregnant women with COVID-19. Amniotic fluid, cord blood samples from six patients, nasopharyngeal specimen from neonates and breast milk samples resulted negative for SARS-CoV-2 (24). In an article suggesting vertical transition and showing that newborns were affected, thrombocytopenia was observed along with 1/10 death

Table 2. Aerosol-forming states and processes (95)

Cough/Sneezing	Endotracheal intubation
Drug administration with nebulization	Separation of ventilator circuits
Oxygen therapy with nasal cannula	Open system tracheal aspiration
Oxygen delivery rate is more than 6 min/liter	Tracheostomy
Oxygen therapy with high flow nasal cannula	Bronchoscopy
Non-invasive mechanical ventilation	Cardiopulmonary resuscitation
Positive pressure ventilation with balloon mask	

incidence, premature birth, fetal distress, respiratory failure, impaired liver function (25). In a letter-type article, it was claimed that a serum-specific IgM-type antibody specific to SARS-CoV-2 was detected in the serum of the newborn, suggesting a vertical transition (26).

The isolation of SARS-CoV-2 in stool and anal swab in mother and infant without gastrointestinal symptoms supports possible faecal-oral passage as a potential passageway. The subsequent positivity of fecal RNA from the positivity of pharyngeal RNA may suggest that the virus has been ingested and passed into the digestive system. Also, fecal RNA negativity occurs much later than pharyngeal RNA negativity. After pharyngeal samples become negative, sputum and stool tests can remain positive for up to 39 and 13 days, respectively. It may be related to the fact that the digestive system clears the virus much slower than the respiratory system (27-29). In the urine sample, RNA was detected in very few patients. Despite this, many studies have not shown virus spread in the urinary system (27,28,30).

Is There a Connection Between Transmission and Viral Load?

Seventy six COVID-19 patients verified with reverse transcription polymerase chain reaction (RT-PCR) were evaluated at Nanchang University. The average viral load of severe cases was found to be 60 times higher on average than mild cases, suggesting that higher viral loads may be associated with serious clinical consequences. In 90% of mild cases, the RT-PCR tests became negative on the 10th day after the onset of the disease, also demonstrating early viral clearance in mild cases. In all severe cases, RT-PCR test was positive on the 10th day or later. Patients with severe COVID-19 disease picture appear to have a high viral load and a long virus release time. This finding suggests that the viral load of SARS-CoV-2 may be a useful marker to assess disease severity and prognosis (31).

Clinical Findings

It is known that the incubation period of SARS-CoV-2 is between 1 and 14 days (an average of 5.2 days) and symptoms of 97.5% of those symptomatic occur within 10.5 days (32). The latest diagnosis was made on day 42 from the onset of the disease (average 2 days, range: 0 to 42 days) (33).

In the series prepared with data of 2,143 children (median age 7), including 731 (34.1%) laboratory-approved cases and 1,412 (65.9%) suspected cases with COVID-19 infection, without gender difference, more than 90% of all patients have asymptomatic, mild or moderate clinical picture. The most common clinical symptoms in 171 confirmed patients were cough (48.5%), pharyngeal erythema (46.2%), fever

(41.5%), diarrhea (8.8%), fatigue (7.6%), nasal flow (7.6%) and vomiting (6.4%). 32.2% of the patients had a high fever of 38 °C. Tachycardia (42.1%) and tachypnea (28.7%) were common findings at admission (33). Another study on 6 children aged 1 to 7 years hospitalized with COVID-19 in Wuhan, all had fever >39 °C and cough, four of them had viral pneumonia on imaging, and one patient was taken into intensive care. All children were recovered and discharged (34). In the study conducted out of the neonatal group, most of the patients' (8/10) fever recovered within 24 hours (35). One of the diagnosed patients had only diarrhea (36). 5.2% of patients had dyspnea, central cyanosis, severe with less than 92% oxygen saturation level and 0.6% of them had respiratory failure, ARDS, shock, multiorgan failure (encephalopathy, heart failure, coagulation disorder and acute renal failure, etc). Only 4 children had oxygen saturation below 92% (33). In the first case series article on children with COVID-19, it was additionally shown that the fever period was shorter and resolved rapidly in mild cases (28). Some patients with or without cough symptoms may have patchy infiltration in their pulmonary X-rays. In a 10-year-old asymptomatic child, frosted glass opacity was observed in his radiological examination. Therefore, in case of doubt, only clinical findings may not be sufficient for diagnosis.

The clinical course of COVID-19 is generally milder in children than in adults. It can range from asymptomatic infection to severe respiratory distress in newborns and children. Critical and severe cases were higher in groups under 1 year and under 5 years. Patients with critical condition and rapidly developing respiratory failure who need invasive mechanical ventilation generally have an underlying disease history. It appeared in 7-months-old patient with intensive care need hydronephrosis, receiving chemotherapy treatment for leukemia, having intussusception (37), congenital heart disease and moderate malnutrition; and in a 13-month-old patient with hydronephrosis and left kidney stone (38). Following the intensive care follow-up and multiorgan dysfunction in a 55-day-old baby with an unknown underlying disease, on the 11th day, the clinical picture started to improve and patient discharged (39). Focal pneumonia finding in computerized tomography (CT) scan in children (4/10) also improved without requiring additional oxygen therapy (35). 1.6-2.5% of 123 children reported in the USA were hospitalized, and none of them needed intensive care (9).

Six child deaths, the diagnosis of which was clarified until March 29, 2020, were reported. Deaths of 10-months-old with intussusception and multiorgan failure (36), 14-years-old whose data are not clearly explained in the study (37), 3-years-old with leukemia in Iran, 6-years-old with asthma and 35-days-old with no information (40), and a child under 1 year in Chicago, 12-years-old girl in Belgium and a 13-year-old male in England has been reported (41,42).

The lowest APGAR scores of the newborns were 8/9 in the study, which was followed by 9 pregnant women who had a cesarean with symptomatic COVID-19 without severe COVID-19 pneumonia. In SARS infection, pregnant women infected with SARS-CoV-2 were monitored more closely because 50% of pregnant women needed intensive care, 33% received mechanical ventilation support, and the mortality rate in this group of patients was 25% higher than the population. However, none of the pregnant women needed intensive care.

Data on newborns are limited. While a 17 day newborn had symptoms of fever, cough and vomiting, the asymptomatic 30 hour newborn born from a mother infected with the SARS-CoV-2 was diagnosed with a viral nucleic acid test. In another newborn, whose mother was infected with SARS-CoV-2, fever occurred on its 5th day of birth, vital signs of these newborns remained stable, and no severe or emergency occurred (43,44).

The classification of the clinical picture of the patients provides guidance for the course of the disease and treatment needs. Clinical condition classification (45):

1. Asymptomatic - silent - infection

Pediatric patients with positive SARS-CoV-2 RT-PCR test without clinical symptoms or abnormal pulmonary imaging

2. Acute upper respiratory tract symptom findings

Only in the presence of cough, fever, sore throat, nasal congestion, fatigue, headache, myalgia and weakness without the appearance of pneumonia or sepsis on pulmonary imaging.

3. Mild pneumonia

In the presence or absence of fever, respiratory system symptoms such as cough and symptoms indicating pneumonia from pulmonary imaging and in the period that have not met the criteria for severe pneumonia.

4. Severe pneumonia

In the presence of one of the following criteria:

- Increased respiratory rate: 70/min respiratory rate under 1-year-old, sedated over 1-year-old and over 50/min without fever,
- Oxygen saturation: <92%,
- In the presence of hypoxia symptoms: nasal wing breathing, difficult respiratory symptoms such as moaning, cyanosis, intermittent apnea, etc,
- Consciousness disorders; somnolence, coma, or convulsion,
- Symptoms of dehydration with difficulty feeding or food rejection.

5. Critical cases

In the presence of one of the following criteria and need of intensive care:

- Respiratory failure requiring mechanical ventilation support,
- Shock,
- Accompanied by other organ failures.

Laboratory Evaluation

The leukocyte count is normal (69.2%) or decreased in the early stage of the disease. 4.6% neutrophilia and 6% neutropenia were observed (46). The lymphocyte count is reduced and lymphopenia deepens as the severity of the disease increases. Lymphopenia may be rarely seen in very young children depending on the immune system response (47,48).

Increased liver enzymes and raise in inflammatory indicators such as C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), sometimes hyperglycemia have been detected in studies conducted on adults (48). Most children cases have high CRP and ESR levels and normal PCT levels. PCT and CRP increase was seen in 13.6% and 10% of the patients, respectively (46). It is recommended that attention should be paid to increase in PCT in children in terms of coinfection (8/20: 40%) -influenza A and B viruses, mycoplasma, RSV and cytomegalovirus- (49). Bacterial coinfections should also be noted. In severe cases, high D-dimer levels are remarkable. Liver, muscle enzymes, troponin I, LDH levels and myohemoglobin levels have increased in some patients (39,45). IL-6 level which also increases in viral diseases may be high during the course of disease in critically ill patients. It may be useful to follow up with the number of CRP and lymphocytes as a prognostic marker (46). Higher plasma cytokines IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A and TNF- α (cytokine storm) in adult patients in intensive care than patients in non-intensive care units were measured (50).

SARS-CoV-2 nucleic acid test positivity in nasopharyngeal swab, sputum, lower respiratory tract secretions, stool and blood samples are diagnostic tests. Although nasopharyngeal swab is the most commonly used test, it provides less than 50% positivity. Repetitive tests are required (51).

Imaging Methods

In diagnosed patients, pulmonary X-ray sensitivity is 59%, CT sensitivity is 98% and RT-PCR sensitivity is 71% (52). In COVID-19 patients, findings in favor of the disease can be detected in lung imaging rate close to clinical and laboratory findings rate. Therefore, it is an important examination in the diagnostic approach. Viral pneumonia-like changes were detected in 70.4% of 134 children in lung imaging (38).

In suspicious and diagnosed cases, pulmonary X-ray should be performed as soon as possible. If necessary, pulmonary CT scan should be performed immediately. Multiple small plaques and interstitial changes in the lung periphery can be observed in the early stages of the disease, and bilateral multiple ground glass opacities and/or infiltrations in later stages. Bilateral pulmonary lesions (more than 50%) are more common than unilateral lesions. Small nodular appearance and pleural effusion are much rarer. The halo sign around the lesion is more specific to pediatric patients. Lung consolidation exists in more serious cases (49).

In 81 adult patients' radiological findings, COVID-19 pneumonia tends to occur as air bronchograms, peripheral infiltration and bilateral, subpleural, ground-glass opacities mostly in the right lower lobe in pulmonary CT scans. Abnormal pulmonary CT findings may be present even in asymptomatic patients. The lesions spread rapidly within 1-3 weeks after the onset of symptoms, and the frosted glass appearance

increases or can turn into a consolidation pattern and peak approximately 2 weeks after the onset. Follow-up age, involvement characteristics in CT, male gender, underlying comorbidities and progressive radiographic deterioration may be risk factors for poor prognosis in patients with COVID-19 pneumonia (53).

In the first newborn case with COVID-19 pneumonia, increased linear opacities were detected on pulmonary CT scan (43). The youngest patient, diagnosed with COVID-19, with viral pneumonia on CT scan without mild fever, is a 24 hour case (38).

Pneumomediastinum was detected in an adult COVID-19 patient's pulmonary CT scan following the development of respiratory distress during hospital follow-up. Spontaneous formation of pneumomediastinum in COVID-19 patients should be closely monitored as a potential indicator of ingravescence disease (54). The classification made by evaluating CTs of adult COVID-19 cases according to their periods (Table 3) will be useful for patient follow-up and staging (55).

Diagnosis

Clinic is often used for diagnosis. In the epidemiological study in China, laboratory values (normal or low white blood cell count, increased CRP) and abnormal chest X-ray were used for diagnosis in the presence of at least two symptoms (fever, respiratory symptoms, gastrointestinal symptoms or fatigue) (37).

Definitive diagnosis of COVID-19 is made using nasal or pharyngeal swabs or blood samples. RT-PCR results should have been found positive by amplifying SARS-CoV-2 nucleic acid on the samples taken. Epidemiological data can be obtained by genetic sequencing. However, this test also has certain limitations; high false negative rates have also been reported. The use of rapid antibody test is also recommended to quickly identify a large number of infected patients and asymptomatic carriers in the fight against the virus. The measurement of IgM and IgG antibodies against SARS-CoV-2 virus in the blood of patients at different stages can be done by immunochromatographic card test within 15 minutes. The sensitivity of this test is 88.66% and its specificity is 90.6%. This test can be used for rapid screening of symptomatic or asymptomatic SARS-CoV-2 vectors (56).

Early Diagnosis of Critical Cases

In the light of experiences from community-acquired pneumonia cases, those who had contact with infected cases or had a concomitant disease (congenital heart disease, bronchopulmonary hypoplasia, respiratory anomaly, severe malnutrition) or immune deficiency or immune compromised (prolonged use of immunosuppressants, etc) can be diagnosed early. Cases with these features are likely to become serious cases in the presence of one of the following criteria (45).

- Dyspnea: In the absence of sedation and no fever, respiratory rates to be >50/min in 2-12 months old, > 40/min in 1-5 years old, >30/min in over 5 years old.
- Persistent high fever for 3-5 days,
- Low mental response, lethargy, mental fog and change,

- Increased enzyme levels (myocardial, liver enzymes and lactate dehydrogenase),
- Unexplained metabolic acidosis,
- Infiltration in bilateral or multiple lobes, lung imaging with pleural effusion, or rapid deterioration in general condition,
- Patients under 3 months,
- Extra pulmonary complications,
- Coinfection with other viruses and or bacteria.

Differential Diagnosis

Influenza, parainfluenza, adenovirus, RSV, rhinovirus, human metapneumovirus, SARS-CoV, other viral infections, mycoplasma pneumonia, chlamydia pneumonia and bacterial pneumonia are important in the differential diagnosis. The possibility of coinfection should also be considered during diagnosis (45).

Patient Management

Depending on their medical condition, suspicious patients should be isolated in a single room or at home. Cases with definitive diagnosis can be kept in the same area (in cohort) at home or hospital. Critical cases should be admitted to the intensive care unit as soon as possible. In case of a pandemic, national (Ministry of Health) algorithms must be followed (57-59).

Medical staff must protect themselves first. Hand hygiene should be provided with alcohol-based hand antiseptic. During the processes causing droplets or aerosolization, protective equipments are bone, goggles and face shield, FFP2 (N95) or FFP3 mask, apron and if possible at least 2 layers of gloves. It is recommended to use in accordance with the dressing and take off algorithm (Figure 1) (23). Especially during operations that produce aerosols, it is necessary to minimize its spread and take protective measures (Table 2) (23).

If medication is required via the inhalation route, an aerochamber or metered dose inhaler may be used. During treatment with the nasal cannula, wearing a surgical mask on the cannula, attaching the bacteria virus filter suitable for the ventilator circuits, using the double circuit in the ventilator in which the expiratory air is not given outside, performing the operations that create an aerosol in a negative pressure room can reduce the risk. Maneuvers should be carried out to use the balloon mask as little as possible. If it is still necessary to use a balloon mask, a virus filter and PEEP valve should be installed between the mask and the balloon. Balloon mask should also be made in accordance with the e-c technique. Low pressure should be used and a transparent pouch should be used to prevent virus spread. Use of laryngeal mask instead of balloon mask may be a good choice in suitable patients. Using a video laryngoscope, if available, during intubation may increase the distance between the patient and the doctor. After the intubation tube passed the vocal cords, the cuff must be inflated using the cuff manometry. Aspiration should be performed with a closed system (23). It is important to make sufficient neuromuscular blockade to reduce aerosol production during interventions such as tracheal intubation and to perform the procedures smooth and uncomplicated.

Isolation for diagnosed pediatric patients;

Inpatients need to be isolated in a single room, and those with high infectivity need to be isolated in a negative pressure ward. Attention should be paid to strict disinfection of children's stool and secretions. Outpatients should be isolated with the guidance of a doctor at home, under the supervision of the parents and treated under the supervision of the community and the doctor's remote guidance. In 14 days after the disease, isolation should be terminated by respecting SARS-CoV-2 nucleic acid in respiratory secretions at least 2 times with a negative result. In daily care, attention should be paid on regular ventilation of the room, 30 minutes each time, 2 times/day; the use of an appropriate size mask and hand cleaning are points to be considered. The patients should rest, drink plenty of water, and eat nutritious foods that are easy to digest and keep balanced diet. Wearing long-sleeved clothing can be good for hygiene. Latex gloves can be worn to hold secretions and contaminated paper towels. The waste is placed in a disposable bag, sealed, and a disinfectant is sprayed on the outer surface of the packaging bag before throwing it in the trash bin. The floor of other rooms in the house, various surfaces and toys should be wiped periodically with disinfectants containing chlorine (disinfectants must remain on the surface for 5 minutes). Children's used clothes, towels and sheets are thoroughly washed with hot soapy water.

General Treatment

General treatment mainly includes bed rest and supportive therapy. Ensuring adequate calorie and water intake; preservation of water-electrolyte balance and homeostasis; monitoring vital signs and oxygen saturation; other necessary biochemical evaluations, including keeping the airways open and supplying oxygen when needed, following routine blood and urine tests, CRP, liver and renal function, myocardial enzyme levels and coagulation parameters, blood gas should be planned according to the patient's condition. Pulmonary imaging may need to be renewed intermittently. CT scan is recommended (45). For patients in critical condition, prophylaxis should not be forgotten for the risk of gastrointestinal bleeding. In addition, besides mechanical protection measures such as variable air pressure beds to protect the patient against venous thromboembolism, pharmacological prophylaxis (preferably low molecular weight heparin or heparin 5000 units can be applied under the skin 2 times a day) can be performed in adolescents if there are no contraindications (60).

Symptomatic Treatment

Patients with high fever are closely monitored. In cases exceeding 38.5 °C, physical cooling (warm water bath, antipyretic patch use etc) or antipyretic drug treatment should be performed. Orally administered ibuprofen 5-10 mg/kg/dose and acetaminophen 10-15 mg/kg/dose are used. Rapid treatment should be performed in case of convulsions or seizures (45).

There are thoughts about the use of ibuprofen, even if it has not been clarified, that it facilitates the formation of the infection. Some clinicians defend the use of acetaminophen as antipyretic because they think that the early use of non-steroidal anti-inflammatory drugs (NSAIDs) has negative effects on the course of the disease. With these concerns and results from the studies conducted with a small number

of young patients suggested that NSAID drugs increased disease severity with the theory that they had negative effects on the patient's immune response. The European Medicines Agency and WHO do not block the use of NSAIDs within clinical indications (61-64).

Oxygen Treatment

When hypoxia occurs, effective oxygen therapy, including nasal cannula, oxygen mask should be performed immediately. Nasal high flow oxygen therapy and noninvasive or invasive mechanical ventilation should be performed when necessary. In non-invasive methods, caution should be exercised in terms of droplet and aerosolization and the risk of late invasive treatment. Information can be obtained from WHO's manual for respiratory support and ARDS management (23,60).

Pharmacotherapy

There is no proven specific treatment for the treatment of COVID-19 patients until results of ongoing clinical trials are revealed. However, since none of these treatments shows significant benefit in the treatment of other coronaviruses (MERS, SARS, etc), it is suspected to be tried in COVID-19 treatment. WHO and The Centers for Disease Control and Prevention (CDC) does not recommend any specific treatment in children or adolescents. However, in the case series mentioned earlier, 59% of 34 children diagnosed with COVID-19 were administered with Lopinavir (LPV)/Ritonavir (RTV) treatment. None of the children received glucocorticoid or immunoglobulin (65).

Antiviral Treatment

While interferons are used in viral respiratory diseases; LPV/RTV and arbidol are used in treatment of Human Immunodeficiency Virus (HIV); oseltamivir is used in the treatment of influenza. Antiviral treatment should be administered only in critical cases. Reducing symptoms and maintaining immune balance is the main target (38).

Interferon (IFN)- α

Interferon (IFN)- α can reduce viral load in the early stage of infection; it can help alleviate symptoms and shorten the duration of the disease. Based on our clinical research and experience of using IFN- α in the treatment of bronchiolitis, viral pneumonia, acute upper respiratory tract infection, foot and mouth disease, SARS and other viral infections in children, the recommended use is as follows (66-71):

1. IFN- α nebulization: In 2 mL of sterile water, IFN- α 200,000-400,000 IU/kg or 2-4 μ g/kg, nebulization twice daily for 5-7 days,
2. IFN- α 2b spray: It is applied to the high-risk population in close contact with patients suspected of being infected with SARS-CoV-2, or patients who have been diagnosed only at an early stage with upper respiratory symptoms. 1-2 sprays should be used on both sides of the nasal cavity and 8-10 sprays on the oropharynx. The interferon- α 2b dose per application is 8,000 IU, it is applied every 1-2 hours, 8-10 sprays per day, for 5-7 days. Since IFN- α 2b nebulization is applied in MERS - CoV and SARS-CoV, it may be considered for COVID-19 infection (72).

In a study published by the Zhejiang University School of Medicine, nebulized IFN- α 2b for children, LPV/RTV with corticosteroids for

complications (ARDS, encephalitis, hemophagocytic syndrome or septic shock), and intravenous immunoglobulin for severe cases are recommended (73).

Lopinavir/Ritonavir (Kaletra®)

It is a protease inhibitor used in the HIV treatment. LPV is usually combined with RTV to increase the half-life of LPV by inhibition of cytochrome P450. It has been tried to apply in the treatment of adult patients with COVID-19 pneumonia, but its effectiveness and safety are still unclear (74,75).

A successful case of MERS - CoV disease has been reported in South Korea who is treated with triple combination therapy LPV/RTV/ribavirin and IFN- α (74). The efficiency and safety of combined LPV/RTV/ribavirin therapy is still being evaluated in clinical studies and pediatric cases need to be treated more cautiously. In critical and appropriate cases, it can be considered if it is suitable for children. It can be dosed considering the anti-HIV treatment in children. HIV antigen/antibody should be checked before starting the medication.

LPV 250 mg / RTV 50 mg blister strip is used orally, twice daily for 5 days. Oral liquid form with LPV content of 16 mg/kg is recommended in children between 14 days-6 months (57). Between 6 months-18 years; 200 mg-50 mg in the range of 15-25 kilograms, 300 mg-75 mg in the range of 26-35 kilograms, 400 mg-1000 mg 2 times a day if more than 35 kilograms (57).

LPV/RTV is safe in pregnant women in category C, syrup and tablet forms are available (76,77).

Remdesivir

Remdesivir (GS5734) is an RNA polymerase inhibitor, adenosine nucleotide analogue with *in vitro* activity against multiple RNA viruses, including SARS, Ebola, MERS-CoV, SARS-CoV-2, both *in vitro* and animal studies (78). The pneumonia and general condition disorder developed in the first adult case in the USA improved after treatment with remdesivir. However, since this is limited to only one adult case, efficiency needs to be further verified (27). It is thought that it may be effective for both

prophylaxis and treatment of human coronavirus infections (79).

Drugs considered to be effective against SARS-CoV-2, such as remdesivir or LPV-RTV, should be considered as rescuer therapy. It is suitable to be used after examining the profit-loss ratio, benefit and features as in adults. The pharmacology of intravenous remdesivir is unknown, phase 3 studies are ongoing and may not be possible as it is not licensed (80).

Adult use is recommended as 200 mg intravenously in a lump, and then 100 mg intravenously daily for 5-10 days (81). For children weighing less than 40 kilograms, following 5 mg/kg intravenous loading, 2.5 mg/kg once a day; and for children weighing more than 40 kilograms, 100 mg intravenously is once a day following 200 mg intravenous loading.

Arbidol, Oseltamivir and Other Anti-influenza Drugs

Arbidol is administered for adults infected with SARS-CoV-2; however, its effectiveness and safety remain uncertain. It has been discovered that Arbidol can block viral fusion of influenza A and B viruses, as well as hepatitis C virus (82). Oseltamivir and other anti-influenza agents can be administered in the presence of coinfection with the influenza virus. In case of clinical necessity, the dose of oseltamivir can be administered for 5 days, in accordance with the dosage schedule in influenza disease (57,83).

Ribavirin

Ribavirin; is a guanosine analogue. It is used in hepatitis C treatment. It has been shown to be ineffective and even harmful and hemolyzed against SARS-CoV and MERS-CoV (67,84-86).

It has been reported that ribavirin and IFN synergistically inhibit SARS-CoV replication in animal and human cell lines. Given the adverse reactions and lack of *in vitro* efficacy, the use of ribavirin for COVID-19 treatment should be seriously considered, even in combination with other antiviral drugs (87).

The use of Ribavirin 200 mg capsules in the presence of clinical indications: for children 2 g (30 mg/kg) loading dose and then 4x1 g (17 mg/kg/every 6 hours/4 days) or 4x0.5 g (8 mg/kg/every 8 hours/6 days), for a total of 10-14 days (57).

Table 3. Progressive stages of computerized tomography imaging in COVID-19 infection (87)

	Phase 1	Phase 2	Phase 3	Phase 4
Stage	Early stage	Progressive stage	Peak stage	Recovery stage
The day the symptom started	0-4 day	(5-8. day)	(9-13 day)	(after 14 th day)
Localization	Peripheral mostly in the lower lobes	Bilateral multilobular	Common	Common Sequelae in places
Properties	Focal ground glass density or consolidation (42%)	New or progressive consolidation	Concentration in consolidation, Widespread ground glass appearance, Parenchymal bands	Resolving consolidation Regression in CT images but full resorption after 26 th day
	Multifocal opacities (42%)	Flagstone view		
	No CT findings (17%)	Diffuse ground glass appearance		

COVID-19: Coronavirus disease 2019, CT: computerized tomography

Other Drug Treatments

Nafamostat

In addition to being a short-acting anticoagulant that prevents clotting, it is a synthetic serine protease enzyme inhibitor with anti-cancer and anti-viral effects. It is used in pancreatitis treatment and renal disease. It is a potential inhibitor that prevents membrane fusion in MERS-CoV infection. Its use for SARS-CoV-2 is under trial (88,89).

Antibiotics

In terms of bacterial or fungal coinfection, unnecessary use of antibiotics should be prevented by monitoring the patients closely. Antibiotics or antifungals should be used correctly and when necessary, with timely collection of samples for clinical status changes and pathogen analysis.

Azithromycin

Preliminary data evaluating the combination of hydroxychloroquine and azithromycin for the treatment of COVID-19 have been published recently. Combination therapy with azithromycin compared to the use of hydroxychloroquine only has more significant reduction in viral load. However, basal viral loads were higher in patients who received hydroxychloroquine monotherapy in the study. Despite this, the negation rate of tests on the sixth day of both groups was similar. It is recommended to avoid routine use due to insufficient data (90,91).

For 1-5 months old children 10 mg/kg/dose (maximum: 500 mg/dose); for children over 6 months, 10 mg/kg in first day, single dose per day (maximum: 500 mg / dose), followed by a single dose of 5 mg/kg per day for 2-5 days (maximum: 250 mg/dose), it is recommended to administer a total of 5 days.

Anakinra and Tocilizumab

In adults, COVID-19 produces secondary hemophagocytic lymphohistiocytosis (HLH; fulminant with multiorgan failure and hypercytokinemia with a mortality), except ARDS. Viral infections in adults are the most common cause of secondary HLH and occur in 3-7.3% of sepsis cases. In studies conducted in China, it is thought that mortality may be caused by virally induced hyperinflammation (92).

Anakinra which blocks IL-1 is beneficial in patients with hyperinflammation (93). In addition, the trial of tocilizumab used for IL-6 receptor blockade has been approved in adults (91,93). There are studies regarding the curative effects of combined use of tocilizumab with chloroquine, especially on its cytokine storm. The dose is 12 mg/kg for children weighing less than 30 kilograms, and 8 mg/kg (maximum: 800 mg/dose) for children weighing more than 30 kilograms (91).

Glucocorticoids

The use of glucocorticoids should be tailored to the severity of the systemic inflammatory response, the degree of dyspnea, the presence of ARDS, and progression in pulmonary imaging. Glucocorticoids are recommended as methylprednisolone at a dose not exceeding 2 mg/kg daily for a short period of time (3-5 days) (45,60).

WHO and CDC do not recommend the use of glucocorticoids in patients with COVID-19 pneumonia unless there is a different indication in adult

patients (eg. exacerbation of chronic obstructive pulmonary disease) (94). Glucocorticoids have been associated with an increased risk of mortality in influenza patients and delayed viral clearance in patients with MERS-CoV infection. Although it is widely used in the treatment of SARS, there is no evidence of its usefulness, as well as convincing evidence for its short- and long-term adverse effects (95).

There are differences between the results obtained in influenza, SARS and different viral pneumonia conditions. Due to the methodological limitations in the current evidence, the use of corticosteroids is controversial. It is known that there are potential risks associated with high-dose corticosteroids, such as secondary infections, long-term complications, and long-term viral scattering, in the treatment of COVID-19 pneumonia. However, in critical patients, excessive inflammation and cytokine-related lung damage can cause rapidly progressing pneumonia. The Chinese Thoracic Society has made recommendations on the use of corticosteroids in COVID-19 pneumonia. According to the expert consensus statement, the following basic principles should be followed when using corticosteroids (96):

- Before using corticosteroids, the benefits and harm should be reviewed;
- Corticosteroids should be used with caution in critical patients with COVID-19 pneumonia;
- For patients with hypoxemia due to underlying diseases or patients who take corticosteroids regularly for their chronic diseases, should be careful in case of more use of corticosteroids;
- Drug dose should be low-medium dose ($\leq 0.5-1$ mg/kg methylprednisolone or equivalent, daily) and should be used for a minimum period of time (≤ 7 days).

Intravenous Immunoglobulin

Immunoglobulin can be used for indication in severe cases, but more research is needed for its effectiveness (97).

Convalescent (Obtained from Recovered Patients) Plasma Support

It may be beneficial to administer serum from patients who recovered and developed antibodies against COVID-19 infection to the patients infected with COVID-19. In a wide metaanalysis, it was observed that the same method was applied in SARS and mortality decreased (98).

Chloroquine

It is widely used in autoimmune diseases and especially against malaria. It inhibits virus-cell fusion by increasing endosomal pH. Therefore, it shows a potential antiviral drug feature. It also affects the glycolysis of cellular receptors of SARS-CoV-2 (99). In *in vitro* studies, chloroquine



Figure 1. The order of wearing and take off personal protective equipment (95)

inhibits the entry and following steps of SARS-CoV-2 into the cell. Chloroquine, being as *in vitro*, stabilizes the immunomodulatory activity by increasing the antiviral effect (100). Chloroquine is also an effective inhibitor of SARS infection by affecting the binding areas on cell surface for S protein of ACE-2 and SARS CoV (99). Suggested usage criteria are as follows: SARS-CoV-2 positivity and increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values 5 times higher than the upper limit or creatinine clearance <50 mL/min or non-pregnant patient receiving mechanical ventilation support.

The recommended dosage for moderate disease in adults; hydroxychloroquine tablets are recommended orally, 200 mg twice a day, then 200 mg once a day for 4 days, or 250 mg twice a day for 5 days (81). The dose in children is 10 mg/kg, twice a day (maximum: 600 mg/dose) after loading 3 mg/kg (maximum: 200 mg/dose) 3 times a day for 4 days, totally 5 days (57).

The time can be extended in case of prolonged ventilation or deep immunosuppression (91). It should be noted that hydroxychloroquine prolongs QTc in electrocardiography (ECG). Basal ECG should be taken. Dose adjustment is not required in renal or liver disorders.

Mefloquine

It is an antimalarial agent, whose effectiveness has not been proven yet, especially in Russia.

Nitric Oxide

It is a selective vasodilator. It can be effective in the case of ARDS, which can be a complication of SARS-CoV-2. The use of inhaled nitric oxide in the SARS-CoV epidemic reduced pulmonary hypertension, cured severe hypoxia, and reduced the duration of ventilation support. Studies on its use in COVID-19 are ongoing. It is applied as 30 ppm on the first day, 20 ppm on the 2nd day and 10 ppm on the 3rd day and decreases with oxygenation control with 10 ppm on the 4th day (101,102).

Drugs in Different Combinations

In addition, three different potential drug combinations (sirolimus and dactinomycin, mercaptopurine and melatonin, toremifene and emodin) are candidates for use (103).

Certain drugs whose effectiveness has been investigated by clinical trials in COVID-19 treatment are shown in Table 4 (13,57,91,104).

Treatment of Severe and Critical Cases

In accordance with the symptomatic treatment bases, preventive therapy, complication therapy, treatment of underlying conditions, treatment of secondary infections and, in case of indication organ functions oriented support should be provided.

Respiratory and Circulatory Support

Children with no change in their condition despite receiving noninvasive ventilation support for 2 hours, or children who are unable to tolerate noninvasive ventilation, have increased secretions, and have severe cough or hemodynamically unstable should be immediately taken

to invasive mechanical ventilation support. In invasive mechanical ventilation, a low tidal volume “lung protective ventilation strategy” should be adopted to reduce lung damage associated with the ventilator. If necessary, ventilation in the prone position, lung recruitment maneuvers or extracorporeal membrane oxygenation (ECMO) can be performed. It is recommended to regulate microcirculation with full fluid support, use of vasoactive drugs, and when necessary, monitor hemodynamic data (60).

ECMO therapy is used as a life-saving approach in resistant ARDS cases. In a study of 6 adult patients who received ECMO treatment, 5 of the patients (83%) died. Even if this number is small, it emphasized certain points to be considered on the application of ECMO therapy. During ECMO therapy, lymphopenia deepened and lymphocyte function impaired. The progressive increase in IL-6 level was thought to be secondary to parenchymal damage during ECMO. This increase is correlated with mortality. Therefore, monitoring the close lymphocyte count and IL-6 level is recommended. IL-6 levels of survivors after ECMO have reached their normal levels in a short time (47). In COVID-19 disease, while keeping in mind that the immune system is significantly affected, the immunological status of the patients should be taken into consideration when selecting candidates for ECMO (105).

Traditional Chinese Medicine

This disease is in the category of epidemic in traditional Chinese medicine. Some traditional treatments have been made in China, depending on the patient's condition, local climatic characteristics and children's physical characteristics.

Recommendations for the Care/Treatment of Neonates Exposed to COVID-19 Disease

Neonatologists should wear their protective equipment (hats, glasses, protective clothing, gloves, N95 masks, etc) to revive newborns born from the confirmed and/or suspected COVID-19 mother. If the mother's SARS-CoV-2 test is positive, the newborn should be isolated and tested for SARS-CoV-2.

Routine corticosteroids are not recommended for all women with confirmed COVID-19 infection between 34th and 37th weeks of pregnancy. Considering the additional risk factors, it is recommended to follow the international recommendations regarding fetal lung maturation while discussing the benefit of this treatment between 34th and 37th weeks of gestation (106).

Although it is recommended in some studies to examine every critical patient in neonatal intensive care for COVID -19 and to monitor all of them in intensive care, there are different opinions on this issue (107). Testing not every intensive care newborn, but newborns from families infected with SARS-CoV-2 or exposed to other infected persons regardless of their symptoms prevents misuse of resources. Early diagnosis and early isolation are mandatory for SARS-CoV-2 control. If the newborn does not have a clinical need for isolation, it does not need to be monitored in intensive care (79).

As in MERS management, newborns infected with SARS-CoV-2 should be placed in negative pressure rooms or in rooms with highly efficient

particulate air filters in outlet ventilation. Treatment mainly depends on the clinical experience of adult patients, as there are few pediatric cases. There is no specific drug treatment for newborns (108). Symptomatic and supportive therapy, oxygen support, pulmonary edema and oxygenation status should be followed closely and appropriate hydration should be performed. In addition, maintaining electrolyte and acid-base balance is the mainstay of treatment. In cases with severe ARDS, due to the lack of adequate evidence-based data, high dose pulmonary surfactant, inhaled nitric oxide, high frequency oscillatory ventilation and ECMO can be used, depending on the diagnosis and classification criteria.

WHO stated that late clamping of the umbilical cord does not increase the risk of transmission of pathogens from the mother to the fetus, even in any identified infection in the mother. Since vernix caseosa contains antimicrobial peptides, washing is not recommended in 24 hours after birth. After birth, it is recommended to minimize transmission from mother with COVID-19 to newborn. In order to prevent contact with respiratory secretions, the mother should pay attention to the use of masks and hand hygiene if there is no other feature in her clinical condition (109). It is not recommended to keep the mother and baby in isolation separately, except in situations that require intensive care. It is emphasized that being separated may cause negative effects on nutrition and attachment. Close monitoring of the newborn is recommended (59,110). It is recommended that mother and baby be separated only by consulting a multidisciplinary board when necessary. Looking at the previous data for separation, although it is a standard practice in pulmonary tuberculosis, it is discussed in maternal influenza infection cases. Patients should be informed about potential risks and benefits (109).

Cases have been reported in 10 newborns born from an infected mother with the COVID-19 virus (25). Although all 9 infants tested once had negative results for COVID-19 infection, neonatal complications following fetal distress were probably secondary to maternal disease. The condition of 2 babies out of 10 has become critical: while 34-week and 6-day-old newborn, whose first complaint was moaning, continued to live with immunoglobulin, platelet, plasma support; 34-week and 5-day-old newborn, whose first complaint was tachycardia, died after going rapidly into disseminated intravascular coagulation and multiple organ failure, not responding to blood transfusions and symptomatic support therapy. For these reasons, maternal-infant couples affected by SARS-CoV-2 should be closely followed up and monitored. In case of symptom development, newborns should be admitted to the neonatal unit immediately and isolated by initiating supportive treatments if necessary.

Criteria for Discharge

Patients with definitive diagnosis can be discharged from isolation or transferred to the relevant departments for the treatment of other diseases if all the following criteria are met:

1. Body temperature in the normal range for more than 3 days,
2. Significant improvement of respiratory symptoms,
3. Negative respiratory SARS-CoV-2 nucleic acid test result 2 times in succession (sampling interval is at least 1 day).

In suspected patients, when the test of the respiratory tract pathogen nucleic acid is negative 2 times in succession, they can be discharged from the isolation (sampling interval is at least 1 day) (45).

Antiviral agents			
Baloxavir	Antiviral	It is effective against influenza viruses. No approved use	80 mg po 1x1, 4 days
Chloroquine Hydroxychloroquine	Antimalarial	Activities shown in Vero E cells as <i>in vitro</i> . Theoretically, it has an immunomodulating effect for anti-inflammatory response to viral infections. Limited data for prevention and treatment. The results of the studies are expected. Positive effects in a limited number of studies using chloroquine and azithromycin have been reported. Both drugs can cause QTc prolongation.	Chloroquine phosphate: 500 mg oral x2/day, 10 days If <50 kg 500 mg oral x2/day for the first 3 days, then 500 mg oral one time for 3-7 days. Hydroxychloroquine (Plaquenil®): oral, 2x200 mg first day and then 1x200 mg 4 days or 2x250 mg 5 days. The dose in children is 10 mg/kg, x2/day (max: 600 mg/dose) after loading, 3 mg/kg (max: 200 mg/dose) x3/day, 4 days, total 5 days (43).
Lopinavir and Ritonavir (LPV/RTV; Kaletra®)	HIV Protease Inhibitor	It has different studies. It was found that it could not decrease clinical recovery time, could not decrease viral RNA load during viral DNA positivity, did not have any positive effect on oxygen treatment time or hospital stay and duration from diagnosis to death. More studies are needed for its combination with different drugs. The combined use with Ribavirin, Arbidol and Interferon is being studied.	Lopinavir 250 mg /Ritonavir 50 mg film tablet, oral x2/day, 5 days. Oral for 14 days-6 months with Lopinavir content of 16 mg kg. 6 months -18 years of age; for 15-25 kg oral 200 mg-50 mg; for 26-35 kg, 300 mg-75 mg, for >35 kg, 400 mg-1000 mg x2/day.

Table 4. continued

Neuraminidase inhibitors (oseltamivir, etc)	Antiviral agents against influenza viruses	Although it is widely used in confirmed or suspected COVID-19 patients, there is no study showing its effectiveness. There is no evidence that oseltamivir or zanamivir inhibits the cytopathic effect of SARS-CoV in <i>in vitro</i> cell cultures.	Oseltamivir; 3-11 months: 3 mg/kg BID oral >15 kg: 2x30 mb 15-23 kg: 2x45 mg 23-40 kg: 2x60 mg > 40 kg 2x75 mg
Remdesivir	Antiviral, unknown	It is a broad-acting antiviral against coronaviruses. It was previously investigated for SARS, MERS and Ebola and its activity as <i>in vitro</i> against SARS-CoV, SARS-CoV-2 and MERS-CoV has been demonstrated. There are phase 2 and phase 3 studies on its use.	In adult critical cases 200 mg IV 1x1, then 100 mg daily for 5-10 days. In children: If <40 kg, 5 mg/kg IV loading, then 2.5 mg/kg IV 1x1. >40 kg 200 mg IV, 100 mg IV 1x1 after loading.
Supportive agents			
Ascorbic acid	Vitamin C	Antioxidant and cofactor in many physiological reactions. It can support host defense by protecting against infection from oxidative stress.	Different doses in adults in sepsis studies; IV 50 mg/kg IV 4x1, 4 days.
Azithromycin	Macrolide	It has antibacterial effect and <i>in vitro</i> activity against some viruses (Influenza A H1N1, Zika). <i>In vitro</i> activity against corona viruses, including SARS-CoV-2, is not specified. It can have an immunomodulatory effect and anti-inflammatory effect.	1-5 months; 10 mg/kg/dose (max: 500 mg/dose), >6 months 10 mg/kg first day, single dose per day (max: 500 mg/dose), followed by 5 mg/kg once daily for 2-5 days (max: 250 mg/dose), total 5 days.
Tocilizumab (Actemra®) Sarilumab (Kefzara®)	Antirheumatoid	Recombinant human monoclonal antibody is specific to the interleukin-6 (IL-6) receptor. It is effective on cytokine release syndrome in critically ill patients. Its studies are ongoing. There are not sufficient studies on Sarilumab (Kefzara®).	Tocilizumab: IV infusion; For children: If <30 kg, dose is 12 mg/kg and if >30 kg, 8 mg/kg (max: 800 mg/dose). Infusion time should be longer than 60 minutes. If the first dose is not sufficient, it can be given again after 12 hours with the same initial dose. It is not recommended to apply for the third time.
Methylprednisolone	Anti-inflammatory antifibrotic, it prevents excessive cytokine response at low doses or accelerates the recovery of pulmonary or systemic inflammation.	Studies suggest that methylprednisolone therapy may be beneficial in patients with COVID-19 pneumonia progressing to ARDS. Chinese Thoracic Society has created a user manual according to the disease level and condition.	It is recommended as a methylprednisolone at a daily dose not exceeding 2 mg/kg (0.5-1) in short periods such as 3-5 days.
Nitric oxide (inhale)	Does selective vasodilation. Ist direct antiviral effect against SARS-CoV has also been demonstrated in <i>in vitro</i> studies.	Although it has been shown to be effective in the case of ARDS, routine use is not recommended. Studies on its use in COVID-19 continue.	It is applied as 30 ppm on the first day, 20 ppm on the 2 nd day and 10 ppm on the 3 rd day, and decreases with oxygenation control with 10 ppm on the 4 th day.
Sirolimus	Immunosuppressive mTor inhibitor	It has activity against MERS-CoV infection in <i>in vitro</i> studies. It has been found that the use of oseltamavir and corticosteroid in H1N1 pneumonia reduces the mechanical ventilation time of the patients and is useful in the treatment of hypoxia and multiorgan failure.	In the studies, it is recommended to use orally with 2 mg daily dose. It is recommended to use together with 20 mg oral prednisolone daily for 14 days and with 75 mg oseltamivir twice daily for 10 days in adults.
RNA: Ribonucleic acid, DNA: deoxyribonucleic acid, SARS: Severe acute respiratory syndrome, MERS: Middle East respiratory syndrome, COVID-19: Coronavirus disease 2019, CoV: coronavirus, ARDS: Acute respiratory distress syndrome, max: maximum, LPV: Lopinavir, RTV: Ritonavir, HIV: human immunodeficiency virus			

Conditions Expected During Post-discharge and Isolation Period

The secondary effects of closed schools and having children spend long periods at home should not be forgotten. It can be predicted that this will have negative effects on children's physical and mental condition. This can result in weight gain following long screen exposure, irregular sleep, unhealthy diets and a lack of movement (111).

In a study not related to the COVID-19 outbreak, tests were conducted by interviewing 398 families, and it was found that the risk of posttraumatic stress disorder increases when children are quarantined and isolated after health-related disasters (112).

Psychological counseling; plays an important role in disease recovery. If patients (especially older children) show mood swings, fear, or psychological disorders, active psychological intervention and treatment is required.

Preventing Social Spread

Infection source control, self-isolation of supercarriers, blocking the transmission routes and infection control applications with sensitive population protection are of great importance.

Prophylaxis

WHO recommended pre-contact prophylaxis before exposure to diseases such as pandemic influenza, invasive meningococemia, or for people at high risk of infection. It is effective in preventing disease after exposure to proven infection and reducing viral load in respiratory secretions, reducing the risk of secondary spread and transmission. In pharmacological models based on invitro tests performed until now, it is predicted that prophylaxis with appropriate doses of hydroxychloroquine against SARS CoV-2 can prevent infection and reduce viral spread. This information will become clear in May 2020 with the results of the study to be carried out in the Spain-Catalonia region (113,114).

Conclusion

Close follow-up of the clinical findings of the pediatric patients and following the rules of isolation will provide a milder circumvention of the pandemic. In COVID-19; while children can usually progress with a mild clinic, children with underlying disease may have more severe pictures. More virological, epidemiological and clinical data are required for specific antiviral treatment and disease management for children.

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