# Prevention and Treatment Approaches in Children with the Coronavirus

Shaqayeq Khosravi, Seyedeh Mahsa Mahmoudinezhad Dezfouli<sup>\*</sup> Emergency Medicine Management Research Center, Iran University of Medical Sciences, Aliasghar Children Hospital, Tehran, Iran

## Corresponding author: Seyedeh Mahsa Mahmoudinezhad Dezfouli

Emergency Medicine Management Research Center, Iran University of Medical Sciences, Aliasghar Children Hospital, Tehran, Iran **Email**: mahmoudinejad.m@iums.ac.ir

#### ABSTRACT

Coronaviruses are a group of highly enveloped, diverse, and RNA-containing viruses that lead into respiratory, intestinal, hepatic, and neurological diseases with varied severity in a wide spectrum of animal species, such as human. In December 2019, a new coronavirus was detected in China that was stronger than the rest of the Coronaviridae family, causing potential hurt to vital organs such as the lungs, heart, liver, kidneys, and pneumonia. Although COVID-19 was reported in adults during early stages of the epidemic, further studies have shown that young children and infants are also vulnerable to the infection. Since this disease occurs in children and infants and since it may in some cases cause a critical and severe condition in them, the present study tries to find methods of prevention and treatment approaches in children with the coronavirus.

#### **INTRODUTION**

Coronaviruses is the subfamily of Coronavirinae, the family of Coronaviridae and the sequence of Nidovirales [1]. This subfamily includes  $\beta$ -coronavirus,  $\alpha$ -coronavirus, γ-coronavirus and delta-coronavirus [2]. Before December 2019, 6 types of coronavirus that cause disease in humans had been identified, including HCoV-229E and HCoV-NL63 (alpha subgroup); and HCoV-OC43, HCoV-HKU1, MERS-CoV, and SARS-CoVs (beta subgroup). There are currently 7 subspecies of coronavirus that infect humans[3]. Coronaviruses cause respiratory system, gastrointestinal tract, and central nervous system diseases [4, 5]. These viruses contain an envelope, a helical capsid, and their genome is a positive single-stranded RNA with a size of approximately 26-32 kb, which is the largest genome size among viruses [6]. These viruses are particles in the range of 80 to 90 nm[7]. The virus genome has at least four major structural proteins, including the Spike (S), membrane (M), envelope (E), nucleocapsid proteins (N), and other proteins required for viral replication and entry [8, 9]. In December 2019, a new coronavirus was discovered in China, first named nCOV-2019 and then SARS-CoV-2, and the resulting disease was named COVID-19 [10] . SARS-CoV-2 has been shown to cause disease through a mechanism similar to SARS coronavirus, causing potential damages to vital organs such as the lungs, heart, liver, kidneys, and pneumonia [11]. Pneumonia is one of the main causes of pediatric death [11]. Since the children's immune systems are not fully functioning, they are more prone to respiratory infections and their symptoms are more varied [12]. Although COVID-19 was reported in adults in the early stages of the epidemic, further studies have shown that young children and infants are also vulnerable to the infection [13, 14] . The first case of infection in children was reported on January 20, 2020, in a 10-year-old boy from Shenzhen, China [15]. The infection affects infants and premature infants, and serious cases are now seen in children. With the outbreak of this epidemic, the number of infected children gradually increased [12]. Since this disease occurs in children and infants and since it may in some cases cause a critical and severe condition in them, the present study tries to find

 ${\bf Keywords:}$  COVID-19, prevention, treatment, children and infants; Coronavirus

#### Correspondence:

Seyedeh Mahsa Mahmoudinezhad Dezfoul Emergency Medicine Management Research Center, Iran University of Medical Sciences, Aliasghar children Hospital, Tehran, Iran **Email:** mahmoudinejad.m@iums.ac.ir

methods of prevention and treatment approaches in children with the coronavirus.

#### **MATERIALS AND METHODS**

The current review research was unfulfilled from January to May 2020 with the aim of examining the aspects of COVID-19 in children and infants, also reviewing medications and treatments as well as methods of preventing this disease. Search engines and scientific databases of Google Scholar, Science Direct, Medline, PubMed, and Cochrane were used to conduct this review and to obtain the desired articles on the findings of children and infants with new coronavirus and treatment. In order to collect information in this field, in terms of content, keywords such as coronavirus, clinical symptoms, prevention, the role of education on prevention, treatment and dosage of drugs, etc. were searched in the desired databases and out of 141 articles, 51 articles that were appropriate in terms of subject coverage and content structure were used in this study.

# Clinical symptoms of Corona in children and clinical results

Compared to influenza, children with COVID-19 are less susceptible to complications and have a lower mortality rate [16]. Most cases reported in children were either asymptomatic or had mild symptoms. The prevalence of asymptomatic, mild, and moderate disease in children was reported to be 4.4%, 50.9% and 38.8%, respectively. In adults, 17.4% of cases were reported asymptomatic [17]. It is not clear why most cases of COVID-19 in children had lower severities compared to adults and might be related to the factors that the child is exposed to and the host factors. Children are usually well-cared at home, which is probably why they have comparatively fewer opportunities to be exposed to pathogens or patients. Probably because of the lower maturity and function (such as binding ability) of ACE2 (receptor for COVID-19 virus in humans) in children than adults, children are less susceptible to COVID-19. In addition, children often develop respiratory infections (such as the RSV respiratory virus) in the winter and may, therefore, have higher levels of antibodies against the virus than adults [13]. Although the clinical indications of COVID-19 are

generally mild in children, in most cases, severe or critical illness has occurred in children less than one year of age [17]. One of the most indications of procedural sedation and analgesia is pediatric imaging. In the pediatric patient, performing CT scan is stressful and results into an increased mental stress, absence of cooperation with the staff, and anxiety, and restlessness in the patient [18]. The most common symptoms reported for this disease in children include fever, cough, nasal symptoms, diarrhea, nausea or vomiting, fatigue and difficulty breathing, and pneumonia (Figure 1). Also, the most common clinical symptoms are pharyngeal erythema, palpitations, and tachypnea at the time of admission [19]. In China, from December 8, 2019, to February 6, 2020, 9 hospitalized

infants were diagnosed with COVID-19. The minimum age of these infants was 1 month, and the maximum was 11 months. Among these nine newborns, four of them experienced fever, two showed mild respiratory symptoms, one was asymptomatic, and no information was available on the symptoms of two. The duration of hospitalization and disease diagnosis lasted from one to three days. All nine newborns had at least one family member infected with coronaviruses, and the infant's infection developed following the infection of family members. None of the 9 infants required intense caring or artificial respiration and had any serious complication [14]. Studies on children with the disease are shown in Table 1.

Table 1: Summary of some studies on children with COVID-19	9
--	---

Reference	Authors name	Title	Clinical symptoms
number	and country	Dediatria corenevirus	Number of notionts, 20 (10 confirmed and 11 probables
[1/]	Jonani et al.	disease 2019 (COVID-19)	hasod on PT PCP and CT scan findings)
	11 d11	An insight from west of	16 girls and 14 hove the youngest one day and the eldest 15
		Iran	vears
		ii uii	The most common symptoms: fever (76.7%), cough (53.3%).
			shortness of breath (66.7%) and the most common symptom
			of tachypnea (76.7%). None of the patients had runny nose.
			Abnormal laboratory results: leukocytosis (40%),
			lymphopenia (13.3%), thrombocytopenia (13.3%),
			thrombocytosis (3.3%) and increased ESR (53.3%)
			CT-scan results: Ground-Glass Opacities in 73.1%, multiple
			consolidations in 42.3%, multiple consolidations with
			surrounding halo in 7.6%, single turbidity in 7.6%, knots in
[20]	Rahimzadeh <i>et</i>	COVID-19 Infection in	9 children 2 to 10 years old (RT-PCR result was positive for
[20]	al	Iranian Children: A Case	three people)
	Iran	Series of 9 Patients	Most frequent symptoms: fever (100%), cough (100%) and
			tachypnea (100%)
			Abnormal laboratory results: lymphopenia in 3 cases,
			increased ESR and CRP in all patients
[11]	Qiu <i>et al</i> .	Clinical and	Number of patients: 36 children
	China	epidemiological	Average age: 8.3 years (1 to 16 years)
		with coronavirus disease	Most common symptoms: lever (36%), cough (19%),
		2019 (COVID-19) in	Abnormal laboratory results: lymphocyte depletion (31%)
		Zheijang, China: an	lymphopenia (19%)
		observational cohort	CT-scan results: pulmonary ground-glass opacities in 53%,
		study	pneumonia with fever or cough in 30%, only pneumonia in
			22%.
[21]	Dong et al.	Epidemiology of COVID-	Number of patients: 2135 children (728 laboratory
	China	19 Among Children in	confirmed and 1407 suspected)
		China	Average age: / years (2 to 13)
			severe 0.6% critical
[22]	Song et al.	Clinical symptoms of	Number of patients: 16 children
L _ 1	China	pediatric patients with	Average age: 8.5 years (11.5 months to 14 years)
		coronavirus disease	Symptoms: only fever (12.5%), fever and cough (18.8%),
		(COVID-19)	only cough (18.8%), none of them had shortness of breath,
			diarrhea, and vomiting.
			Abnormal laboratory results: leukopenia (12.5%),
			Iymphopenia (6.3%), increased CRP (6.2%)
			C1-scan results: In 31.3% normal, knot in 31.3%, turbidity in 37.5% Ground-Class Opacities in 43.8%
[23]	Iones <i>et al</i>	COVID-19 and Kawasaki	A 6-month-old haby
[23]	United states	Disease: Novel Virus and	Symptoms: fever, refusal to eat, the appearance of
		Novel Case	erythematous and non-itchy rash, and no cough and runny
			nose.
			Abnormal laboratory results: Increased CRP
			The chest radiograph showed slight turbidity in the left lung.

[24]	Riphagen et al.	Hyperinflammatory	Number of patients: 8 children (4 to 14 years)
	England	shock in children during	Symptoms: fever, abdominal pain, skin rash, diarrhea
		COVID-19 pandemic	Microbiological results: SARS-CoV-2 test in 5 negative and 3
		_	positives
			Imaging results: lung consolidations, impaired lung function





Figure 1. Chest CT of a 5-year-old boy showing consolidation with halo sign within inferior lobe of the left lung surrounded by ground-glass opacities[20].

# The association between breastfeeding and coronavirus

It is not yet recognized whether acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could pass into the breast milk and be transferred through breastfeeding. Recent research has not illustrated any indication of SARSCoV2 in breast milk [25]. However, in a study by Groß et al., the results showed that the milk test of one of the two mothers with SARSCoV2 was positive for four consecutive days, and her baby was also infected with the virus. They reported that the mother wore a surgical mask from the first appearance of the symptoms and took the preventive measures when handling or feeding the baby, such as appropriate hand and breast sanitization and washing of pumps and milk tubes. However, it is unclear whether her infant contracted the disease due to breastfeeding or other forms of transmission were effective [25]. Infants may take nutrition from diverse sources, but the most important source is breast milk, even for infants whose mothers have confirmed or suspected coronavirus infection. An infected mother can breastfeed her baby as long as she takes the necessary precautions. These include using a mask while breastfeeding, washing hands with soap and water for 20 seconds before and after touching the baby, and cleaning and disinfecting surfaces. Breast milk contains antibodies and other immune system benefits that can help protect the baby against respiratory diseases. There is a plenty of evidence to support the importance of breastfeeding for the growth, development, and health of the baby, as well as helping them prevent obesity and non-communicable diseases in later life [26].

### PREVENTION

### Health and social prevention

Social, economic, and environmental factors related to human bustles change the patterns of infectious diseases in humans. These factors affect the facility of adaptation of microbes to new environments and hosts, the speediness of microbial insusceptibility to antimicrobial agents used for treatment, and the limitations of their geographical spread. Social factors contain the impacts of urbanization on health and water supply, the behavior of employees of health organizations when performing their normal duties, and the behavior of the overall public in trying to obviate and dominate the regular threat of infectious diseases. Environmental factors contain natural changes in temperature, rainfall, and the effects of economic expansion on rivers, forests, and agricultural land. Whereas economic factors contain the amount of investment in public health, the pattern of trade, and international travel. Lack of vaccine for many infectious diseases reduces improvement in prevention, while constant changes in climate and precipitation and human impact on agricultural lands, forests, and rivers in some cases enhance the population of vector insects and change their geographical distribution, which leads to the appearance of new human infections or the re-appereance of known ones [27]. Preventing the spread of the COVID-19 virus is the first step in controlling this epidemic[28]. In order to prevent it, people should acknowledge the awareness of the latest information on the prevalence of the virus provided by the WHO, follow their local health guidelines, and prevent further spread by breaking the transmission chain [29, 30]. Developed countries are more specialized in studying and managing such cases than developing countries. Developing countries are likely to bear the brunt of the COVID-19 virus due to lack of awareness, fiscal status, substructures, human resources, and expertise. Thus, these countries should concentrate on science-based preventive measures before the outbreak and science-based treatment and counseling during and after the outbreak [31, 32]. Owing to the fact that the virus stays active in the air for up to 3 hours, preventative actions against this epidemic disease include regular hand washing, cleansing with soap and water, or disinfectant, particularly after touching shared surfaces in public transport and places, use of masks and gloves, coverage of the mouth and nose when coughing and sneezing, not touching the face with dirty hands, and keeping regular social distance [28, 31]. Teaching and training on preventive actions and the manners of dealing with infection and infected people are the most important measures to deal with COVID-19. Convenient risk identification, design of appropriate informative protocols on the wide outbreak of the virus, and the providing active, timely, and efficacious public education must also be marked. Simple, practical, and gratis online courses must be available for all people, and user-friendly software for

the illiterate and disabled people should also be contemplated. Training increases people's preparedness and response to the virus. Therefore, with the aim of controlling the virus, policymakers in the health system and all involved organizations must take steps to provide ingenious, integrated, and practical educational content for everyone. Also, organizations and people in these educational fields have special importance for promoting resistance in society [33].

## **Biological and nutritional prevention**

Nutrition and strengthening the immune system could be effective in preventing coronavirus disease. Proper nutrition could help reduce the risk of contracting the virus. Consumption of vitamins and antioxidants and enhancing functions of the immune system and health play an important role in preventing disease [34, 35].

# **Table 2.** Important nutritional factors effective in the prevention of corona

Effective factor		Preventive role		
Vitamins and	Vitami n D	Vitamin D is an acquired immune modulator. This vitamin regulates the inflammatory responses of helper T cells by inhibiting the production of inflammatory cytokines IL-2 and interferon-gamma (INF $\gamma$ ).	nce [34, 36]	
mmerais				
	Vitami n B	B vitamins are another group of vitamins that play a role in the metabolism of all cells. Vitamin B3 or nicotinamide could kill Staphylococcus aureus via a specific myeloid transcription factor and is effective in treatment. In addition, vitamin B3 inhibits the permeation of neutrophils into the lungs with a strong anti-inflammatory impact due to ventilator-induced lung damage.	[37-39]	
	Vitami n E	Vitamin E as an antioxidant has a major role in reducing oxidative stress by binding to free radicals (50). Consumption of antioxidants in the diet of people exposed to the virus could be effective in strengthening their immune system.	[40]	
	Zinc	The growth and development of the body, especially in children, largely depends on the presence of zinc. Most enzymes and many important cellular proteins involved in biological cycles contain zinc in their structure. Zinc deficiency reduces the function of enzymes that are effective in inflammation and impairs wound healing and chronic diseases. The immune system is critically affected by the level of zinc in the body. Brain and bone stem cells require zinc to express immune genes such as B lymphocytes during illness. So far, no significant research has been conducted on zinc in COVID-19, but it is safe to say that zinc supplementation could have a beneficial effect on the prevention and treatment of coronavirus disease.	[41-43]	
Antioxidants		Antioxidants are the first line of defense against inflammatory damage and are very important for maintaining good health. Antioxidants have beneficial structures that prevent further oxidation in the cell space, which affects the metabolism and better functioning of cells. Antioxidants reduce the inflammation caused by the virus. Researchers are looking for drugs that contain antiviral properties among antioxidants. Increasing the consumption of antioxidants has a positive effect on the immune system.	[35, 44- 46]	
Immune system		Strengthening the immune system is probably another important factor in the prevention and treatment of the disease. The innate immune system is made up of mucus and the body's first defensive layers; In the first step, they kill viruses. One of the factors that strengthen the immune system is mobility and exercise. Exercise helps the immune system to react more efficiently against pathogens by reducing cellular stress and regulating cytokines. Studies have shown that all people who suffer from certain illnesses, even colds, are exposed to levels of cellular oxidative stress. Reducing stress is an important issue in controlling inflammation.	[47-50]	

### TREATMENT

Given the potential threat of this epidemic to the public health, scientists and physicians are competing to understand this new virus and the pathophysiology of the disease, to discover possible treatments and effective vaccines [51]. Mild cases may be treated at home. These patients must be isolated and monitored for clinical deterioration to prevent transmission. The patient must receive adequate calories and water and be evaluated for vital signs and oxygen saturation. In case of fever and pain presence, the use of antipyretics or analgesics such as acetaminophen or ibuprofen is recommended. In addition, acetaminophen was more effective in managing moderate pains than severe pains. Also, these medicines were found to be more effective in pain reduction in younger ages. Most of pharmacologic and non-pharmacologic strategies are for the management and treatment of pediatric pain [52]. Pharmacological and integrative nonpharmacological therapies have been indicated in acute and chronic pain treatment [53]. In hypoxic patients, oxygen must be provided through a nasal mask or catheter, but in severe cases, patients should be admitted to the intensive care unit (ICU)[54]. In the lack of particular antiviral drugs for the new coronavirus, broadspectrum antiviral drugs including interferon alpha and beta, or Ribavirin could be consumed by the patients to treat SARS-CoV, including in children. However, it is harmful because Ribavirin could induce hemolytic anemia or liver dysfunction [55]. Remdesivir is also used in laboratory and animal studies to treat COVID-19 due to its effect on SARS-CoV-2. Chloroquine could inhibit the proliferation and spread of viruses, especially SARS-CoV; it also has efficacy on the immune system and suppresses IL-6 and TNF- $\alpha$  and interferes with glycosylation of receptors. Therefore, it is used for the treatment of COVID-19 [54]. There is evidence that intravenous corticosteroids could provide clinical and radiological improvement in people infected with SARS-CoV. However, in another study, the results showed that corticosteroids may also be harmful (avascular necrosis, osteoporosis, new onset of diabetes) [55]. Medications used for children include interferon  $\alpha$ 2b nebulization at a rate of 200000-100000 kg / IU for mild cases and 400000-200000 kg / IU for severe cases, twice daily for 5-7 days, and also, Lopinavir / Ritonavir (Kaletra) (200 mg in 50 mg) and the recommended doses are as follows:

For weight 7-15 kg dose 12 mg in 3 mg / kg (12 mg / 3mg / kg); for weight 15-40 kg dose 10 mg / 2.5 mg / kg (10 mg / 2.5mg / kg); and for weight above 40 kg as adults' dose 400 mg per 100 mg (400 mg / 100 mg) twice daily for 1-2 weeks [56]. Oseltamivir medication, for premature infants should be consulted by a pediatric infectious disease specialist, for infants 0 to 12 months, dose 3 mg/kg twice daily, for children older than 12 months with bodyweight less than or equal to 5 kg dose of 30 mg twice daily, weight between 15-23 kg dose of 45 Mg and twice a day, for a weight between 23-40 kg dose of 60 mg and twice a day, for a weight of more than 40 kg dose of 75 mg twice a day, and for adults a dose of 75 mg and twice a day; The duration of use of this drug is at least 5 days. Hydroxychloroquine medication (Hydroxychloroquine sulfate is used for infants and children) at a dose of 3-5 mg/kg per day (maximum dose of 400 mg), BID for 5 days. Ribavirin (oral) for children over 3 years of age weighing less than 47 kg 15mg/kg/day-BID, weighing between 47-59 dose of 400mg-BID, weighing between 60-73 dose of 400 mg in the morning and 600 mg in the evening, and for

weights above 73 kg, the dose is 600 mg-BID, which is used for up to 14 days depending on the patient's reaction [57].

#### CONCLUSION

As an emerging disease, COVID-19 has posed a major challenge in managing and controlling the disease. Also has created a lot of difficulties for the health system, while the disease is highly epidemic and there are no specific guidelines for diagnostic and therapeutic management, particularly in children. SARS-CoV-2 infection appears to be less common in the children compared with the adults. This may be because children are less exposed to the main sources of transmission and less exposed to animals. On the other hand, inhibiting the spread of the COVID-19 virus is the first step to control this epidemic in which education and parents play an important role. With the aim of managing the virus, policymakers in the health system and other involved organizations must take further steps to provide ingenious, integrated, and practical educational content for everyone. So far, various drugs such as interferon, Kaletra, and hydroxychloroquine have been used for the treatment of this disease in children. Vaccines are also being studied, and researchers are examining the laboratory phase of the corona vaccine and according to estimates, the introduction of a new vaccine in the future could play an effective role in reducing the incidence.

### REFERENCES

- 1. Khan ZH, Samadi S, Makarem J, Mireskandari SM. Tests with proven value in diagnosis of COVID-19. Iran J Microbiol. 12(3):261-262.
- 2. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. Journal of medical virology. 2020;92(5):479-490.
- 3. Nokhostin F, Saffarieh E, Sharami SRY. Investigating the effect of COVID-19 on Pregnant Women. Journal of Critical Reviews. 2020;7(7):1141-1145.
- 4. Caselli D, Aricò M. 2019-nCoV: Polite with children! Pediatric reports. 2020;12(1).
- Khosravi M. Neuroticism as a Marker of Vulnerability to COVID-19 Infection. Psychiatry Investigation. 2020;17(7):710.
- 6. Pillaiyar T, Meenakshisundaram S, Manickam M. Recent discovery and development of inhibitors targeting coronaviruses. Drug discovery today. 2020;25(4):668-688.
- Gui M, Liu X, Guo D, Zhang Z, Yin C-C, Chen Y, Xiang Y. Electron microscopy studies of the coronavirus ribonucleoprotein complex. Protein & cell. 2017;8(3):219-224.
- 8. Seah I, Su X, Lingam G. Revisiting the dangers of the coronavirus in the ophthalmology practice. *Nature Publishing Group*; 2020.
- 9. Khosravi M. Stress Reduction Model of COVID-19 Pandemic. Iranian Journal of Psychiatry and Behavioral Sciences. (In Press).
- 10. Schwartz DA. An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. Archives of pathology & laboratory medicine. 2020;144(7):799-805.
- 11. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. The Lancet Infectious Diseases. 2020.

- 12. Huang X, Wei F, Hu L, Wen L, Chen K. Epidemiology and clinical characteristics of COVID-19. Archives of Iranian medicine. 2020;23(4):268-271.
- 13. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics. 2020.
- Yu H, Shao J, Guo Y, Xiang Y, Sun C, Zhang H-T, Yuan Y. Data-driven discovery of clinical routes for severity detection in COVID-19 pediatric cases. medRxiv. 2020.
- 15. Choi S-H, Kim HW, Kang J-M, Kim DH, Cho EY. Epidemiology and clinical features of coronavirus disease 2019 in children. Clinical and experimental pediatrics. 2020;63(4):125.
- 16. Rasmussen SA, Thompson LA. Coronavirus disease 2019 and children: what pediatric health care clinicians need to know. Jama Pediatrics. 2020.
- 17. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145(6).
- Barzegari H, Zohrevandi B, Masoumi K, Forouzan A, Darian AA, Khosravi S. Comparison of oral midazolam and promethazine with oral midazolam alone for sedating children during computed tomography. Emergency. 2015;3(3):109.
- Soltani J, Sedighi I, Shalchi Z, Sami G, Moradveisi B, Nahidi S. Pediatric coronavirus disease 2019 (COVID-19): An insight from west of Iran. Northern Clinics of İstanbul. 2020;7(3):284.
- de Souza TH, Nadal JA, Nogueira RJ, Pereira RM, Brandão MB. Clinical manifestations of children with COVID-19: a systematic review. Pediatric Pulmonology. 2020.
- Rahimzadeh G, Ekrami Noghabi M, Kadkhodaei Elyaderani F, Navaeifar MR, Enayati AA, Manafi Anari A, Hujati M, Rezai S, Rezai MS. COVID-19 infection in Iranian children: a case series of 9 patients. Journal of Pediatrics Review. 2020;8(2):139-144.
- Song W, Li J, Zou N, Guan W, Pan J, Xu W. Clinical features of pediatric patients with coronavirus disease (COVID-19). Journal of Clinical Virology. 2020:104377.
- Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, Nguyen EL, Barsh GR, Maskatia S, Mathew R. COVID-19 and Kawasaki disease: novel virus and novel case. Hospital Pediatrics. 2020;10(6):537-540.
- 24. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. 2020;395(10237):1607-1608.
- 25. Groß R, Conzelmann C, Müller JA, Stenger S, Steinhart K, Kirchhoff F, Münch J. Detection of SARS-CoV-2 in human breastmilk. The Lancet. 2020;395(10239):1757-1758.
- 26. Organization WH. The WHO recommended classification of pesticides by hazard and guidelines to classification 2019: World Health Organization; 2020.
- Heymann DL. Effects of social, environmental and economic factors on current and future patterns of infectious diseases. Interactions Between Global Change and Human Health (Scripta Varia. 2004;106:290-303.
- Chhikara BS, Rathi B, Singh J, Poonam F. Corona virus SARS-CoV-2 disease COVID-19: Infection, prevention and clinical advances of the prospective chemical

drug therapeutics. Chemical Biology Letters. 2020;7(1):63-72.

- 29. Hafeez A, Ahmad S, Siddqui SA, Ahmad M, Mishra S. A Review of COVID-19 (Coronavirus Disease-2019) Diagnosis, Treatments and Prevention. 2019.
- 30. Fini MB. What dentists need to know about COVID-19. Oral Oncology. 2020:104741.
- Khadka S, Hashmi FK, Usman M. Preventing COVID-19 in low-and middle-income countries. Drugs & Therapy Perspectives. 2020:1-3.
- 32. Fini MB. Oral saliva and CVID-19. Oral Oncology. 2020:104821.
- Peyravi M, Marzaleh MA, Shamspour N, Soltani A. Public Education and Electronic Awareness of the New Coronavirus (COVID-19): Experiences From Iran. Disaster Medicine and Public Health Preparedness. 2020:1-2.
- 34. Rondanelli M, Miccono A, Lamburghini S, Avanzato I, Riva A, Allegrini P, Faliva MA, Peroni G, Nichetti M, Perna S. Self-care for common colds: the pivotal role of vitamin D, vitamin C, zinc, and echinacea in three main immune interactive clusters (physical barriers, innate and adaptive immunity) involved during an episode of common colds—practical advice on dosages and on the time to take these nutrients/botanicals in order to prevent or treat common colds. Evidence-Based Complementary and Alternative Medicine. 2018;2018.
- 35. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497-506.
- Cantorna MT, Snyder L, Lin Y-D, Yang L. Vitamin D and 1, 25 (OH) 2D regulation of T cells. Nutrients. 2015;7(4):3011-3021.
- 37. HJ P. Hilary. Riboflavin (vitamin B-2) and health. Am J Clin Nutr. 2003;77:1352-1360.
- Kyme P, Thoennissen NH, Tseng CW, Thoennissen GB, Wolf AJ, Shimada K, Krug UO, Lee K, Müller-Tidow C, Berdel WE. C/EBPɛ mediates nicotinamide-enhanced clearance of Staphylococcus aureus in mice. The Journal of clinical investigation. 2012;122(9):3316-3329.
- 39. Jones HD, Yoo J, Crother TR, Kyme P, Ben-Shlomo A, Khalafi R, Tseng CW, Parks WC, Arditi M, Liu GY. Nicotinamide exacerbates hypoxemia in ventilatorinduced lung injury independent of neutrophil infiltration. PLoS ONE. 2015;10(4):e0123460.
- 40. Galmés S, Serra F, Palou A. Vitamin E metabolic effects and genetic variants: a challenge for precision nutrition in obesity and associated disturbances. Nutrients. 2018;10(12):1919.
- 41. Krężel A. Artur Krężel and Wolfgang Maret 2. 2016.
- 42. Kimura T, Kambe T. The functions of metallothionein and ZIP and ZnT transporters: an overview and perspective. International Journal of Molecular Sciences. 2016;17(3):336.
- 43. Fukada T, Kambe T. Molecular and genetic features of zinc transporters in physiology and pathogenesis. Metallomics. 2011;3(7):662-674.
- Fedoreyev SA, Krylova NV, Mishchenko NP, Vasileva EA, Pislyagin EA, Iunikhina OV, Lavrov VF, Svitich OA, Ebralidze LK, Leonova GN. Antiviral and antioxidant properties of echinochrome A. Marine drugs. 2018;16(12):509.
- 45. Nobakht M. Gh BF, Oskouie AA, Aliannejad R, Rezaei-Tavirani M, Tavallaie S, Baghban AA, Taheri S, Keramati MR, Alamdari DH. Pro-oxidant–antioxidant

balance in Iranian veterans with sulfur mustard toxicity and different levels of pulmonary disorders. Drug and chemical toxicology. 2016;39(4):362-366.

- 46. Jin Y-H, Cai L, Cheng Z-S, Cheng H, Deng T, Fan Y-P, Fang C, Huang D, Huang L-Q, Huang Q. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Military Medical Research. 2020;7(1):4.
- 47. Mirowsky JE, Dailey LA, Devlin RB. Differential expression of pro-inflammatory and oxidative stress mediators induced by nitrogen dioxide and ozone in primary human bronchial epithelial cells. Inhalation toxicology. 2016;28(8):374-382.
- Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. Journal of sport and health science. 2019;8(3):201-217.
- 49. LeRoy AS, Murdock KW, Jaremka LM, Loya A, Fagundes CP. Loneliness predicts self-reported cold symptoms after a viral challenge. Health Psychology. 2017;36(5):512.
- 50. Guo Y-R, Cao Q-D, Hong Z-S, Tan Y-Y, Chen S-D, Jin H-J, Tan K-S, Wang D-Y, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak-an update on the status. Military Medical Research. 2020;7(1):1-10.
- 51. Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ, Smoot J, Gregg AC, Daniels AD, Jervey S. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. *ACS Publications*; 2020.
- 52. Dezfouli SMM, Khosravi S. Pain in child patients: A review on managements. European Journal of Translational Myology. 2020.
- 53. Mahshidfar B, Rezai M, Abbasi S, Farsi D, Hafezimoghadam P, Mofidi M, Almasi R, Khosravi S. Intravenous acetaminophen vs. ketorolac in terms of pain management in prehospital emergency services: a randomized clinical trial. Advanced Journal of Emergency Medicine. 2019;3(4).
- 54. Wojtyniak K, Horvath A, Dziechciarz P, Szajewska H. Lactobacillus casei rhamnosus Lcr35 in the management of functional constipation in children: a randomized trial. The Journal of pediatrics. 2017;184:101-105. e101.
- 55. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. The Pediatric infectious disease journal. 2020;39(5):355.
- 56. Chen Z-M, Fu J-F, Shu Q, Chen Y-H, Hua C-Z, Li F-B, Lin R, Tang L-F, Wang T-L, Wang W. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World journal of pediatrics. 2020:1-7.
- 57. Fan H-H, Wang L-Q, Liu W-L, An X-P, Liu Z-D, He X-Q, Song L-H, Tong Y-G. Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus-related coronavirus model. Chinese medical journal. 2020.