REVIEW

COVID-19 in Children: An Ample Review

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Abstract: The aim of this review was to describe the current knowledge about coronavirus disease 2019 (COVID-19, which is caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) in children, from epidemiological, clinical, and laboratory perspectives, including knowledge on the disease course, treatment, and prognosis. An extensive literature search was performed to identify papers on COVID-19 (SARS-CoV-2 infection) in children, published between January 1, 2020 and April 1, 2020. There were 44 relevant papers on COVID-19 in children. The results showed that COVID-19 occurs in 0.39–12.3% of children. Clinical signs and symptoms are comparable to those in adults, but milder forms and a large percentage of asymptomatic carriers are found among children. Elevated inflammatory markers are associated with complications and linked to various co-infections. Chest computed tomography (CT) scans in children revealed structural changes similar to those found in adults, with consolidations surrounded by halos being somewhat specific for children with COVID-19. The recommended treatment includes providing symptomatic therapy, with no specific drug recommendations for children. The prognosis is much better for children compared to adults. This review highlights that COVID-19 in children is similar to the disease in the adult population, but with particularities regarding clinical manifestations, laboratory test results, chest imaging, and treatment. The prognosis is much better for children compared to adults, but with the progression of the pandemic; the cases in children might change in the future.

Keywords: pediatric, COVID-19, SARS-CoV-2 infection, child

Introduction

The recently declared coronavirus pandemic represents the "sword of Damocles" in societies used to protocols and guidelines. It started at the end of 2019, when many adult patients with a new form of pneumonia that was frequently fatal were admitted to Chinese hospitals; this illness was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1]

In this time of modern medicine, when evidence-based medicine prevails, we find ourselves in the face of a difficult situation, where the necessary evidence is lacking; while there are some large studies for the adult population, for the pediatric population, the evidence is extremely limited.

The new coronavirus was initially named 2019-nCoV but was later renamed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] The virus is a single-stranded, zoonotic RNA virus that is a member of the group of respiratory tract viruses. It is related to Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV).[3] The disease, known internationally as coronavirus disease 2019 (COVID-19), affects a significant proportion of people, but it has been reported less frequently in

children, especially in the initial studies, in which only 0.9% of the positive cases involved children <15 years.[4]

The current transmission is from human to human, and both intra-family and intra-community spread occurs, although it is assumed that it was initially from bats and had an animal intermediate host.[5] The virus is excreted via the respiratory and digestive routes.[6] It has been found that the virus is excreted via the digestive route even at 4 days after a negative respiratory sample is obtained, which may be due to a longer time requirement for clearing the virus from the digestive route compared to the respiratory route.[7,8] Contamination occurs via Pffluge drops (produced by coughing, sneezing, and talking) or by contact with contaminated surfaces,[9] with contamination of feces also occurring.[10] Because having children (especially toddlers) follow sanitary practices is extremely difficult (depending on their age), it is expected that child carriers transmit the infection easily. Major problems among children include the high degree of contagiousness, the healthy status of carriers of the virus (leading to an increased potential for transmission), and the lack of knowledge we have about the disease. Not much is known about mother-to-child transmission, but there are studies reporting on positive newborns being born to positive mothers. In these cases, it is not clear whether infection occurred intranatally or perinatally (via secretions such as Pflugge drops or milk), with no clear transmission route having been established.[11–13]

This study aimed to review the current data on SARS-CoV-2 infection in children, from epidemiological, clinical, and laboratory perspectives, including data on the disease course, treatment, and prognosis.

Methods

"COVID-19" or "SARS-CoV-2" and "children" were used as the keywords in the search and the additional terms included epidemiology, diagnosis, clinic, laboratory, treatment, and outcome. The search period was January 1, 2020 to April 1, 2020. LitCovid (the US National Library of Medicine's curated hub of scientific literature on SARS-CoV-2, https://www.ncbi.nlm.nih.gov/research/coronavirus) was searched, along with searching for additional records in Medline (PubMed interface), Springer Link and Web of Science. All retrieved records (including original articles, letters to editor, editorials, and case reports) in English and records with English translation were downloaded and evaluated. Preprints, in-press articles, and accepted-for-publication studies were also evaluated, given the current scarcity of

evidence. Subsequently, the abstracts were evaluated for eligibility, duplicates were removed, and the data were analyzed.

Results

A total of 147 published papers were found on SARS-CoV-2 in general populations, 48 full-text articles that involved children were published between January 1, 2020 and April, 1 2020 and 44 considered relevant were reviewed for this study.

Epidemiology

SARS-CoV-2 has triggered a significant number of illnesses; (as of 1st of April 2020), the World Health Organization (WHO) reported 1,133,758 confirmed cases, with 62,784 deaths.[14] Although data on the pediatric population are currently limited, there are several studies that provide valuable information.

Based on the first published research, the disease was diagnosed in only 0.39% of children.[15] A later Chinese study of 72,314 patients of all ages reported the virus in 1% of children.[16] A large-scale testing study in Korea (involving children representing 18% of the country's population) reported that the proportion of children with COVID-19 among the confirmed cases was 4.8%.[17] After the initiation of more widespread testing, Lu et al conducted a recent study in China and reported that the incidence of confirmed COVID-19 among children rose to 12.3% (171 out of the 1391 children assessed), with a mean an average age of 6.7 years.[18] Dong et al studied 2143 cases of children with COVID-19 in a large study in China (34.1% of cases were confirmed by laboratory testing and 65.9% were clinically diagnosed). The average age of these children was 6.7 years. There was no significant difference in the proportion of males (56%) and females,[19] but other research has shown a slightly higher prevalence in adult males.[17]

It was presumed that children were infected via exposure to infected family members,[17,19] without specifying from which family member the infection occurred, whether the infection was contracted simultaneously by all family members, or the incubation period in children. Xia et al conducted a small study of 20 children with COVID-19 and reported that 65% had clear contact with a family member, while the contact was indeterminate for the remainder of the children.[21]

Clinical Picture

Pediatric symptoms are variable, depending on the stage of the disease, the prior health status, and the presence of

comorbidities and other individual features. The clinical picture in children includes fever, cough, dyspnea, and malaise, which is the tetrad of symptoms frequently reported in adults.[20] In children, fever is present in 41.5%[17] to 60%[21] of cases, being reported by most studies as a significant symptom, associated with both cough and common symptoms of rhinopharyngitis (such as sore throat and rhinorrhea).[18,22]

Based on the WHO case definition, in the majority of countries, only patients (including children) with respiratory symptoms would be suspected of having COVID-19.[23] However, Dong et al reported that 4.4% of children were completely asymptomatic, while 55.3% had mild forms such as rhinopharyngitis.[19] Digestive symptoms are also present in 8–10% of cases involving children,[24] including abdominal pain or discomfort, diarrhea, and vomiting; these symptoms may precede respiratory symptoms.[22]

Cardiac manifestations specific to myocarditis were also found in children: sinus tachycardia and minor right bundle branch block (RBBB); however, the prevalence was not significantly different from that in the general pediatric population.[21] Depending on the affected organs, manifestations of the associated complications may be adjoining.

The physical signs of COVID-19 include rhinorrhea, pharyngeal congestion,[21] and pulmonary rales,[25] associated with pneumonia. Compensatory signs such as polypnea, dyspnea, chest retractions, and other signs of respiratory failure have been observed,[26] but specific COVID-19 signs were not highlighted. Thus far, there have been no confirmed cases of hemoptysis or anosmia in children, unlike in adults,[27] but this might be because of the difficulty of describing the absence of smell by children.

Pediatric outcomes are usually excellent due to the mild forms of disease often present in children, although deaths have also been registered among children.[4] Asymptomatic carriers among the pediatric population have been described, raising concerns, because infected children might be asymptomatic spreaders of the disease.[21]

Recently, the occurrence of a multisystemic inflammatory syndrome in children was reported.[28] It was initially named "Kawasaki like-disease" and then renamed pediatric multisystem inflammatory syndrome (PIMS), and it is similar to the vascular multisystem inflammatory involvement in adults with COVID-19.The disease onset is usually preceded by gastrointestinal symptoms, which are followed by systemic vasculitis with prolonged, nonresponsive fever associated with rash, palmar erythema, conjunctivitis, oral mucositis, and laterocervical lymphadenopathy, and sometimes complicated

with myocarditis and/or severe coronaritis. PIMS has been reported in the UK, France, Italy, and the USA but, fortunately, the treatment for Kawasaki vasculitis has proven to be effective.[28]

However, Dong et al reported that 4.4% of children were completely asymptomatic, while 55.3% had mild forms such as rhinopharyngitis.[19] Additionally, a recent study in China of 2143 children with COVID-19 found that 94% of them had mild or moderate forms of the disease.[19] Fang et al published the following COVID-19 classification system for children, according to disease severity (based on the clinical picture):[29]

- Asymptomatic infection: no clinical signs or symptoms and normal chest imaging, with positive SARS-CoV-2 nucleic acid test result.
- Mild disease: symptoms of acute upper respiratory tract infection, such as fever, cough, odynophagia, rhinorrhea, sneezing, fatigue, and myalgia. Physical examination only shows discrete congestion of the pharynx without auscultatory abnormalities. Some children may have no fever, and only digestive symptoms such as nausea, vomiting, abdominal pain, and diarrhea.[1,29]
- Moderate disease: typical signs and symptoms of pneumonia, such as fever, predominant productive cough and/or wheeze, but no hypoxemia, dyspnea, or other signs of respiratory failure. Some cases may have no clinical signs or symptoms, but only positive computed tomography (CT) findings.[29]
- Severe disease: fever, cough, and dyspnea (associated with central cyanosis and oxygen saturation <92%), tachypnea, or severe diarrhea. The disease usually progresses in 7–10 days. Signs of respiratory distress are present, such as gasping, chest retractions, bradypnea, and, rarely, apnea. No cases of silent hypoxia without compensatory signs have been reported in children, unlike in adults.[30]
- Critical disease: progression to acute respiratory distress syndrome (ARDS) or respiratory failure, with complications such as intravascular disseminated coagulation, shock, encephalopathy, myocarditis, cardiac failure, and acute kidney disease.

The clinical manifestations of the virus in children have been mild and less severe than those in adults, being linked to their age and development.[1,4,5,8,9] This needs to be kept under close supervision, and identifying the asymptomatic carriers is paramount for limiting the virus spread.

Although the clinical manifestations in children are more indistinct and less severe than in adults, this age category is distinct and must be considered with special care, particularly as early diagnosis influences the diseases outcome and, crucially, detecting asymptomatic carriers can limit the transmission of the disease.

Risk Factors for Mortality and Morbidity in Children

Most studies suggest that the same risk factors in adults apply to children, including comorbidities such as diabetes, chronic pulmonary disease, and cardiac pathology,[4] and unfavorable outcomes are more frequent in adults with comorbidities such as hypertension, diabetes, kidney disease, immunosuppression (drug-induced immunosuppression and HIV), and chronic obstructive pulmonary disease (including asthma).[30] Prompt diagnosis is vital, given the evolution of the disease, with ARDS potentially occurring at 1 week after symptom onset.[31]

The most frequent complications observed in children with severe forms of COVID-19 were septic shock, toxic encephalopathy, multiple organ dysfunction syndrome, disseminated intravascular coagulation, and status epilepticus.[26]

Fortunately, in a study that included 2173 children, only one child (aged 14 years) died, but the proportion of severe and critical cases was 10.6% among infected infants, and this decreased with increasing age to 3.0% for infected 16–18-year-olds.[19] More severe forms were more common in children < 3 year of age (10.6%) compared to in children aged 16–18 years (3%) infected with the virus, suggesting that younger children are more at risk of having severe forms than older children, but the study did not report if underlying diseases were pre-existent among any of the children.[19] Another study reported the death of a 10-month-old baby with associated intestinal occlusion.[18] The comorbidities associated with severe cases in the study were leukemia (taking chemotherapy), intestinal occlusion, and hydronephrosis.[18]

As of March 31, 2020, four deaths among children caused by COVID-19 were reported in the international media. A 16-year-old died in France, and then a 12-year-old girl died in Belgium and a 13-year-old boy died in the UK (https://www.euronews.com/2020/03/31/).

Diagnosis

The presence of clinical signs and symptoms in a relevant epidemiological context (eg, an endemic area) indicates a suspected case of COVID-19, especially if contact with a confirmed COVID-19 case is known. The diagnosis can be confirmed by viral detection laboratory tests. It is important to ascertain the timing of the onset of infection, based on the incubation period of 2–14 days,[9] with a mean of 3–7 days.[1] There may be suspicion of a case of COVID-19 in a child if at least one of the following exists:[9]

1. Fever, specific respiratory symptoms, digestive symptoms, or fatigue
2. Suggestive biological findings: normal leukocyte level, leukopenia, and increased C reactive protein (CRP) and procalcitonin (PCT) levels
3. Specific imaging findings (based on chest X-ray [CXR] and CT scans)

In a suspected case, the confirmation involves laboratory confirmation, although some clinicians would advocate that in the presence of clinical signs and symptoms and contact with a COVID-19 case, a diagnosis can be made.[23] The laboratory diagnosis is performed by detecting a nucleic acid antigen (SARS-CoV-2 RNA) from nasopharyngeal or pharyngeal secretions using Reverse transcription polymerase chain reaction (RT-PCR). The tests involving nasopharyngeal secretions had a better sensitivity (65%) compared to the tests involving pharyngeal swabs (30%).[32] This is why the US Centers for Disease Control and Prevention (CDC) recommend screening involving nasal secretions or nasopharyngeal aspirate.[33]

The timing of the sample collection[34] is very important: screening tests should ideally involve nasopharyngeal secretions collected at the beginning of the disease (when there are signs of rhinopharyngitis), as the viral load decreases in the upper airway and increases in the lower airways with the onset of lung disease;[35] thus, after the onset of lung disease, sputum samples are recommended. Using nasopharyngeal secretions leads to a lower sensitivity than using bronchial secretions, but the required bronchoalveolar lavage for children without sputum excretion is invasive[35] and may increase the risk of infection among the medical personnel[36] and so is not indicated.

Screening tests based on the detection of specific immunoglobulin M, A, and G (IgM, IgA, and IgG) in serum have been developed, but IgM and IgA only become positive from the fifth day from COVID-19 onset, so the diagnosis is made retrospectively and the tests cannot be used for early diagnosis.[36,37] IgG levels can be detected after 14 days of disease evolution.[38] Unfortunately, the number of screening

tests is limited internationally due to the widespread nature of the pandemic, which makes it very difficult to establish precise diagnoses and to identify the healthy carriers acting as viral reservoirs.

Laboratory Findings

Biological investigations are not specific, as expected in viral diseases. As in other viral infections, in COVID-19, several hematological disorders have been reported. Several studies have reported the presence of leukopenia in adults and children, associated with lymphopenia and neutropenia.[36,39] Another study reported normal leukocyte levels with leukopenia among children.[1] Sun et al reported normal leukocyte levels (lymphocytes and neutrophils), platelets, and hemoglobin in some patients, but leukopenia with lymphopenia, thrombocytopenia, and anemia were linked with severe outcomes.[26]

Increased inflammatory markers such as CRP, erythrocyte sedimentation rate,[1] and PCT have been noticed in some children with COVID-19,[40] signifying a bacterial co-infection and associated complications.[21,25,26] It has been shown that a large percentage (80%) of children had abnormal PCT values, requiring antibiotics, but no deaths were registered among these children.[21] PCT was normal in children with mild and moderate COVID-19.[1,21,25]

While studies involving adults revealed that PCT and leukopenia were risk factors for increase mortality rates, this connection was not confirmed in children. Increased troponin was present in adults with myocarditis, and myoglobin (also known as myohemoglobin) and muscle enzymes were increased in adults due to COVID-associated muscular injury[1,40,41] but these findings were not reported in children. High CRP and ferritin levels were associated with a poor prognosis in adults[42] as well as increased D dimers and thrombocytopenia.[21,27,30] Other biological findings included idiopathic metabolic acidosis and increased serum levels of proinflammatory cytokines such as interleukin (IL)-6.[42] Increased transaminases, muscle enzymes, and lactic dehydrogenase[1,21,25,43] can occur, depending on the affected organ, and alanine transaminase and direct bilirubin were associated with severe disease in children.[43,44]

Chest Imaging

Chest imaging, including chest Xray (CXR), CT, and lung ultrasonography (LUS), is often used for evaluation and monitoring of respiratory diseases.[45] Therefore, it may be advisable to use one of the imaging techniques for COVID-19 assessment. However, it would not be appropriate to use CT as a screening diagnosis tool for COVID-19 diagnosis in children because of the lack of specificity of the lesions, which can occur in other viral lung diseases.[46] Ai et al published a study on adults that concluded that CT scans should be considered for COVID-19 diagnosis,[47] based on the good sensitivity of CT for detecting lung changes, which was biased by the fact that CT is the gold standard for the detection of morphological changes. A comprehensive report stated that chest CT scans would be normal in 35–50% of pediatric COVID-19 patients with minor upper airway respiratory symptoms, which implies an unjustifiably high percentage of children, without injuries, who would be exposed to CT radiation if chest CT scans were used. To be used for screening, chest CT scans should detect lung changes in asymptomatic children as well as in symptomatic cases, but the median sensitivity of CT of 60% in pediatric patients with confirmed COVID-19 is not sufficient to expose asymptomatic children to harmful radiation. As it is unusual to perform CT scans in cases of viral non-complicated pneumonia, there are currently no valid arguments for the use of CT scans as a screening tool in the pediatric population with asymptomatic SARS-CoV-2 infection. Because CT scans lack specificity for COVID-19, caution was recommended by an expert panel regarding imaging choices, especially when they necessitate patient transport.[48]

CXR

In most cases of pneumonia, CXR is a key diagnostic tool, but its diagnostic utility for COVID-19 is limited. The initial and mild stages of COVID-19 can lead to a normal CXR image.[4,27,49] However, uni- or bilateral patchy or diffuse asymmetric airspace opacities, interstitial alterations, and nodularity can be detected in severe COVID-19 cases.[50] Nevertheless, CXR is neither an indispensable nor a mandatory COVID-19 diagnostic tool due to its lack of specificity.

Chest CT Scans

CT is highly sensitive at detecting pulmonary lesions in all lung pathologies, including COVID-19. However, many studies described COVID-19 lesions on CT scans that are non-specific and bear some resemblance to other lung pathologies.[49–51] Ground-glass opacities were described, mostly subpleural[52] and predominantly in the lower lobes, while fine-mesh shadows occurred in the early stages of the disease.[21,49,51,52] Among children with moderate forms of COVID-19, there was a bilateral multi-lobular distribution with diffuse ground-glass, crazy-paving pattern, and

consolidation.[21,47,53] As the infection progressed, severe lesions and dense consolidation became more prevalent.[53]

Xia et al reported that consolidation surrounded by a halo was found in half of children with severe or moderate COVID-19 lung disease, suggesting that there is some specificity regarding these lesions in children.[21] Lesions such as ground-glass opacities and fine-mesh shadows were also described in children, while "patch-like shadows" and "white lung" have been found in severe cases.[26] A recently developed COVID-19 CT score showed a reliable, sensitive association with decreased mortality risk in adults.[53]

Despite studies indicating that non-contrast chest CT scans could be used as an early diagnostic tool compared to RT-PCR[54] (CT being frequently delayed because of the high burden of cases during pandemics), CT is not recommended as a first-line diagnosis technique in children. This is due to irradiation risks, lack of specific lesions, and the potential increased contamination risk during patient transport. The results of a study by Fang et al support the use of chest CT scans for screening in patients with clinical and epidemiological features compatible with COVID-19, particularly when RT-PCR test results are negative.[55]

Lung Ultrasound

Various studies have demonstrated that LUS is a valuable tool for identifying changes that can occur in COVID-19 such as consolidations, pleural effusions, small subpleural consolidations, areas of white lung, and B lines in a variety of patterns including focal, multifocal, and confluent lesions.[56,57] LUS can indicate suggestive signs of interstitial-alveolar damage involving variable consolidations, irregularities of the pleura, nontranslobar consolidation, and consolidation with air bronchogram.[58] However, LUS can detect lung artefacts that are not specific to COVID-19, including consolidations with air bronchogram that occur in pneumonia,[58] subpleural consolidations that occur in pneumonia and bronchiolitis,[59] pleural line irregularities that occur in bronchiolitis, lung fibrosis, pleural malignancies, and COPD,[60–62] and B-lines that occur in interstitial alveolar inflammation present in bronchiolitis and viral interstitial cases of pneumonia,[60] as well as in chronic lung pathologies such as fibrosis,[61] cystic fibrosis,[62] and bronchiectasis.[60]

The limitations of LUS is relied to the lesion localization, deeper lung lesions have no contact with the pleura and cannot be easily detected as the air is a very weak conductor of ultrasound.[63] However, in contrast to other methods of investigation, LUS is easily available at the bedside[57] and portable probes that are easy to disinfect can be used, involving less exposure to infection among medical staff.[64]

Treatment

There are currently no etiological treatments or prophylactic for COVID-19.[66] The treatment of mild cases addresses current symptoms, and isolation to prevent human-to-human transmission is the most important prophylactic treatment.[9,67] For moderate and severe COVID-19, the therapeutic recommendations involve supportive therapy, supplemental oxygen and, if bacterial infection (which is frequent in children) is suspected, empirical antibiotics.[1,25,29,30] Very severe cases involving refractory hypoxia and respiratory failure will need admission to an intensive care unit for mechanical ventilation; fortunately, children do not require this as often as adults.[19,20,26] Non-invasive ventilation (NIV) and high-flow oxygen therapy (HFOT) are associated with a high risk of virus aerosolization, and the virus can be spread via mask leaks, so NIV and HFOT may only be used in specific cases and when the mask is precisely positioned, with an optimal fit.[67]

Retrospective studies on COVID-19 suggest starting antiviral medication in the initial treatment window, when the evolution of the disease can still be changed, due to the lack of treatment efficiency once complications occur.[67] Etiological treatment would require the administration of antivirals targeting RNA viruses. So far, no antiviral has been shown to be effective for the treatment of COVID-19 in humans, but there are multiple randomized clinical trials in progress. Some antiretroviral drugs (such as lopinavir/ritonavir, darunavir/cobicistat, favipiravir, remdesivir, ribavirin, oseltamivir, tocilizumab, and umifenovir as well as angiotensin-converting enzyme [ACE] inhibitors) have been indicated in adults.[1,67] However, as there are no studies to demonstrate the benefit of any antivirals in children with COVID-19, the use of this type of medication would not be recommended.

Chloroquine and its derivatives (including hydroxychloroquine and chloroquine phosphate) have been successfully used for SARS-CoV and Ebola, and have also been shown to be effective in children with SARS-CoV-2.[68] Co-administration of azithromycin increases the therapeutic success, according to a French study.[69] Most of the therapeutic regimens for children include chloroquine (or derivatives) and lopinavir/ritonavir, which have been reported to show a degree of efficiency and a safety profile that is

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acceptable for children.[9] Ribavirin has been reported to have been used to treat severe COVID-19 in children.[25,65]

Inhaled interferon-alpha has been used to treat COVID-19 in children, but the efficiency and safety remain to be determined.[1,65] Non-specific immunity-boosting treatments such as immunoglobulins and intravenous interferon have been used to treat severe cases in adults, but additional consideration is required before it is used for children.[1,9,65]

Corticosteroids are recommended for the treatment of COVID-19 complications such as ARDS, septic shock, encephalopathy, and bleeding disorders, and in other specific pathologies, steroids are required.

The multicentric CITRIS-ALI trial demonstrated the effectiveness of high-dose ascorbic acid for treating ARDS due to other causes, lowering the mortality rate,[70] and this could be extrapolated to COVID-19.

Antibiotics are recommended for secondary chest infections associated with COVID-19. The majority of studies suggest using empirical broad-spectrum antibiotics until culture results become available.[1,4] Given the frequency of *Mycoplasma* infections in children[9,21] and the well-described anti-inflammatory properties of azithromycin, this could be the antibiotic of choice in children with COVID-19 and bacterial superinfection.

Further studies should be carried out to gather evidence on the best therapeutic options. Prevention, aimed at reducing transmission in the community, remains the only proven efficient option to combat COVID-19, until further discoveries are made.

Outcomes and Prognosis in Children

According to several studies, COVID-19 has a milder clinical course with faster recovery and a better prognosis in children compared to in adults.[1,9,15] However, a recent study reported similarly severe forms of COVID-19 in children with good outcomes.[40] The reasons for these particularities are still being investigated. Some researchers have hypothesized that lung epithelial cells in children may express fewer or perhaps even differently shaped ACE2 proteins, leading to a lower morbidity rate,[71] but further studies are needed to understand the mechanisms of the diverse manifestations of COVID-19 in children.

It has been shown that influenza virus, parainfluenza virus, respiratory syncytial virus (RSV), rhinovirus, or adenovirus, which are the most common viruses that cause acute lower respiratory infections in young children, might cross-react with coronavirus,[72] giving children partial protection against COVID-19,[73] but co-infections were

also reported.[9] The most common co-infections in children involved *Mycoplasma pneumoniae*, influenza A and B, RSV, and cytomegalovirus.[21]

Children of all ages are predisposed to acquire COVID-19, considering the human-to-human transmission, but the majority of them have mild forms of COVID-19 and a favorable evolution.

Prognosis is much better in children compared to in adults, yet asymptomatic carrier transmission is presumed to be more common among the pediatric population.[73] Nevertheless, with the progression of the pandemic, the cases in children might change in the future.

Conclusion

This review highlights that even if COVID-19 is rare in children, asymptomatic SARS-CoV-2 infection is more frequent than in adults. Collecting further high-quality evidence is essential to understand COVID-19 in children and to determine the most efficient case management strategies. Infection prophylaxis through isolation of infected children is essential, involving proper monitoring, early detection of disease complications, and the opportunity for on-time treatment and limiting secondary spread. Being caught up in a pandemic involving the "sword of Damocles" and a "crown" of SARS-CoV-2 proteins, children might be a key element in the battle.

Disclosure

The author reports no conflicts of interest in this work.

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