REVIEW

Onder Kilicaslan [1]
Nadide Melike Sav[1]
Seda Erisen Karaca[1]
Kenan Kocabay[1]

[1]Department of Pediatrics, Duzce University Medical School, Duzce., Turkey

Corresponding Author:
Onder Kilicaslan
Department of Pediatric Health and Diseases, Duzce University School of Medicine, Turkey
mail: dronderklcsln@gmail.com
Phone: +90 5065962784

Received: 17.04.2020
Acceptance: 21.05.2020
DOI: 10.18521/ktd.722266

COVID-19 Disease in Children: Clinical Course, Diagnosis and Treatment Overview and Literature Data Compilation

ABSTRACT
The novel Coronavirus is named as SARS-CoV-2 is a highly contagious infection agent compared to the previous human coronaviruses. Each previous outbreak had distinctive danger. The high potential of infectiousness is the primary danger of novel coronavirus. While MERS-CoV infection is known to have higher mortality rate, SARS-CoV-2 has spread to many people all over the world in a concise time. SARS-CoV-2 (like SARS-CoV and MERS) infects fewer children and results in milder clinical symptoms than in adults. The primary pathogenesis of it is not known; the difference in children's immunities, less likelihood of exposure to the agent may be the reasons. Nevertheless, along with being mostly asymptomatic, the child population is a potential source for infection spread.

Key Words: Children, Coronaviruses, COVID-19

Çocuklarda COVID-19 Hastalığı: Klinik Seyir, Tanı ve Tedaviye Genel Bakış ve Literatür Verilerinin Derlemesi

ÖZET
Yeni Coronavirus, SARS-CoV-2 olarak adlandırılmıştır ve önceki insan koronavirüslerine kıyasla oldukça bulaşıcı bir enfeksiyon ajanıdır. Önceki her salgının kendine özgü bir tehlikesi vardı. Yüksek bulaşıcılık potansiyeli, yeni koronavirüsün birincil tehlikesidir. MERS-CoV enfeksiyonunun daha yüksek mortalite oranına sahip olduğu bilinmekle birlikte, SARS-CoV-2 kısa sürede tüm dünyadaki birçok insana yayılmıştır. SARS-CoV-2 (SARS-CoV ve MERS gibi) çocukları daha az enfekte eder ve çocuklarda yetişkinlere göre daha hafif klinik semptomlarla sonuçlanır. Birincil patogenezi bilinmemektedir; çocukların bağışıklıklarında bulunan farklar, ajana maruz kalma olasılığının daha az olması olabilir. Bununla birlikte, çoğunlukla asemptomatik olmakla birlikte, çocuk popülasyonu enfeksiyon yayılması için potansiyel bir kaynaktır.

Anahtar Kelimeler: Çocuklar, Coronavirüsler, COVID-19

Konuralp Medical Journal
e-ISSN1309–3878
konuralptipdergi@duzce.edu.tr
konuralptipdergisi@gmail.com
www.konuralptipdergi.duzce.edu.tr

Introduction and Virology

Coronaviruses (CoVs) are member of the family Coronaviridae, a large family of enveloped viruses. CoVs are single-stranded RNA viruses and zoonoviruses (1). They can infect many animals, including farm animals and birds, and cause severe respiratory, cardiovascular, enteric and neurological symptoms among them (2, 3). The CoV that infects people affects the respiratory and gastrointestinal system and causes mild upper respiratory system symptoms such as bronchitis, pneumonia or acute respiratory distress syndrome (4) or symptoms which can lead to coagulopathy, multiple organ failure and death. Human Coronaviruses (HCoVs) also cause exacerbation of chronic obstructive pulmonary disease, aggravation of cystic fibrosis and asthma symptoms (5, 6).

Identification members of the family Coronaviridae (virulence potentials, ways they cause disease), based upon endemic and sporadic cases they caused previously, will be guiding on identification and predicting treatment and prevention protocols of COVID-19 disease, a new threat today. CoVs are grouped as Alpha and Beta (mostly seen in bats, civet cats, rodents and humans, and may cause infection among humans), Gamma and Delta coronaviruses (mostly seen in birds). Four strains of CoVs are known to circulate and cause endemic and widespread infections at intervals among humans. Sources of infection to humans are known to be bats (NL63, 229E), one-humped camels (229E) and cattles (OC43). While most CoVs are known to switch between animals and not infect humans, due to their very rapid mutation and recombination capacity, new CoV species that infect humans from animals are emerging. An example of this is the new CoV (SARS-CoV), which appeared in China, in 2002, infects humans from civet cats and bats and causes acute respiratory syndrome (2, 7-11). Another example is the other new CoV, which appeared in Saudi Arabia in 2012, infects humans from one-humped camels and causes Middle East Respiratory Syndrome (MERS-CoV) (12, 13). Summary information comparing SARS-CoV, MERS-CoV and SARS-CoV-2 diseases and their characteristics, which are HCoVs that cause disease in children, circulate among humans, were shown in Table 1.

The new coronavirus CoV (SARS-CoV-2), originated in China and causing worldwide outbreaks as of 2019, is a strain of the Beta coronavirus family, which also includes SARS-CoV. Since the genetic sequence of the new virus resembles at the rate of 87-89% to bat origin SARS-CoV (bat-SL-CoVZC45), it is named as SARS-CoV-2. The SARS-CoV-2 outbreak emerged in Wuhan, China, on December 31, 2019 with detection of pneumonia of unknown etiology in a number of adults by the Hubei Health Commission. Although it was initially thought to spread from markets of seafood and animal products, the main source of the spread is known to be by respiratory aerosols or direct contacts of symptomatic or asymptomatic persons infected with SARS-CoV-2. Today, SARS-CoV-2 has spread across the world and caused a global pandemic. With a reference to the onset of disease in 2019, this clinical disease developed with SARS-CoV-2 is named as COVID-19 (Coronavirus disease 2019). World Health Organization (WHO) called attention to the COVID-19 outbreak and declared Public Health Emergency of International Concern (PHEIC) for the event that threatens international public health (14). Declaration of PHEIC is a high-level emergency call to international authorities for steps involving public health, political and financial measures to be taken to prevent the outbreak. After the SARS outbreak in Guangdong, China in 2003, WHO declared PHEIC 5 times; H1N1 (2009), Polio (2014), Ebola in West Africa (2014), Zika (2016) and Ebola in Democratic Republic of the Congo (2019).

Epidemiology and Prevalence

Since the early stage of the SARS-CoV-2 outbreak, the actual spread has been shown to be through person-to-person contact (15). Similar to SARS-CoV and MERS-CoV spread, it has been revealed that person-to-person contact is the most dangerous reason. Additionally in MERS-CoV infection, nosocomial reinfection cases were shown and were mortal. No human SARS-CoV infection has been detected since July 2003, zoonotic presence in bats were shown (16). Considering that SARS-CoV can infect a human cell without an adaptation mechanism, there is a risk that SARS-CoV will resurrect if animal contact is not paid attention to. Beside this, infections of MERS-CoV from animals to humans are still reported. This is due (as opposed to human-bat contact) to the fact that humans still have close contact with camels (17). We should kept in mind this reinfection and contact information for SARS-CoV-2 infection. After the pandemic is taken under control, we need to pay attention to animal contact again and consider the possibility of reinfection with hidden strains and nosocomial infection.

Table 1. Human coronaviruses and their characteristics

Features	Commonly observed Human Coronaviruses (HCoV)	New coronaviruses (nCoV)		
	HCoVs, NL63, 229 EOC43	**SARS-CoV**	**MERS-CoV**	**SARS-CoV-2**
Zoonotic transmission	Bat (NL63, 229E), One-humped camel(229E), Cattles (OC43)	Civet cats (bats, reservoir carrier)	One-humped camels (bats, reservoir carrier)	Bat and Anteater are suspected, not proven yet.
Epidemic prevalence (adult and children)	Unknown	29 countries. 8000 cases, 774 deaths.	27 countries. 2494 cases. 858 deaths	108 countries, 1,897,373 cases, 118,304 deaths (April 11, 2020)
Transmission in adults	Unknown	30% nasocomial transmission (mostly health professionals), 13-21% personal contact	44-100% nasocomial transmission (mostly patients), 22-39% personal contact	Nasocomial transmission unknown. Personal contact +
Transmission in children	Unknown	50-80% personal contact, 30% nasocomial transmission	19% nasocomial transmission, 55% personal contact	82% personal contact
Incubation time	2-5 Days	4-6 average (2-10) days	5-7 average (4-13) days	5-6 average (2-14) days
Asymptomatic case rate in children	13% asymptomatic	2% asymptomatic	42% asymptomatic	9-11% asymptomatic
Clinical symptoms in children	Fever, nasal discharge, conjunctivitis, otitis, pharyngitis, laryngitis, croup, headache, bronchitis, bronchiolitis, wheezing, asthma exacerbation, pneumonia, gastrointestinal symptoms, febrile seizure, neurological symptoms.	Fever (91-100%), myalgia (10-40%), nasal discharge (33-60%), sore throat (5-30%), cough (43-80%), dyspnea (10-14%), headache (10-40%), nausea (20%), abdominal pain (10%), febrile seizures (10%)	Fever (57%), nausea (28%), diarrhea (28%), cough and shortness of breath (14%)	Fever (44-50%), cough(38%), nasal discharge, fatigue, headache, diarrhea, dyspnea, cyanosis, nutrition deterioration.
Laboratory symptoms in children	Unreported	Decreased neutrophil count, decreased lymphocyte count, thrombocytopenia, Elevated LDH, increased alanine aminotransferase. D-dimer increase and coagulopathy in severe cases	WBC is normal, thrombocytopenia, KC and kidney function values are normal.	Normal or decreased WBC, decreased neutrophil count, decreased lymphocyte count, CRP and PCT values are normal in general, liver dysfunction. LDH and D-dimer values increased in severe cases.
Imaging findings in children	Unreported	Lung graphy: bilateral irregular consolidations around lungs and upper lobes, linear atelectasis, peribronchial thickening, ground glass opacities. Chest CT: ground glass opacities, consolidations, air bronchograms.	Lung graphy: bilateral consolidations	Chest CT: bilateral multiple irregular, nodular ground glass opacities, speckled ground glass opacities and / or infiltration shadows in the middle and outer parts of the lung or below the pleura
Mortality rate in adults	Reported immunosuppressed sporadic cases	6-17%	20-40%	0.9-2.9%
Mortality rate in children	Unknown	0-05%	6%	0.2-0.7%

The RN (reproductive number) of SARS-CoV-2 has been determined as 2.7 and is higher than SARS-CoV and MERS-CoV (18). The median incubation period was found to be 5-6 days. Case serial intervals were reported as 8 days. According to WHO April 2020 data, SARS-CoV-2 infection has spread to more than a hundred countries and caused deaths. Mortality rate of SARS COV-2 infection has been reported between 0.9-3%, which is much lower than the SARS-CoV (6-17%) and MERS-CoV (20-40%) infections mortality rates (14, 19).

Clinic of COVID-19 Disease in Children

1. Symptoms

The presence of symptomatic infection in children is not common. When symptoms appear, they are usually mild. Cases with severe symptoms have also been reported. According to data of February-March-April 2020 from the United States Committee on Disease Control, less than 5% of diagnosed COVID-19 cases are in the 0-19 age group (1.7% in April 2020), cases requiring hospitalization in the 0-19 age group are less than 1% and 15% of cases in the childhood age group are neonates. The number of cases requiring hospitalization and intensive care follow-up is relatively low in children. Hospital admission rates are between 5.7-20% and the number of cases requiring intensive care is between 0.5% and 2% (20, 21). Data from a Chinese study that presented over 72000 cases series analysis reports also showed that individuals aged 20 count up less than 2% of the total cases (22). According to South Korean data, the rate of individuals under the age of 19 is 6.3% (out of 8000 cases). Neonatal COVID-19 cases of pneumonia, liver damage, cardiomyopathy and gastroenteritis symptoms have also been reported in Chinese Case Reports (23, 24).

According to joint data of World Health Organization and China, the accompanying clinical symptoms and rates of COVID-19 disease were found in adult patients and are as follows: fever 99%, fatigue 70%, dry cough 59%, loss of appetite 40%, muscle pain 35%, shortness of breath 31% and sputum 27% respectively. More rarely coexisting symptoms are smell and taste disorders, headache and sore throat and gastrointestinal symptoms such as nausea and diarrhea (25, 26).

Clinical presentation rates of children are again determined mostly by China data. Revealed rates in studies vary slightly. The results of the largest case series study with 2143 child cases diagnosed with COVID-19 (27) and 171 child cases reports (28) are as follows:

*_Distribution of patients according to clinical symptoms; total of asymptomatic, mild and moderate cases is 94.1%_.

Asymptomatic cases 4.4%

Mild cases 50.9%

Moderate cases 38.8%

Severe cases 5.2%

Critical cases 0.6%

*_Distribution of admission symptoms:_

Cough 48.5%

Pharyngeal edema 46.2%

Fever 41.5%

Average fever incidence time is 3 days (1-16 days)

Rates of fever incidence during hospitalization: <37.5°C 58.5%; 37.5-38.0°C 9.4%; 38.1-39.0°C 22.8% and >39.0°C 9.4%.

Diarrhea 8.8%

Fatigue 7.6%

Nasal discharge 7.6%

Vomiting 6.4%

Nasal congestion 5.3%

Dyspnea 2.3%

Rare accompanying symptoms; tachycardia, tachypnea, fall in oxygen saturation

*_As the age younger, the course of the disease becomes more severe. Newborns are at greater risk_ (Severe and critical case rates and ages were as follows; 10.6% among <1-year-olds, 7.3% between 1-5-year-olds, 4.1% between 6-10-year-olds and 3.0% between 11-15-year-olds. Death of a 14-year-old male case was also reported).

*_Sex is not a risk factor in children_. (According to data from previous studies from China, the male gender has been reported as a risk factor for COVID diseases in adults. The number of boy patients has been reported higher than girls. However, the difference was not statistically significant (27, 29, 30)).

2. Radiology

There is no specific clinical feature that can reliably distinguish COVID-19 from other viral respiratory infections.

Lung computerized tomography (CT) findings of children are often similar to those of adult patients. Typical findings are; single-sided or double-sided subpleural ground glass opacities, consolidations surrounded by halo. As consolidation surrounded by halo finding was detected in 50% of pediatric cases, this finding should be considered as a typical finding (31). Pleural effusion is not typical. In the first evaluation, the findings of CT in children may not be detected. Repetitive CT follow-up may be required with clinical follow-up (32).

Lung CT findings and rates in children are as follows (31, 32):

Pulmonary lesions

None 20%

Single-sided 30%

Double-sided 20%

Consolidations surrounded by halo sign 50%

Ground glass opacities 60%

Small nodules 15%

Subpleural lesions

None 0%

Present 100%

It is recommended to repeat lung CT in children with clinical follow-up. Changes in CT findings over time can be summarized as follows (32, 33):

Early stage: No findings (symptom) (10-20%), begin with single-sided lesions (25-30%), signs (symptoms) of subpleural inflammation may be seen.

Advanced stage: Lesions may increase in size and density, may involve double-sided and many lobes. Commonly seen ground glass densities, interlobular septal thickening and fibrotic band appearances may be detected.

Critical stage: the formation of 'white lung' appearance. Lesions show bilateral and diffuse increase. Air bronchograms and pleural thickening may accompany.

Recovery stage: Decreasing and shrinking of consolidations (15%), residual fibrotic bands remain (15%), total recovery (10-70%) are seen.

Another important thing is to differentiate CT symptoms of COVID-19 infection from viral pneumonia findings such as influenza virus, parainfluenza virus, respiratory syncytial virus and adenovirus, which are other respiratory tract viral pathogens (34).

Diagnosing COVID-19 pneumonia with CT findings alone is not enough, especially if there is a coinfection with other pathogens. The most rational protocol applicable in pediatric cases is to combine clinical and laboratory findings with lung screening (chest X-ray/CT).

3. Laboratory

Laboratory findings of SARS-CoV-2 infection in children show similarities with other new CoV (4, 35-37).

WBC values are typically normal or decreased

Decrease in neutrophil number

Decrease in lymphocyte count

Thrombocytopenia

C-reactive protein and procalcitonin values are generally normal

In severe cases: elevated liver enzymes, increased LDH and D-dimer levels, and coagulopathy are seen.

4. Diagnosis

The main basis for SARS-CoV-2 (and all the HCoV in common) detection is a real-time polymerase chain reaction (RT-PCR) on secretions from upper or lower respiratory track (38). RT-PCR testing is positive by 67% within 1-7 days, and remains positive 45% within 15-39 days. Viral load is higher detected in lower respiratory tract infection rather than the tract upper infection. Therefore initial negative reasults in nasopharyngeal or throat swab should be repeated in clinically suspected cases. Even not performed in routinely, RT-PCRs on stool samples might be positive for HCoV (11). Detecting antibody responses to SARS-CoV-2 infection is another method for diagnosing COVID-19 diseases. Total antibody response differs within time schedule: it is 38% (Ig M 29%, Ig G 19%) positive within 1-7 days, 90% (Ig M 73%, Ig G 54%) within 8-15 days, and 100% (Ig M 94%, Ig G 80%) up to 39 days (39).

Criteria for Clinical Diagnosing COVID-19 Disease in Children

The case identification scheme developed by the Zhejiang University School of Medicine, National Clinical Research Center for Child Health is a follows (40):

***A suspected or probable case meets the following: two clinical criteria and one epidemiological criterion**

Clinical criteria:

1. Fever, fatigue, dry cough (some children cases may show no signs of fever)

2. Patients with the following chest X-ray findings: Multiple small irregular shadows and interstitial changes, bilateral multiple opacities and pulmonary consolidation, mostly in the peripheral lung in chest X-ray. In lung CT, ground glass opacities and bilateral segmental lung consolidations, especially in the periphery.

3. Normal or decreased leukocyte number, decreased lymphocyte number.

Epidemiological criteria:

1. Children with history of travel to or residence in an area where local prevalence is intense, 14 days before the disease.

2. Children with fever or respiratory symptoms and a history of contact 14 days before with a patient who has a history of travel to or residence in an area where local prevalence is intense.

3. 14 days before the disease, children with a history of contact with a definitive diagnosis or suspected SARS-CoV-2 infection.

4. Newborns born to mothers suspected or with definitive diagnosis of SARS-CoV-2.

***Confirmed case meets any of the following criteria:**

1. RT-PCR test on Throat swab, positive detection of SARS-CoV-2 nucleic acid in sputum, stool or blood samples.

2. High homology of genetic sequences viewed on throat swab, sputum, stool or blood samples with SARS-CoV-2.

3. Isolation of SARS-CoV-2 granules in a culture environment created with throat swab, sputum, stool or blood samples.

Treatment Protocols in Children

Based on our experiences from HCoV infections so far, we know that supportive care, fluid replacement, calorie intake and oxygen support are important. The main goal is to prevent development of ARDS, organ failure and secondary nosocomial infections. If there is a suspicion of bacterial infection, broad spectrum antibiotics such

as second or third generation cephalosporins may be used.

It is known that in vitro trials of some agents for treatment have been conducted and human data and observational series have been published. However, it should be noted that no controlled patient study supporting the use of any agent has been published, and that their effectiveness on SARS-CoV-2 infection is not known yet.

Research Institute of Zhejiang University's only published treatment recommendation in pediatric CoV cases is the use of corticosteroids and *nebulized interferon alpha-2b oral lopinavir/ritonavir* combination and complications (such as ARDS, encephalitis, hemophagocytic syndrome, or septic shock) (40). It is not certain whether this treatment protocol will be helpful on the SARS-CoV-2 treatment due to its lack of effectiveness over the previous new CoVs. Neither WHO nor American Centers for Disease Control (20) have a recommended treatment protocol for use in SARS-CoV-2 infection in children (14, 41).

Remdesivir is a new nucleotide analogue which has in-vitro efficacy (also its efficacy against SARS and MERS-CoVs has been demonstrated both with in-vitro and animal studies) against the SARS-CoV-2 agent. Several clinical studies are being conducted to investigate its effectiveness in moderate and severe COVID-19 cases (42-44). Remdesivir is an intravenous agent. Its side effects include nausea, vomiting and elevated transaminase. It should be carefully used on children.

Other treatment options: Some agents, whose in-vitro efficacies have been shown or observational data from previous HCoV outbreaks are present, may be evaluated for use in SARS-CoV-2. These are monoclonal antibodies, protease inhibitors, chloroquine and RNA synthesis inhibitors (Table 2) (11, 42).

SARS-CoV-2 Vaccine Studies

Vaccine studies aiming to prevent the spread and reduce the severity of SARS-CoV-2 infection, which threatens the world, have begun. The antigenic structure used in vaccine development based on previous HCoV vaccines is the structural spike glycoprotein (S) or its receptor-binding domain. The rapid mutation potential of HCoVs is the main reason that no effective vaccine has been developed so far (45-47). Vaccine protocols attempted to be developed in vaccine trials are live attenuated vaccines, inactive vaccines, subunit-containing and recombinant vaccines, viral vector vaccines and DNA vaccine studies (45, 47).

What Makes COVID-19 Diseases Different in Children?

It is not fully understood why childhood COVID-19 cases are less severe than those of adults. Both the host and the virus may be the reason. The fact that children are in a better protected environment and are less likely to be exposed to the pathogen and carrier patients may play a role.

Angiotensin-converting enzyme II (ACE2) is known to be a cell receptor for SARS-CoV (48). It is claimed that 2019-nCoV has some amino acid homology with SARS-CoV and may use ACE2 as a receptor. Some studies also suggest that the ACE2 receptor is likely to be the 2019-nCoV cell receptor (49, 50). The fact that maturity and function (e.g. binding capacity) of ACE2 receptors in children are lower than in adults may be one reason of children being less susceptible to 2019-nCoV.

When we think of children's resistance to COVID-19 disease in terms of immunity, we can think that the children's immune system is still developing, thus creating more different responses to new pathogens than adults. In addition, children are more likely to be exposed to respiratory diseases (e.g. RSV) during winter that’s why high levels of antiviral antibodies in children's blood than in those of adults, may be a factor.

Determining the cause that determines the difference of the mechanism and clinical reflection of COVID-19 disease between children and adults is still a matter to be investigated.

Summary

When compared with SARS-CoV and MERS-CoV, SARS-CoV-2 is a highly contagious infection agent. Although MERS-CoV infection is known to have higher mortality, SARS-CoV-2 has spread to many people all over the world in a very short time. In addition to this, SARS-CoV-2 (like SARS-CoV and MERS) infects less children and results in milder clinical symptoms than in adults. Although the reason of it is not known, difference in their immunities or being less likely to be exposed to the source of the infection is thought to be the reason. However, it should not be forgotten that children can contribute to the spread of infection among adults and population, along with being mostly asymptomatic.

Table 2. Drugs commonly used in treatment of pediatric SARS-CoV-2 infection

Drug	General Information	Mechanism of Action	Usage	Side effects
Lopinavir 250 mg/ ritonavir 50mg tablet **a. Darunavir/ritonavir** **b. Remdesivir (GS-5734)**	Protease inhibitor, widely used in HIV treatment	Inhibits Viral replication, reduces SARS-CoV-2 replication, Ritonavir increases plasma lopinavir level	**Children between 14 days - 6 months:** Lopinavir component 16 mg/kg PO BID **6 months - 18 years old:** 15-25 kg: 200 mg-50 mg PO BID 26-35 kg: 300 mg-75 mg PO BID >35 kg: 400 mg-100 mg PO BID Treatment time 10 -14 days	QT prolongation, Torsade de Pointes, Pancytopenia, Pancreatitis, Hepatotoxicity, Hypersensitivity Reactions, Angioedema, Nausea.
Azithromycin 200 mg/5 ml susp 500mg tb	Macrolide group antibiotic		1-5 months children 10mg/kg/dose (max dose 500mg/dose) > 6 months children and adolescents 10mg/kg first day single dose (max dose 500 mg/dose), 5 mg/kg then single dose a day for 2-5 Days (max dose 250 mg/dose) 5 days total Treatment time 5 days	Diarrhea, Abdominal pain, Nausea Leukopenia, Acidosis
Tocilizumab	Monoclonal antibody	Human IL-6 receptor antibody Used in moderate ARDS	8mg/Kg iv, maximum 800mg/dose, to be infused in 1 hour	Hepatitis, severe infections. Used during pregnancy, breastfeeding, active tuberculosis and chemotherapy.
Chloroquine and hydroxychloroquine 200 mg tablet	Antimalarial drug Antiinflammatory drug Its efficacy in SARS infection was shown Hydroxychloroquine: an analogue of SARS-Cov-2, its efficacy on SARS-CoV-2 was shown	Cell membrane pH change, prevention of viral fusion to cell, prevention of viral protein glycosylation.	First day 6.5 mg/kg/dose 2 times a day Hydroxychloroquine sulfate; first day maximum dose: 400 mg/dose; on 2-5. days 3.25 mg/kg/dose 2 times a day Hydroxychloroquine sulfate: maximum dose 200 mg/dose Treatment time 5 days	Vomiting, headache, allergic reactions, vision changes and muscle weakness

REFERENCES

1. Kasmi Y, Khataby K, Souiri A, Ennaji MM. Coronaviridae: 100,000 Years of Emergence and Reemergence. In: Ennaji MM, editor. Emerging and Reemerging Viral Pathogens. Elsevier London; 2020. p.127-49.
2. Lee PI, Hsueh PR. Emerging threats from zoonotic coronaviruses-from SARS and MERS to 2019-nCoV. J Microbiol Immunol Infect 2020. [Epub ahead of print].
3. Ye Z-W, Yuan S, Yuen K-S, Fung S-Y, Chan C-P, Jin D-Y. Zoonotic origins of human coronaviruses. Int J Biol Sci. 2020;16(10):1686-97.
4. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63(3):364-74.
5. Chiu SS, Hung Chan K, Wing Chu K, Kwan SW, Guan Y, Man Poon LL, et al. Human coronavirus NL63 infection and other coronavirus infections in children hospitalized with acute respiratory disease in Hong Kong, China. Clin Infect Dis. 2005;40(12):1721-9.
6. Thumerelle C, Deschildre A, Bouquillon C, Santos C, Sardet A, Scalbert M, et al. Role of viruses and atypical bacteria in exacerbations of asthma in hospitalized children: a prospective study in the Nord-Pas de Calais region (France). Pediatr Pulmonol. 2003;35(2):75-82.
7. Wang M, Yan M, Xu H, Liang W, Kan B, Zheng B, et al. SARS-CoV infection in a restaurant from palm civet. Emerg Infect Dis. 2005;11(12):1860-5.
8. Shi Z, Hu Z. A review of studies on animal reservoirs of the SARS coronavirus. Virus Res. 2008;133(1):74-87.
9. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8):523-34.
10. Luk HK, Li X, Fung J, Lau SK, Woo PC. Molecular epidemiology, evolution and phylogeny of SARS coronavirus. Inf Genet Evol. 2019;21-30.
11. Zimmermann P, Curtis N. Coronavirus Infections in Children Including COVID-19. Pediatr Infect Dis J. 2020;39(5):355-68.
12. de Groot RJ, Baker SC, Baric RS, Brown CS, Drosten C, Enjuanes L, et al. Commentary: Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. J Virol. 2013;87(14):7790-2.
13. Ommeh S, Zhang W, Zohaib A, Chen J, Zhang H, Hu B, et al. Genetic evidence of Middle East respiratory syndrome coronavirus (MERS-CoV) and widespread seroprevalence among camels in Kenya. Virol Sin. 2018;33(6):484-92.
14. World Health Organization. WHO Director General's Statement on IHR Emergency Committee on novel Coronavirus (2019-nCoV) [Internet]. World Health Organization; 2020 Jan [cited 2020 Mar 3]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-statement-on-ihr-emergency-committee-on-novel-coronavirus-(2019-ncov).
15. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet. 2020;395(10223):514-23.
16. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020;55(3):105924.
17. Meo SA, Alhowikan AM, Al-Khlaiwi T, Meo IM, Halepoto DM, Iqbal M, et al. Novel coronavirus 2019-nCoV: prevalence, biological and clinical characteristics comparison with SARS-CoV and MERS-CoV. Eur Rev Med Pharmacol Sci. 2020;24(4):2012-9.
18. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. The Lancet. 2020;395(10225):689-97.
19. Yuan H, Cao X, Ji X, Du F, Zhou X, He J, et al. A Current Emerging Respiratory Infection: Epidemiological and Clinical Characteristics, Diagnosis and Treatments of COVID-19. (3/6/2020). Available at SSRN: https://ssrn.com/abstract=3551344.
20. Centers for Disease Control and Prevention. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States February 12–March 16 [Internet]. CDC MMWR 2020 Mar 69(12);343-6). [cited 2020 Mar 18]. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm
21. Centers for Disease Control and Prevention. Coronavirus Disease 2019 in Children — United States, February 12–April 2 [Internet]. CDC MMWR 2020 Mar 69(14);422-6). [cited 2020 Apr 7]. Available from: www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm.
22. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13)1239-42.

23. Cui Y, Tian M, Huang D, Wang X, Huang Y, Fan L, et al. A 55-Day-Old Female Infant Infected With 2019 Novel Coronavirus Disease: Presenting With Pneumonia, Liver Injury, and Heart Damage. J Infect Dis. 2020;221(11):1775-81.
24. Tang A, Tong Z, Wang H, Dai Y, Li K, Liu J, et al. Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China. Emerg Infect Dis. 2020;26(6).
25. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
26. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology. 2020:200370.
27. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics. 2020. [Epub ahead of print].
28. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. N Engl J Med. 2020;382(17):1663-5.
29. Novel CPERE. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua liu xing bing xue za zhi. 2020;41(2):145-51.
30. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
31. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr Pulmonol. 2020;55(5):1169-74.
32. Feng K, Yun YX, Wang XF, Yang GD, Zheng YJ, Lin CM, et al. Analysis of CT features of 15 Children with 2019 novel coronavirus infection. Zhonghua Er Ke Za Zhi. 2020;58(0):E007.
33. Li W, Cui H, Li K, Fang Y, Li S. Chest computed tomography in children with COVID-19 respiratory infection. Pediatr Pulmonol. 2020;50(6):796-9.
34. Virkki R, Juven T, Rikalainen H, Svedström E, Mertsola J, Ruuskanen O. Differentiation of bacterial and viral pneumonia in children. Thorax. 2002;57(5):438-41.
35. Hon K, Leung C, Cheng W, Chan P, Chu W, Kwan Y, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. The Lancet. 2003;361(9370):1701-3.
36. Sun D, Li H, Lu XX, Xiao H, Ren J, Zhang FR, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. World J Pediatr. 2020. [Epub ahead of print].
37. Wang D, Ju XL, Xie F, Lu Y, Li FY, Huang HH, et al. [Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China]. Zhonghua Er Ke Za Zhi. 2020;58(4):E011.
38. Chim SS, Tong Y-K, Hung EC, Chiu RW, Lo YD. Genomic sequencing of a SARS coronavirus isolate that predated the Metropole Hotel case cluster in Hong Kong. Clin Chem. 2004;50(1):231-3.
39. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis. 2020. [Epub ahead of print].
40. Chen Z-M, Fu J-F, Shu Q, Chen Y-H, Hua C-Z, Li F-B, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World J Pediatr. 2020. [Epub ahead of print].
41. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected [Internet]. World Health Organization; 2020 Jan [cited 2020 Mar 5]. Available from: https://apps.who.int/iris/handle/10665/330893.
42. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen K-Y. Coronaviruses—drug discovery and therapeutic options. Nat Rev Drug Discov. 2016;15(5):327-47.
43. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. Travel Med Infect Dis. 2020:101615.
44. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269-71.
45. Ahmed SF, Quadeer AA, McKay MR. Preliminary Identification of Potential Vaccine Targets for the COVID-19 Coronavirus (SARS-CoV-2) Based on SARS-CoV Immunological Studies. Viruses. 2020;12(3).
46. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020;38(1):1-9.
47. Shanmugaraj B, Siriwattananon K, Wangkanont K, Phoolcharoen W. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19). Asian Pac J Allergy Immunol. 2020;38(1):10-8.
48. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450-4.
49. Song W, Gui M, Wang X, Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLoS Pathog. 2018;14(8):e1007236.

50. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.