



# Prevention, Diagnosis, and Treatment of COVID-19 in Infants and Children: A Systematic Review Study of Performed Protocols

Mohammad Karimian <sup>1</sup>, Feizollah Mansouri<sup>2</sup>, Milad Borji <sup>3</sup>, Asma Tarjoman <sup>3</sup>, Somayeh Mahdikhani<sup>4</sup>, Behrouz Soltany <sup>5,6</sup>, Gholamreza Kalvandi<sup>7</sup>, Hamed Tavan <sup>3</sup> and Mehdi Shokri <sup>8,\*</sup>

<sup>1</sup>Ilam University of Medical Sciences, Ilam, Iran

<sup>2</sup>Infectious Diseases Department, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

<sup>3</sup>Department of Nursing, Faculty of Nursing and Midwifery, Ilam University of Medical Sciences, Ilam, Iran

<sup>4</sup>Università degli Studi "La Sapienza" di Roma, Public Health and Infectious Diseases, Roma, Italy

<sup>5</sup>Student Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran

<sup>6</sup>Department of Nursing, Faculty of Nursing and Midwifery, Kermanshah University of Medical Sciences, Kermanshah, Iran

<sup>7</sup>School of Medicine, Ilam University of Medical Sciences, Ilam, Iran

<sup>8</sup>Department of Pediatrics, Ilam University of Medical sciences, Ilam, Iran

\*Corresponding author: Department of Pediatrics, Ilam University of Medical sciences, Ilam, Iran. Email: [mehdishokri557@gmail.com](mailto:mehdishokri557@gmail.com)

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## Abstract

**Context:** Coronavirus disease 2019 (COVID-19) is one of the most dangerous viral diseases that started spreading in China in 2019 and has caused many deaths so far. Therefore, this study aimed to systematically review studies on the prevention, diagnosis, and treatment of coronavirus in infants and children.

**Evidence Acquisition:** This is a systematic review study conducted in PubMed/Medline, Scopus, Embase, Cochrane Library, Science Direct, and Web of Science (ISI) databases on October 8 2020. Also, we searched Google Scholar to find all in-press articles. To extract data, a checklist was used, which included the author's name, year of publication, purpose, age group of patients under study, and the protocol applied for coronavirus prevention, diagnosis, and treatment. The search was done with AND, OR, NOT strategies. The results of the study were reported in a descriptive manner using Endnote version 8 software.

**Results:** According to the results of the basic search, 120 articles were extracted on the management of coronavirus. Of the articles extracted, 30 were articles related to children, of which only eight developed protocols for prevention, diagnosis, and treatment in infants and children. Of the studies extracted, six were from China, one from Iran, and one from Australia. It should be noted that the protocols for infants were extracted from two studies on infants and four studies on the pediatric group.

**Conclusions:** It is proposed to consider and study this systematic review of coronavirus management in infants and children.

**Keywords:** Coronavirus, COVID-19, Neonates, Children, Protocol, Prevention, Diagnosis, Treatment

## 1. Context

Infants and children are one of the most vulnerable groups at a higher risk of diseases than other age groups, and they may experience different diseases in the early days of life (1-3). Attention to their health leads to the health of the community, and it is necessary to prevent the disease in this age group (4, 5).

Coronavirus disease 2019 (COVID-19) is one of the most dangerous viruses that began spreading in China in 2019 and has caused many deaths so far (6-8). The disease has affected many countries, and until now, none of these coun-

tries have been able to find a cure for the disease (9). In the early days of the outbreak, it was thought that children and infants were not susceptible to the disease, but after some time, the health system realized that the disease may also occur in children and infants (10).

There have been several studies aiming at the management of COVID-19 in infants and children, but no systematic review and meta-analysis study has been performed. Therefore, this study aimed to systematically review studies on the prevention, diagnosis, and treatment of coronavirus in infants and children.

## 2. Evidence Acquisition

### 2.1. Study Protocol

This is a systematic review study conducted as per the PRISMA protocol (11).

### 2.2. Search Strategy

The study was conducted in PubMed/Medline, Scopus, Embase, Cochrane Library, Science Direct, and Web of Science (ISI) databases at all time intervals. Also, we searched Google Scholar to find all in-press articles. The keywords with which the search was performed included infant, child, coronavirus, COVID-19, diagnosis, treatment, prevention, and protocol.

### 2.3. Inclusion Criteria

Articles aiming at developing a protocol for the management of coronavirus in infants and children were included in the study.

### 2.4. Exclusion Criteria

Non-English language articles were excluded.

### 2.5. Data Extraction

We used a checklist to extract data, which included the author's name, year of publication, purpose, age group of patients under study, and protocols for coronavirus prevention, diagnosis, and treatment. The search was done with the AND, OR, NOT strategy.

### 2.6. Statistical Analysis

The results of this study were reported in a descriptive manner using Endnote version 8 software.

## 3. Results

In line with the findings of the initial search, 120 articles were extracted that focused on the management of coronavirus. Of the articles extracted, 30 were articles related to children, of which only eight developed protocols for the coronavirus management (prevention, diagnosis, and treatment) in infants and children that were included in the study. Extracted studies included the study by Wang et al. (12) in a Chinese infant group, the study of Chen et al. (13) in a pediatric group from China, the Lu and Shi study (6) in an infant group from China, Shen et al. study (14) in a Chinese pediatric group and the study by Karimi et al. (15)

in an Iranian pediatric group. Of the studies extracted, six were from China, one from Iran, and one from Australia. It should be noted that the protocols for infants were extracted from two studies on infants and four studies on the pediatric group (Tables 1-3).

## 4. Discussion

Coronavirus disease 2019, as a worldwide epidemic (19, 20), and now it is facing a severe outbreak in Iran (21), needs special remedial measures (21). For this reason, this study was performed, and it is proposed to consider the prevention, diagnosis, and treatment of coronavirus in infants and children.

## 5. Conclusions

It is suggested to consider this systematic review of the prevention, diagnosis, and treatment of coronavirus in infants and children.

## Footnotes

**Authors' Contribution:** MK presented an initial idea. BS and MB searched for articles and collected data. MK and MSH wrote the different parts of the first draft. AT contributed papers and guidance to initial submission. After reviewing and requesting more information, FM, GK, and HT updated the document. All authors made final recommendations and editing. All authors approved the final version of the manuscript.

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**Table 1.** Clinical Symptoms in Neonates and Children with Coronavirus Undergoing the Systemic Review

	Author's Name	Country	Year	Target Group	Protocol
1	Wang et al. (12)	China	2020	Infants	Non-specific symptoms (especially in premature babies); unstable temperature may increase or decrease or be normal; respiratory and cardiovascular symptoms: tachypnea, grunting, trembling of the nose, hard breathing, apnea, cough, or tachycardia; other possible symptoms: poor nutrition, lethargy, vomiting, diarrhea, or abdominal bloating
2	Chen et al. (13)	China	2020	Children	Incubation period: 2 to 14 days, although in most cases, it is three to seven days; children's primary symptoms at onset: fever, cough, and fatigue, which may be accompanied by symptoms such as runny nose and congestion, headache, sputum, and diarrhea; in most kids, fever is mild or moderate, and some may even be fever-free; symptoms such as dyspnea (shortness of breath) and cyanosis may occur a week after the onset and progression of the disease with symptoms of systemic toxicity such as weakness, restlessness, loss of appetite, poor nutrition, and decreased activity; in some children, the condition may progress rapidly within one to three days and cause a respiratory failure that is not responsive to routine oxygen delivery techniques such as nasal catheter and mask. In such severe cases, metabolic acidosis, septic shock, coagulation disorders, and uncontrolled bleeding can occur; increased respiratory rate (hyperpnea) and wet rales indicate pneumonia. Hyperpnea criterion (times/min) in children: $\geq 60$ : under two months; $\geq 50$ : 2 to 12 months; $\geq 40$ : 1 to 5 years; $\geq 30$ : over 5 years; with exacerbation of the situation, respiratory tract distress, opening of the nasal passages during respiration, intercostal and supranatural retraction, moaning, and cyanosis may happen; intrauterine asphyxia and preterm labor can occur because of maternal hypoxemia; most children have a good prognosis, and mild cases will heal one to two weeks after the onset of the disease.
3	Lu and Shi (6)	China	2020	Infants	Incubation period: 1 to 14 days; coronavirus infection in infants and children can range from asymptomatic to severe respiratory distress. Clinical symptoms are milder in children than in adults; common symptoms: fever, fatigue, and hack; patients rarely show upper respiratory tract disorder symptoms such as sore throat, obstruction, and runny nose; symptoms of gastrointestinal disorders such as abdominal disorders, diarrhea, abdominal pain, and vomiting may occur.
4	Shen et al. (14)	China	2020	Children	Incubation period: 1 to 14 days, often between three and seven days; affected children may be asymptomatic or have a fever, hack, and fatigue, and some may have symptoms of upper respiratory tract involvement such as hyperemia and runny nose and symptoms of gastrointestinal involvement such as abdominal pain, vomiting, nausea, diarrhea, or abdominal disorders; most children have mild symptoms. Most of them have no symptoms of pneumonia or fever and have a good prognosis and improve during one to two weeks after the onset of symptoms; infections of the lower respiratory tract develop in few patients; children often have milder symptoms than adults.
5	Karimi et al. (15)	Iran	2020	Children	Warning clinical symptoms: tachypnea criteria in children; $> 60$ : under two months; $> 50$ : 2 to 12 months; $> 40$ : 1 to 4 years; $> 30$ : over 5 years; respiratory distress; lips and tongue's cyanosis; inability to eat and drink; inability to communicate; dry mouth mucosa; decreased urine volume and lack of tears; fever over $40^{\circ}\text{C}$ or higher for three to five days; symptoms return after partial recovery
6	Qiu et al. (16)	China	2020	Children	Fever (body temperature $> 37^{\circ}\text{C}$ ) in 36%; dry cough in 19%; headache in 8%; vomiting or diarrhea in 6%; sore throat in 6%; dyspnea or tachypnea in 3%; pharyngeal congestion in 3%; no symptoms in 28%; pneumonia in 53%.
7	Jiehao et al. (17)	China	2020	Children	Cough in 60%; sneezing in 20%; stuffy nose in 30%; rhinorrhea in 20%; sore throat in 40%.
8	Zimmermann and Curtis (18)	Australia	2020	Children	Fever (44% - 50%); cough (38%); poor feeding; diarrhea; headache; fatigue; dyspnea; rhinitis; cyanosis

**Table 2.** Diagnosis in Infants and Children with Coronavirus Who Entered the Systematic Review

	Author's Name	Country	Year	Target Group	Protocol
1	Wang et al. (12)	China	2020	Infants	Diagnostic tests should include CBC, CRP, and RT-PCR to find COVID-19; complete blood cell count (CBC): in the early stages, it may be normal, or the number of lymphocytes and leukocytes decreases; other possible findings: mild thrombocytopenia, elevated alkaline phosphatase, creatinine kinase, lactate dehydrogenase, and alanine aminotransferase; the COVID-19 virus may be found in the upper and lower respiratory systems, blood, and stool; chest X-ray or sonography: pneumonia symptoms may be present; abdominal radiography: the radiographic characteristics of the intestinal ileus may be demonstrated.
2	Chen et al. (13)	China	2020	Children	Blood test: WBC counts are usually normal or decreased. In severe cases, progressive lymphocytopenia occurs; procalcitonin: it is normal in most cases; CRP: normal or reduced; in severe cases, increased hepatic and muscle enzymes and myoglobin, and increased D-dimer are seen; chest X-ray shows interstitial changes in the margins of the lungs and numerous small patchy shadows; the CT scans show the pulmonary lesions more clearly. Multiple lobar lesions may occur in both lungs in severe infections; severe cases may include infiltrating shadows, bilateral multiple ground-glass opacities, unrequented pleural effusion, and pulmonary consolidation.
3	Lu and Shi (6)	China	2020	Infants	CRP is normal or temporary upregulated, ALT and myocardial enzymes are without abnormal changes, and chest X-ray images of asymptomatic pediatric patients are normal ;virus's gene or nucleic acid testing in nasopharynx sample, sputum sample, secretions of the lower respiratory tract, blood sample, and stool sample; the most common test is the nasopharyngeal sample test, but repeat sampling is necessary because the nasopharyngeal test detection positive rate is less than 50%; bronchoalveolar lavage fluid positive rate is high but not suitable for many patients because of the increased risk of cross-infection.
4	Shen et al. (14)	China	2020	Children	In the early phase, the number of WBC is normal or decreases along with a decrease in the number of lymphocytes. Myoglobin levels and hepatic and muscle enzymes are elevated in some patients; many patients show increased levels of CRP and ESR. Prolactin levels are normal; severe cases of the disease show an increase in D-dimer levels and a sharp decrease in the number of lymphocytes; pharynx swabs, lower respiratory tract secretions, sputum, blood, and feces contain the nucleic acid of the COVID-19 virus; suspected or infected people should have a chest X-ray taken as soon as possible. In the early phases of the disease, the CX-ray shows interstitial changes and numerous small plaques seen on the margins of the lungs. In further destruction, one can see infiltrating shadows and bilateral multiple ground-glass opacities; In severe cases, pulmonary consolidation may occur; pleural effusion is rarely seen.
5	Karimi et al. (15)	Iran	2020	Children	Chest X-ray sensitivity is low. In the early phase of the disease, it may be normal and does not show ground-glass lesions. In the severe stages of the disease, multiple bilateral consolidations even advanced to the white lung can be observed; - CT scan to detect multiple unilateral or bilateral ground-glass opacity and environmental consolidation of the lungs; complete blood cell count: lymphocytopenia or leukopenia less than normal depending on the patient's age; CRP-LDH; upper respiratory system sampling; PCR test
6	Qiu et al. (16)	China	2020	Children	-Leucopenia in 19%; lymphopenia in 31%; elevated myocardial enzymes in 31%; elevated liver enzymes in 6%; elevated C-reactive protein in 3%
7	Jiehao et al. (17)	China	2020	Children	Chest X-ray: normal in 60%; opacities in the right lung in 30%; retrocardiac opacity on the left in 10%; white blood cell count: increased in 30%; decreased in 10%; hemoglobin: Normal in 100%; neutrophil count: decreased in 30%; increased in 10%; lymphocyte count: increased in 10%; platelet count: increased in 20%; C-reactive protein: increased in 30%; creatine kinase-MB: increased in 50%; alanine aminotransferase: Increased in 10%; aspartate aminotransferase: Increased in 20%; urea: decreased in 30%; creatinine: decreased in 20%; Lactate dehydrogenase: increased in 30%; D-dimer: increased in 20%; detection of 2019-nCoV RNA; nasopharyngeal/throat swabs: positive in 100%; stool: positive in 50%
8	Zimmermann and Curtis (18)	Australia	2020	Children	WBC: normal or decreased; neutrophil count: decreased; lymphocyte count: decreased; CRP and PCT levels: usually normal; liver function tests: abnormal; lactate dehydrogenase: increased; D-dimers in severe cases: increased

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**Table 3.** Treatments for Infants and Children with Coronavirus Entering the Systematic Review

	Author's Name	Country	Year	Target Group	Protocol
1	Wang et al. (12)	China	2020	Infants	Remedial measures in infected and suspected infants: admission to the Quarantine Section; third-level prevention; accurate and continuous monitoring of vital signs, oxygen saturation, glycemia, and gastrointestinal symptoms; supportive care; breastfeeding depends on the mother if she is infected or not. The baby should not be breastfed by the suspected or infected mother. The baby can be breastfed only if the tests of the infected or suspected mother and her milk test are negative for coronavirus; remedial measures for symptomatic suspected infants: admission to the Quarantine Section; third-level prevention; breastfeeding depends on the mother if she is infected or not; - If the patient's coronavirus test is negative, treatment should be based on the etiology of the infection; Remedial measures for symptomatic infected infants: admission to the Quarantine Section; third-level prevention; treatment is based on the treatment of complications and supportive care; for infants with severe ARDS, inhaled nitric acid, high-dose surfactant, and high-frequency oscillatory ventilation (HFOV) may be effective; in critically ill patients, extracorporeal membrane lung treatment and continuous renal replacement therapy (CRRT) may be required; multidisciplinary team therapy for infants with coronavirus is recommended; there are currently no effective anti-coronavirus drugs, and the inappropriate use of broad-spectrum antibiotics should be avoided; there is no supporting evidence for the effectiveness of interferon, hormone therapy, and gamma globulin.
2	Chen et al. (13)	China	2020	Children	Admit suspected cases to a separate room; continuously monitor the vital signs and oxygen saturation; complete bed rest (CBR); supportive treatment; get enough calories and fluids; balance fluids and electrolytes and maintain homeostasis; psychotherapy if needed; there are currently no effective antiviral drugs for children; interferon- $\alpha$ 2b nebulization can be used; lopinavir/litonavir (200 mg/50 mg) according to weight may also be used., although the efficacy, course of treatment, and safety of these drugs are unclear; avoid unreasonable prescribing antibiotics. Appropriate antibiotics should be used if there is evidence of secondary infection; avoid prescribing corticosteroids in common infections; in severe cases, intravenous immunoglobulin can be used, but its efficacy needs to be further evaluated; bronchoalveolar lavage is not suitable for most patients because it increases the risk of other infections. This procedure can be used in the following patients: clear symptoms of airway obstruction, extensive atelectasis, a significant increase in peak pressure during mechanical ventilation, reduction in vital volume, and poor oxygenation; supportive cardiovascular and cerebral therapies; respiratory support; blood purification: It should be considered in multiple organ failure; extracorporeal membrane oxygenation (ECMO): In cases where blood purification, mechanical ventilation, and other procedures are ineffective and respiratory failure occurs, this treatment should be considered.
3	Lu and Shi (6)	China	2020	Infants	Rapid diagnosis and isolation; babies with COVID19+ must be kept in a room with negative pressure or in a room where the air is purified by high impact filters; prohibit infected infants visits; due to the low number of infant infections, treatment is usually based on adult treatment experiences; there are currently no specific drugs for the treatment of coronavirus symptoms, and supportive treatment, oxygen delivery, fluid, and electrolyte balance, and acid-base balance are the basis of the treatment in infants; in infants with severe ARDS, inhaled nitric oxide, high-frequency pulmonary surfactants, extracorporeal membrane lung, and high-frequency oscillatory ventilation may be effective; Interferon- $\alpha$ 2b nebulization used in SARS-CoV and MERS-CoV may be of interest in the treatment of SARS-CoV-2; possible drug combination (mercaptapurine plus melatonin, sirolimus plus dactinomycin, and toremifene plus emodin are the recommended drugs).

4	Shen et al. (14)	China	2020	Children	Depending on the clinical situation, suspected patients may be admitted to an isolated room or isolated at home under medical care; affected patients can be admitted to the same ward; As soon as possible, critical patients should be admitted to the ICU; general treatment includes CBR, supportive treatment, ensuring adequate calorie and fluid intake, maintaining homeostasis, continuous monitoring of oxygen saturation and vital signs, keeping the airway open, and delivering oxygen as needed; High fever in patients should be controlled. If the patient's temperature is above 38.5 °C, non-pharmacological or medicines such as ibuprofen and acetaminophen should be used; keep the baby calm and take sedative medications if seizures occur; get started quickly oxygen therapy if hypoxia occurs; mechanical ventilation if needed; interferon $\alpha$ : It can decrease the viral load in the early stages, reduce symptoms, and decrease the duration of treatment; lopinavir/litonavir: It has been attempted to treat infection in adults, but its efficacy and safety are still unclear; Avoid unreasonable prescription of broad-spectrum antibiotics; arbidol: It is prescribed for adults, but its safety and efficacy are unclear; oseltamivir: It can be used for patients who have been infected with other influenza infections; glucocorticoids: the order of these drugs must be based on the severity of the systemic inflammatory response; Immunoglobulin: ordered in severe cases (its effect needs further assessment); in acute and severe cases, the need for respiratory and cardiovascular supportive treatment should be checked regularly.
5	Karimi et al. (15)	Iran	2020	Children	Patients hospitalized in a negative pressure isolation room (at least 6 to 12 times of air exchange/hour); Supportive therapies, fluid and electrolyte replacement, pyretic, analgesic medicines, oxygen delivery, and respiratory support are required; the following combination therapy is used for patients admitted to intensive care: hydroxychloroquine + oseltamivir + Kaletra (lopinavir + ritonavir) $\pm$ ribavirin and antibiotics if needed depending on the patient's condition; the following combination therapy is used for patients with moderate to severe pneumonia: hydroxychloroquine + oseltamivir + Kaletra (lopinavir + ritonavir) and, if necessary, antibiotics based on patient status; For patients with mild pneumonia with a risk factor, the following combination therapy is used: hydroxychloroquine + oseltamivir and, if needed, antibiotics based on patient status; patients with mild pneumonia without a risk factor: These cases should be monitored and treated as per the patient's condition and physician's decision, which may include oseltamivir $\pm$ hydroxychloroquine; It is noteworthy that because of insufficient evidence on the treatment of children with COVID-19, the treatments suggested are not based on strong clinical evidence, and they may change in subsequent studies.
6	Qiu et al. (16)	China	2020	Children	Interferon alfa in 100%; oxygen inhalation in 17%; lopinavir-ritonavir in 39%
7	Jiehao et al. (17)	China	2020	Children	Symptomatic treatment in 100% of patients; antibiotic therapy in 50% of patients
8	Zimmermann and Curtis (18)	Australia	2020	Children	Lopinavir/ritonavir (oral) and nebulized interferon alpha-2b together with corticosteroids; monoclonal antibodies; protease inhibitors; chloroquine; RNA synthesis inhibitors (however, none of these treatments have shown clear effectiveness)