Prevention and Treatment Approaches in Children with the Coronavirus

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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 humans. In December 2019, a new coronavirus was detected in China that was stronger than the rest of the Coronaviridae family, causing potential harm 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.

INTRODUCTION
Coronaviruses is the subfamily of Coronavirinae, the family of Coronaviridae and the sequence of Nidovirales [1]. This subfamily includes β-coronavirus, α-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 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 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

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Authors name and country</th>
<th>Title</th>
<th>Clinical symptoms</th>
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<tbody>
<tr>
<td>[17]</td>
<td>Sokani et al. Iran</td>
<td>Pediatric coronavirus disease 2019 (COVID-19): An insight from west of Iran</td>
<td>Number of patients: 30 (19 confirmed and 11 probable based on RT-PCR and CT-scan findings) 16 girls and 14 boys, the youngest one day and the eldest 15 years 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%, knobs in 15.4%.</td>
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<td>[20]</td>
<td>Rahimzadeh et al. Iran</td>
<td>COVID-19 Infection in Iranian Children: A Case Series of 9 Patients</td>
<td>9 children 2 to 10 years old (RT-PCR result was positive for three people) Most frequent symptoms: fever (100%), cough (100%) and tachypnea (100%) Abnormal laboratory results: lymphopenia in 3 cases, increased ESR and CRP in all patients</td>
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<td>[11]</td>
<td>Qiu et al. China</td>
<td>Clinical and epidemiological symptoms of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study</td>
<td>Number of patients: 36 children Average age: 8.3 years (1 to 16 years) Most common symptoms: fever (36%), cough (19%), shortness of breath or tachypnea (1%) Abnormal laboratory results: lymphocyte depletion (31%), lymphopenia (19%) CT-scan results: pulmonary ground-glass opacities in 53%, pneumonia with fever or cough in 30%, only pneumonia in 22%</td>
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<td>[21]</td>
<td>Dong et al. China</td>
<td>Epidemiology of COVID-19 Among Children in China</td>
<td>Number of patients: 2135 children (728 laboratory confirmed and 1407 suspected) Average age: 7 years (2 to 13) 4.4% asymptomatic, 51% mild, 38.7% moderate, 5.3% severe, 0.6% critical</td>
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<td>[22]</td>
<td>Song et al. China</td>
<td>Clinical symptoms of pediatric patients with coronavirus disease (COVID-19)</td>
<td>Number of patients: 16 children Average age: 8.5 years (11.5 months to 14 years) Symptoms: only fever (12.5%), fever and cough (18.8%), only cough (18.8%), none of them had shortness of breath, diarrhea, and vomiting. Abnormal laboratory results: leukopenia (12.5%), lymphopenia (6.3%), increased CRP (6.2%) CT-scan results: in 31.3% normal, knot in 31.3%, turbidity in 37.5%, Ground-Glass Opacities in 43.8%</td>
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</table>
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 SARS-CoV2 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 SARS-CoV2 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-appearence 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 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

|      | England        |                        | Symptoms: fever, abdominal pain, skin rash, diarrhea |
|      |                |                        | 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 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>
<thead>
<tr>
<th>Effective factor</th>
<th>Preventive role</th>
<th>Reference</th>
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<tr>
<td><strong>Vitamins and minerals</strong></td>
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<tr>
<td>Vitamin D</td>
<td>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 (INFγ).</td>
<td>[34, 36]</td>
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<td>Vitamin B</td>
<td>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.</td>
<td>[37-39]</td>
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<td>Vitamin E</td>
<td>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.</td>
<td>[40]</td>
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<td>Zinc</td>
<td>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.</td>
<td>[41-43]</td>
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<td><strong>Antioxidants</strong></td>
<td>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.</td>
<td>[35, 44-46]</td>
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<td><strong>Immune system</strong></td>
<td>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.</td>
<td>[47-50]</td>
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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 non-pharmacological 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, broad-spectrum 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-α 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 α2b nebulization at a rate of 20000-1 0000 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 / 2.5 mg / kg); and for weight above 40 kg as adults’ dose 400 mg per 100 mg (400 mg / 100mg) twice daily for 1-2 weeks [56]. Oselfamivir 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 between 40 kg dose of 75 mg and 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 15 mg/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, it 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, 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.

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