





Coronavirus Disease 2019 (COVID-19) Outbreak in Pediatrics and the Role of Pediatricians: A Systematic Review

Seyed Javad Seyedi¹, Reza Shojaeian ^{1,*}, Mehran Hiradfar¹, Ahmad Mohammadipour² and Seyed Ali Alamdaran ¹

¹Mashhad University of Medical Sciences, Mashhad, Iran

²Golestan University of Medical Sciences, Gorgan, Iran

*Corresponding author: Mashhad University of Medical Sciences, Mashhad, Iran. Email: drshojaeian@gmail.com

Received 2020 March 16; Revised 2020 March 26; Accepted 2020 March 29.

Abstract

The coronavirus disease 2019 (COVID-19) outbreak initiated in Wuhan, China and has spread rapidly all around the world and labeled as a pandemic with almost 168,000 infected cases and 6,500 deaths globally up to March 16, 2020. It is believed that children are less likely than adults to be infected with COVID-19. In this review, we discuss different aspects of COVID-19 infection in pediatrics. COVID-19 in pediatrics occurs in the early stages of its outbreak at a high rate with a family cluster pattern mainly. Children infected with COVID-19 are mostly asymptomatic carriers and the main potential causes of the spread and transmission of the disease in communities. Asymptomatic children with no underlying disease or red flags should follow home isolation protocols. Children with red flags, comorbidities and risk factors or those with severe pneumonia must be admitted to the hospitals. Children's hospitals should be equipped with the acute respiratory diseases ward, quarantine rooms, and intensive care unit to protect other patients and health care staff during the COVID-19 outbreak.

Keywords: Pediatrics, Neonates, COVID-19, Coronavirus

1. Context

The novel coronavirus (SARS-CoV-2 [2019-nCoV]) belongs to the broad family of viruses known as coronaviruses, which is a positive-sense single-stranded RNA (+ssRNA) virus causing coronavirus disease 2019 (COVID-19). It is a highly contagious pathogen with an incubation period of 5.2 - 8 days (range, 1 - 14 days) (1, 2). The person-to-person transmission rate of SARS-CoV-2 has estimated to be 1.2% - 2.2% (2, 3). The 2019-nCoV outbreak initiated in Wuhan, China in late November 2019 and has spread rapidly all around the world and was labeled as a pandemic with almost 168,000 infected cases and 6,500 deaths globally up to March 16, 2020.

Although coronavirus disease 2019 (COVID-19) has less commonly reported in children. However, doubt has been cast on this concept based on the recent improvements and availability of screening methods. This study was a comprehensive review of literature considering different aspects of COVID-19 in pediatrics.

2. Evidence Acquisition

We conducted a comprehensive search for published or unpublished (pre-print or even pre-proof accepted)

studies in PubMed Central, Medline, Scopus, EMBASE, Scielo, Google Scholar, and Cochrane Databases from 2019 up to March 16, 2020. Four combinations of MeSH words were used including 'COVID-19' or 'Coronavirus' in combination with 'Pediatrics' or 'Neonates'. A total of 168 articles were primarily retrieved.

The inclusion criteria included acceptance for being published in an indexed journal, English-language studies, and studying on 2019-nCoV. Duplicate articles, non-English studies, and letters to editor with no references were excluded. Finally, 34 studies met the inclusion criteria and their data regarding the necessary information needed for pediatricians, pediatric surgeons, and pediatric caregivers about COVID-19 in children were extracted from these articles.

3. Results

3.1. COVID-19 in Pediatrics and Neonates

It is believed that children are less likely than adults to be infected with COVID-19. It is estimated that less than 1% of pediatric younger than 10 years old are infected by COVID-19 outbreak (1), which is almost 2.4% for those less than 18 years old (4). The mortality rate of COVID-19 among

children under 10 years old is almost zero (2). Primary reports about COVID-19 outbreak in children were misleading as most infected children were asymptomatic and remained unidentified. It has reported that after widespread screenings children can be easily and highly infected in a family cluster pattern (4).

COVID-19 is mainly transmitted by human-to-human transmission through respiratory droplets, close contact, aerosols, and possibly the fecal-oral route (4). Vertical transmission of COVID-19 has not approved yet (5), however, its possibility has highly considered recently after reporting infected neonates born to mothers with COVID-19 in the UK and Iran. Some other previous reports also have presented infected neonates in the first few hours after birth (2, 6, 7).

Clinical manifestations of COVID-19 in pediatrics are mild and non-specific. Most of the identified cases have confirmed by screening tests among affected families. This may explain the lower reported rate of COVID-19 among children (8).

3.2. Importance of COVID-19 in Pediatrics

Symptomatic infection with COVID-19 is not common in children, which may be due to higher respiratory reserve, fewer underlying diseases, and more effective innate immune response in this group (1). The general prognosis may result in favorable outcomes in pediatrics.

2019-nCoV like other coronaviruses (CoVs) uses angiotensin-converting enzyme 2 (ACE2) as a cell receptor. ACE2 has a protective role against severe inflammatory lung injuries (1) and there is a negative relation between tissue ACE2 expression and severity of pneumonia and susceptibility to COVID-19 (9, 10). Animal studies and human evidence have shown downregulation of ACE2 expression by aging and also ethnicity (1, 9).

Regarding these age-related differences, other reports, and clinical experiences, most of the children infected with COVID-19 will be asymptomatic carriers and the main potential causes of disease transmission, especially in early stages of COVID-19 outbreak (11, 12). All these special considerations in pediatrics infected by COVID-19 suggest children as one of the main potential causes for spread and transmission of COVID-19 in communities affected by COVID-19 outbreak (8).

Besides, pediatrics have shown suboptimal protection against COVID-19 as they do not cover their coughs or sneezes, do not wear a face mask, touch their faces frequently, and put other objects into their mouths with ineffective hand hygiene. Also, children have a closer contact with family members and their urinary and fecal material is discarded with delay and with a higher probability of contamination (4, 13).

We should screen and identify children positive for COVID-19, especially in a family cluster pattern and con-

sider this group for early isolation to control the diseases outbreak efficiently (4).

Kindergartens and children's hospitals must be supervised closely to stop the spread of the virus and protect the caregivers.

3.3. Clinical Manifestations of COVID-19 in Pediatrics

Neonates born to mothers with COVID-19 may have problems, such as respiratory distress, abnormal liver function, thrombocytopenia, and thermal instability (7).

It has believed that COVID-19 is an asymptomatic infection or with mild and nonspecific symptoms among infants and children (8). The infected neonates and infants may present with fever, mild respiratory symptoms, like dry cough, distress, nasal discharge, sore throat, and fatigue (14).

The gastrointestinal tract may also be affected resulting in abdominal discomfort, diarrhea, vomiting, and feeding intolerance (2, 3).

Children with underlying diseases, such as malignancies, cirrhosis, chronic kidney disease, cardiovascular or pulmonary diseases or immunosuppression may experience more severe symptoms, like respiratory distress syndrome, septic shock, deep acidosis, and respiratory or even cardiovascular collapse (3, 15).

3.4. Diagnosis of COVID-19 Infection in Pediatrics

Most of the confirmed children with COVID-19 have diagnosed by family clusters (8). All neonates born to mothers with COVID-19 should be isolated and screened (2, 16). It is suggested to stop breastfeeding in mothers with confirmed COVID-19 (17).

Nucleic Acid test (NAT) or real-time polymerase chain reaction (PCR) combined with new fluorescent techniques are suggested as the gold standard diagnostic methods for all patients suspected to COVID-19 (2, 17, 18). Although these tests are considered as gold standard tools for COVID-19 diagnosis, they are time-consuming, may not be accessible widely, with highly probable false-negative results, which can be improved by repeated sampling (8).

It is suggested to combine all findings obtained from a history of contact, clinical characteristics, blood cell count, and chest CT scan with NAT/PCR test as the standard diagnostic protocol in vulnerable children (5, 19).

Sampling can be done by nasopharyngeal swab (Dacron or rayon sterile swab is preferred) (3, 17, 19). Detection rate for bronchoalveolar lavage specimen is supposed to be higher, however, the procedure will increase the cross-contamination and cross-infection risk (2). The blood sample or fecal specimens have shown positive for COVID-19 in PCR test among some cases (17).

3.5. Laboratory Tests in Pediatrics with COVID-19

White blood cell count may be normal in most affected children (almost 76%). Leukopenia and lymphopenia (< 3000 in infants, < 2000 in 1 - 5 years old cases and < 1100 in cases over 5 years) and increased C-reactive protein (CRP > 3) are expected, but they are not as common as in adults. (almost 35%) (14, 19).

Leukopenia and lymphopenia have reported just in 30% of pediatrics with COVID-19 in Iran, whereas all cases had elevated CRP (20).

Increased procalcitonin (PCT), creatine kinase-MB, alanine aminotransferase (ALT), aspartate aminotransferase, and lactate dehydrogenase (LDH) have also reported with different ratios, but without significant diagnostic value (14, 17, 19).

Increased direct bilirubin (> 6.1) and ALT (> 24.5) have reported as biomarkers to predict the severity of COVID-19 among children (21).

3.6. Imaging in Pediatrics with COVID-19

A plain chest x-ray will be normal in most cases in the early phase of COVID-19 infection, especially among asymptomatic children (14). A chest CT scan without contrast is suggested as a valuable diagnostic and prognostic tool in COVID-19 (14, 22).

Chest CT scan findings include unilateral or bilateral peripheral ground-glass opacities that gradually spread in a patchy pattern and may be accompanied by interlobular septal thickening and sub-pleural lesions (5, 14, 22).

Consolidation, fibrosis and air bronchogram will appear later and may progress to white lung appearance in the critical stage (22).

Lung opacities in COVID-19 are mostly patchy, with less density compared with other types of pneumonia (14). Although chest CT scan is suggested as one of the best timely diagnostic tools in COVID-19 infection, the results can be normal or with minimal changes among infants with asymptomatic infection with COVID-19 (22).

3.7. Treatment of Pediatrics with COVID-19

Children with asymptomatic infection with COVID-19 should follow a home isolation protocol for two weeks to ensure the termination of virus shedding (19).

Symptomatic children should be investigated for red flags consisting of serious hypoxemia (O_2 saturation < 90% in normal room condition), respiratory fatigue and hypercapnia, decreased level of consciousness, or hemodynamic instability (19).

Patients with mild symptoms in the absence of red flags must be isolated at home after consulting with parents about the importance of protections and signs of deterioration in health condition (warnings and education) (19).

Supportive home care must be provided, such as prescribing antipyretics (acetaminophen), antiemetic agents or other symptom-relieving agents and medications. Antibiotics or antiviral drugs are not recommended for this group of children with no underlying disease, however, the efficacy of antiviral agents in pediatrics has not yet clearly proven (3, 19).

Children with red flags, comorbidities and risk factors or those with severe pneumonia must be admitted to specially designed COVID 19 Ward or Intensive Care Unit (ICU), if needed (19).

Respiratory support also can be considered, including oxygen supplementation, intubation and ventilation support. High-frequency oscillatory ventilation is the preferred mode of ventilation (6).

High-dose surfactant, nitric oxide, corticosteroids, and interferon- α 2b nebulization should be regarded in critically ill children and infants (2, 6). Intravenous immunoglobulin and steroids are also suggested (5).

Children with severe 2019-nCoV pneumonia or those with underlying diseases are suggested to be managed with hydroxychloroquine (3 - 5 mg/kg/day twice daily) in combination with oseltamivir (3 mg/kg/dose, twice daily) for a five-day course (19).

Cardiac monitoring for long QT syndrome is recommended before and during treatment. Kaletra (16 mg/kg/dose twice daily) is added for critically ill patients (19) and these cases may rarely need extracorporeal membrane oxygenation (ECMO) (2).

Antibiotics are suggested just for cases with clinical or paraclinical signs of bacterial superinfection (3, 19).

Upon the resolution of respiratory symptoms and imaging abnormalities, two negative consecutive tests for COVID-19 (2 days apart), and the absence of fever for 3 days, the cases can be discharged from the hospital (16, 17).

The length of hospital stay for children with COVID-19 has estimated about 12 - 13 days (20).

Protective considerations and ward designation for pediatrics with COVID-19.

Children with a positive family history or at a higher risk of contact with infected cases, and those highly vulnerable to be infected with COVID-19 clinically or radiologically should be identified in triage units of the children's hospitals and transferred to the 'acute respiratory diseases ward (ARDW)'.

All involved caregivers must be protected by latex gloves, surgical masks, long sleeve suits, face shield and surgical caps (16). Strict hand hygiene policies should be applied, as well.

It is recommended to designate separate working and resting areas for caregivers, ARDW (transit), quarantine rooms, and ICU (17).

No visitor is allowed to enter ARDW and related divisions and there should not be a playing room in this ward.

All patients' belongings and toys should be sterilized regularly everyday (2).

Quarantine or private rooms should be equipped with negative-pressure ventilation (minimum of 10 air changes per hour) and HEPA filters (19). Transit ward beds should be at least one meter away from each other (19).

Parents should be provided with protective equipment and must be supported psychologically (16).

4. Conclusions

COVID-19 in pediatrics occurs in the early stages of its outbreak at a high rate and in a family cluster pattern.

Children infected with COVID-19 are mostly asymptomatic carriers and the main potential causes of the spread and transmission of the disease in communities.

Children with asymptomatic infection with COVID-19 with no underlying disease or red flag symptoms are recommended for home isolation and palliative care.

Children's hospitals should be equipped with the ARDW, quarantine rooms and ICU to protect other patients and health care staff during the COVID-19 outbreak.

Acknowledgments

Thanks to clinical research development unit of Akbar hospital for helps and supports and Mrs Touka Banaee for English editing.

Footnotes

Authors' Contribution: Reza Shojaeian designed the research and wrote the document. Ahmad Mohammadipour and Mehran Hiraifar reviewed the articles. Seyed Javad Seyedi and Seyed Ali Alamdaran revised the article.

Conflict of Interests: There is no conflict of interest.

Funding/Support: No funding was needed for this study; however, it was supported by the Clinical Research Development Unit of Akbar Hospital.

References

- Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19? *J Microbiol Immunol Infect*. 2020. doi: [10.1016/j.jmii.2020.02.011](#). [PubMed: [32147409](#)].
- Lu Q, Shi Y. Coronavirus disease (COVID-19) and neonate: What neonatologist need to know. *J Med Virol*. 2020. doi: [10.1002/jmv.25740](#). [PubMed: [32115733](#)].
- Cai J, Xu J, Lin D, Yang Z, Xu L, Qu Z, et al. A Case Series of children with 2019 novel coronavirus infection: Clinical and epidemiological features. *Clin Infect Dis*. 2020. doi: [10.1093/cid/ciaa198](#). [PubMed: [32112072](#)].
- Mission W. *Report of the who-china joint mission on coronavirus disease 2019 (covid-19)*. Geneva: WHO; 2020.
- Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: A retrospective review of medical records. *Lancet*. 2020;**395**(10226):809-15. doi: [10.1016/s0140-6736\(20\)30360-3](#).
- Hong H, Wang Y, Chung HT, Chen CJ. Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children. *Pediatr Neonatol*. 2020. doi: [10.1016/j.pedneo.2020.03.001](#). [PubMed: [32199864](#)].
- Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr*. 2020;**9**(1):51-60. doi: [10.21037/tp.2020.02.06](#). [PubMed: [32154135](#)]. [PubMed Central: [PMC7036645](#)].
- Yang P, Liu P, Li D, Zhao D. Corona virus disease 2019, a growing threat to children? *J Infect*. 2020. doi: [10.1016/j.jinf.2020.02.024](#). [PubMed: [32142929](#)].
- Chen J, Jiang Q, Xia X, Liu K, Yu Z, Tao W, et al. Individual variation of the SARS-CoV2 Receptor ACE2 gene expression and regulation. *Preprints*. 2020.
- Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet*. 2020;**395**(10224):565-74. doi: [10.1016/S0140-6736\(20\)30251-8](#). [PubMed: [32007145](#)].
- Liu W, Zhang Q, Chen J, Xiang R, Song H, Shu S, et al. Detection of Covid-19 in children in early January 2020 in Wuhan, China. *N Engl J Med*. 2020. doi: [10.1056/NEJMc2003717](#). [PubMed: [32163697](#)].
- Kam KQ, Yung CF, Cui L, Lin Tzer Pin R, Mak TM, Maiwald M, et al. A well infant with coronavirus disease 2019 (COVID-19) with high viral load. *Clin Infect Dis*. 2020. doi: [10.1093/cid/ciaa201](#). [PubMed: [32112082](#)].
- Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel coronavirus infection in hospitalized infants under 1 year of age in China. *JAMA*. 2020. doi: [10.1001/jama.2020.2131](#). [PubMed: [32058570](#)]. [PubMed Central: [PMC7042807](#)].
- 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. doi: [10.1002/ppul.24718](#). [PubMed: [32134205](#)].
- Zhang G, Yang H, Zhang A, Shen Q, Wang L, Li Z, et al. The impact of the COVID-19 outbreak on the medical treatment of Chinese children with chronic kidney disease (CKD): A multicenter cross-section study in the context of a public health emergency of international concern. *MedRxiv*. 2020. doi: [10.1101/2020.02.28.20029199](#).
- Li F, Feng ZC, Shi Y. Proposal for prevention and control of the 2019 novel coronavirus disease in newborn infants. *Arch Dis Child Fetal Neonatal Ed*. 2020. doi: [10.1136/archdischild-2020-318996](#). [PubMed: [32132140](#)].
- Wang L, Shi Y, Xiao T, Fu J, Feng X, Mu D, et al. Chinese expert consensus on the perinatal and neonatal management for the prevention and control of the 2019 novel coronavirus infection (first edition). *Ann Transl Med*. 2020;**8**(3):47. doi: [10.21037/atm.2020.02.20](#). [PubMed: [32154287](#)]. [PubMed Central: [PMC7036629](#)].
- Ping K. Epidemiologic characteristics of COVID-19 in Guizhou, China. *MedRxiv*. 2020. doi: [10.1101/2020.03.01.20028944](#).
- Karimi A, Rafiei Tabatabaei S, Rajabnejad M, Pourmoghaddas Z, Rahimi H, Armin S, et al. An algorithmic approach to diagnosis and treatment of coronavirus disease 2019 (COVID-19) in Children: Iranian expert's consensus statement. *Arch Pediatr Infect Dis*. 2020;**8**(2). e102400. doi: [10.5812/pedinfect.102400](#).
- Rahimzadeh G, Ekrami Noghabi M, Kadkhodaei Elyaderani F, Navaeifar MR, Enayati AA, Manafi Anari A, et al. COVID-19 infection in Iranian children: A case series of 9 patients. *J Pediatr Rev*. 2020;**8**(2):139-44. doi: [10.32598/jpr.8.2.139](#).
- Yu H, Shao J, Guo Y, Xiang Y, Sun C, Yuan Y. Data-driven discovery of clinical routes for severity detection in COVID-19 pediatric cases. *MedRxiv*. 2020. doi: [10.1101/2020.03.09.20032219](#).
- Li W, Cui H, Li K, Fang Y, Li S. Chest computed tomography in children with COVID-19 respiratory infection. *Pediatr Radiol*. 2020. doi: [10.1007/s00247-020-04656-7](#). [PubMed: [32162081](#)].