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REVIEW ARTICLE

Narrative literature review on COVID-19 in Pediatrics: factors of poor prognosis

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Abstract

Objectives: The objective of this narrative review is to synthesize the main knowledge regarding the clinical characteristics and the poor prognostic factors related to COVID-19 infection in children, given the importance of these data for better case management. Therefore, it is intended to give visibility to the gaps that require clarification. **Methods:** A bibliographic search was made for materials available in electronic media from several renowned databases, such as The New England Journal of Medicine, Brazilian Society of Pediatrics, PubMed, among others. **Results:** 34 articles were selected, all of them with publications dated in 2020, from reliable and high impact sources. Most of the selected studies showed pediatric patients who developed a milder form of COVID-19, especially due to differences involved in the virus receptor in the children's body and the development of their immunity. Despite this, it was possible to verify, with this narrative review, that, when associated with other comorbidities such as heart disease, diabetes, obesity, liver disease and others, COVID-19 has different outcomes, being, in most cases, more aggressive and with a worse prognosis. **Conclusion:** Although it is milder or asymptomatic in pediatric patients, it is mandatory to know the factors of poor prognosis for COVID-19 in this group. This article reveals the need for new studies and reports capable of fully and consistently elucidating the course of this pathology in children.

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INTRODUCTION

In December 2019, in the Wuhan province, China reported patients who had developed a type of pneumonia of unknown origin. After some tests, they concluded that the pneumonia was caused by a new virus of the Coronaviridae family, called SARS-CoV-2, which originates a disease, later called by the World Health Organization (WHO), COVID-19[1]. On March 11, 2020, after reaching a global scale, the WHO declared that SARS-CoV-2 contamination had become a pandemic.

The average age of affected patients varies between 49 and 56 years. Elderly patients, who have comorbidities (diabetes, chronic lung diseases, cardiovascular diseases, cancer) and immunocompromised patients, were especially prone to more severe conditions and admission to intensive care units (ICU). Pediatric patients, in turn, represented a small portion in relation to these groups[2].

This happens because, in children, unlike adult patients, cellular and humoral immunities are less developed and do not have an exacerbated inflammatory response capacity. For this reason, as the appearance of inflammatory cytokines contributes incisively to viral sepsis with shock and multiple organ failure, pediatric conditions are milder[3].

Thus, given this condition of lower prevalence and severity when compared to the general population, few studies focused on detailing the pediatric signs and symptoms of COVID-19. Given the importance of consistent information for better case management, the main objective of the present study is to summarize and discuss the main knowledge and gaps regarding the clinical characteristics and poor prognostic factors related to COVID-19 infection in children.

METHODS

The present study is a narrative literature review. In order to carry out this study, we ran a manual search in journals and publications of high-impact international and national bodies, among which the following stood out: New England Journal of Medicine, The Lancet, Pediatrics, World Health Organization, Brazilian Society of Pediatrics, and automatic search in international databases such as PubMed, Cochrane, Scielo and Google Scholar. The keywords used for the searches were “coronavirus”, “COVID-19”, “pediatric patients”, “children”, “clinical characteristics”, “prognosis” and “risk factors”.[34] publications were selected, among them randomized studies, systematic reviews, prospective studies and other publications from aforementioned agencies.

The inclusion criteria used as a basis were studies in English, Portuguese or Italian, that were relevant in this field. The exclusion criteria were papers in languages other than those mentioned or with biases that compromised the results.

RESULTS AND DISCUSSION

In pediatric patients, Sars-CoV-2 infection has been shown to be relatively rare and mild, with approximately 2.4% of the total cases reported among individuals under 19 years of age. A very small number of children under 19 years of age develop severe (2.5%) or critical illness (0.2%)[4] associated with Covid-19. To illustrate this, in a study carried out in China with 44,672 patients with a confirmed diagnosis of COVID-19, children from 0 to 9 years old represented only 0.9% of the cases (416 patients) and there was no death in this group. Patients between 10 and 19 years of age accounted for 1.2% of the total (549 cases), with only 1 death of a 13-year-old teenager. Notoriously, initial case descriptions reveal a tendency in infants, children and adolescents to present asymptomatic cases: in a series of 731 pediatric patients with laboratory confirmation of COVID-19 infection in China, 97% were asymptomatic, had mild or moderate symptoms[5].

The SARS-CoV-2 virus uses the cell’s angiotensin-2-converting enzyme (ECA2) receptor to penetrate the human body. Differences in the distribution, maturation and functioning of these viral receptors are often mentioned as possible reasons for the divergence between the incidence of the virus in different age groups. Although some studies show that the amount of ACE2 decreases progressively with age, it is believed that in children the maturity and function, such as the binding capacity of this enzyme, especially in type I and II alveolar epithelial cells, is lower than in adults[6,7,8,9]. Other studies also point out that this receptor is involved in lung protection mechanisms, for example, against severe lung injuries induced by infection caused by the respiratory virus, in addition to protecting against severe acute lung injuries that can be triggered by sepsis, acid aspiration, SARS and lethal virus from H5N1 avian influenza infection[7].

The entry of the virus by the ACE2 receptor into the human body generates systemic complications involving several organs such as heart, liver, pancreas and kidneys, in addition to lymphocyte and immune system changes[9,10].

In addition, children often have respiratory infections, for example, from respiratory syncytial virus (RSV) in winter and can produce higher levels of antibodies to viruses than adults[6]. It is worth remembering that the flu can cause more ARDS in adults and much less in children[11].

In addition, there may be a relationship between exposure factors and the host. Children were generally well cared for at home and may have had less exposure to the pathogen[6].

The clinical picture of this group of patients, when symptomatic, is commonly characterized by fever, dry cough and fatigue; some have gastrointestinal symptoms, including abdominal discomfort, nausea, vomiting, abdominal pain and diarrhea. Recovery usually takes 1-2 weeks after disease onset[11].

According to the Ministry of Health, they should be stratified as severe cases of Flu Syndrome with dyspnea or signs and symptoms of severity or comorbidities that contraindicate home isolation. In children, the signs and symptoms of severity include those that represent a deficit in the respiratory system (shortness of breath or difficulty in breathing; snoring, severe sub/intercostal retraction; central cyanosis; nose alae flapping; paradoxical movement of the abdomen; bradypsy and irregular breathing rhythm; pulse oximetry saturation <95% in room air; tachypnea; cardiovascular system deficit; signs and symptoms of hypotension; decrease in peripheral pulse, and those considered to be of additional alert (lack of appetite for breastfeeding or fluid intake; worsening in the clinical conditions of underlying diseases; altered mental status; confusion and lethargy; seizures)[12].

Regarding comorbidities that contraindicate outpatient follow-up, we found the following in this review:

HEART DISEASES

To date, there is no data regarding the incidence of COVID-19 specifically in children with congenital heart disease; however, a document published by the Brazilian Societies of Pediatrics, Cardiology and Cardiovascular Surgery gives us a joint official statement in relation to heart diseases. According to them, one must remember that there are two quite distinct groups in relation to behavior in face of COVID-19, which are the following: (a) Congenital or acquired heart diseases without hemodynamic repercussions, and heart diseases that have been corrected by surgery or catheterization, and that are clinically well and with no signs of heart failure: in this group, the risk is similar to that of the general pediatric population and the evolution of the disease is likely to be benign in most cases; (b) Congenital or acquired heart diseases that have significant hemodynamic repercussions (heart failure, pulmonary hypertension or hypoxemia) and heart diseases that have already undergone surgical correction, but maintain the signs of repercussion: this is a risk group for COVID-19, as it may present worsening of ventilatory conditions earlier and more intensely in the face of this infection[13].

In this group of patients, some precautions should be emphasized, such as the use of Ibuprofen and corticosteroids with caution (other medications such as diuretics, beta-blockers, anticoagulants and ACE and BRA inhibitors, there is no evidence for suspension) and updating the vaccination card of children and adults with heart disease - especially against influenza, respiratory syncytial virus and pneumococcus[13].

The document also mentions that although there is no specific data referring to COVID-19 in transplanted children, these is a group at high risk for viral infections due to the state of immunosuppression to which they are subjected, and may have a very rapid evolution and very high severity[13].

DIABETES AND OBESITY

There is no evidence that children with well-managed endocrine conditions (including Type 1 Diabetes mellitus) are at increased risk of becoming infected or of developing severe conditions[14]. However, in cases of poorly controlled Diabetes mellitus, chronic hyperglycemia negatively affects the immune function and increases the risk of morbidity and mortality, being associated with organic complications[15]. There are some indications that healthy but severely obese children are at a higher risk for complicated pulmonary infection[14].

In a study carried out in Geneva, Switzerland, 1,199 PCR tests for coronavirus (SARS-CoV-2) were performed, and 57 pediatric patients tested positive. This document described the clinical characteristics of three adolescents who had septic shock. All three reported patients had a body mass index greater than the 97th percentile for their age, which raises the issue of obesity as a risk factor for serious illness, as reported in studies with adults[16].

LIVER DISEASES

In general, there is still little clear information regarding the influence of liver disease on the evolution of SARS-CoV-2 infection or vice versa, especially in children, but the liver damage found is generally mild, with transient increases in liver enzymes and without reports of deaths due to severe hepatic decompensation in previous liver disease patients[8,17].

Studies indicate that higher levels of alanine aminotransferase (ALT), thrombocytopenia and hypoalbuminemia, at the time of admission of the patient affected by COVID-19 were related to a higher mortality rate. However, it was not clear whether these laboratory changes were due to previous liver disease, liver damage caused by the virus or an exacerbated inflammatory response with disseminated intravascular coagulation[8].

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Hepatic involvement in coronavirus infection may or may not occur in patients with previous liver disease. One study showed that changes in liver enzymes in adults were present in 14% to 53% of cases, with the most severe cases of hepatic involvement being only found in very severe cases of COVID-19[18,19]. One study showed that in children with severe coronavirus infection, 50% had liver enzyme changes, but without any worsening of the liver condition[20]. To date, there are no reports of severe hepatic involvement by coronavirus in children[21].

INNATE ERRORS OF IMMUNITY

To date, there are no studies or reports on coronavirus infection in patients with Inborn Immunity Errors (IIE); however, the Brazilian Society of Pediatrics, along with other organs, issued a position clarifying the main points of the correlation between COVID-19 with the IIE and stratifying them into different risk groups. Patients with primary immunodeficiencies in general have the same probability of being infected with SARS-CoV-2 as the general population, but they present different risks to develop a serious disease, depending on the type of immune defect[21].

Patients with IIE are divided into three distinct risk groups for coronavirus infection, according to the type of immune defect. They are 1 - extremely vulnerable (e.g. combined T and B cell immunodeficiency), 2 - moderately vulnerable (e.g. congenital agammaglobulinemia) and 3 - low risk (e.g. selective IgA deficiency)[21].

Group 1 patients are considered the most delicate and must follow strictly all measures for groups at risk, especially social isolation. Group 2 and 3 patients must also follow social isolation and other preventive measures; however, in accordance with the provisions for the general population[22,21].

OTHER COMORBITIES

In addition to the above, the Department of Primary Health Care also mentions: poorly controlled asthma; cystic fibrosis with recurrent infections; bronchopulmonary dysplasia with complications; children with chronic lung disease due to prematurity; transplanted solid organs and bone marrow; carriers of chromosomal diseases and those with states of immunological fragility, such as Down's Syndrome[12].

FINAL CONSIDERATIONS

In conclusion, even though it represents a condition of lower prevalence and with more favorable clinical results, it is mandatory to know the factors of poor prognosis in pediatric cases of COVID-19. The present review gives visibility to several gaps on this theme, which need new studies capable of fully and consistently elucidating them.

CONFLICTS OF INTEREST

This study did not receive financial resources from any commercial organization and has no conflicts of interest.

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