Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

COVID-19 infection prevalence in pediatric population: Etiology, clinical presentation, and outcome

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ABSTRACT

Novel COVID-19 infections caused major morbidity and mortality globally in the adult age group. Likewise, SARS-COV-2 infections in children are highly risky in the selected patient population. We performed a focused literature search of published reports from December 1, 2019, till August 20, 2020. The aim was to explore the etiology, clinical presentations, and outcome of pediatric COVID-19 patients. Viral respiratory infections are associated with high societal costs for children. In addition, children with asymptomatic SARS-COV-2 infections can be a source of COVID-19 spread to parents and caregivers. The major reported risk factors for pediatric COVID-19 cases were close contact with a SARS-COV-2 positive family member, a history of travel, and/or living in endemic areas. Children with COVID-19 who required ICU care had various comorbidities, such as malignancy. As the pandemic evolved, multiple cases of multisystem inflammatory syndrome in children and adolescents temporarily related to covid-19 (MIS-C) were reported. A unique population is neonates born to COVID-19 affected mothers, as there is an urgent need to optimize their management and outcome during this rapidly evolving pandemic. The early identification of SARS-COV-2 infection in infants and children has important direct management effects in these children and public health implications because of the effects on disease transmission control measures.

Contents

Abbreviation: COVID-19, Coronavirus Disease 2019; MERS-CoV, Middle East Sever Respiratory Syndrome; SARS-CoV, SARS coronavirus; ICU, Intensive care unit; CRP, C-reactive protein; CBC, Cell blood count; Rt, PCR reverse transcriptase real time polymerase chain reaction; RBD, Receptor binding domain; ACE2, Angiotensin Converting Enzyme 2; GGO, ground-glass opacity; EBM, expressed breast milk.

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Introduction

In December 2019, pneumonia due to a novel coronavirus (SARS-COV-2) emerged in the city of Wuhan in China and caused increased number of cases and deaths worldwide [1]. Interestingly, data from the Chinese CDC showed that the fatality rate of COVID-19 varies tremendously according to the age of the patient, with a higher mortality rate among the older population (>50 years) having co-morbidities. However, the precise estimate of mortality rate might not be accurate due to the lack of estimation of the infection in the community. Recently, a large amount of data from the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) suggested a fatality rate of 14.8% in ≥80 years, 8% in 70-79 years, 3.6% in 60-69 years, 13% in 50-59 years, 0.2-0.4% in 10-40 years of age and no deaths rates in ≤9 years of age [2–3].

Coronavirus belongs to the coronaviridae family and is an enveloped virus with a positive-sense single-stranded RNA. The coronaviridae (CoVs) family is classified into four genera: Alpha, Beta, Delta and Gamma coronavirus, as well as several subgenera and species. In addition to humans, α, β. Coronaviridae can cause the disease in other mammals like bats and birds. The usual presentations of most of the known virus belonging to this family like HCoV-229E, HKU1, NL63 and OC43 include mild upper respiratory tract infection and common cold in adult, but some can cause pneumonia, bronchiolitis and croup in susceptible pediatric patients [4–5]. However, two emerging viruses belonging to β-CoVs were documented to cause severe respiratory syndrome during the outbreak of Severe Respiratory Syndrome CoV (SARS-CoV-1) in China. Subsequently, it had spread worldwide involving other Asian countries in the year 2002 [6]. Also, Middle East Severe Respiratory Syndrome (MERS-CoV) had a large outbreak in Saudi Arabia and Middle East countries in 2012 and recently in South Korea. Thus, severe cases of coronavirus infection have only been occasionally reported [7–9].

The newly emerging SARS-CoV-2 comes from the same genus of the coronaviridae family (beta coronavirus) with 90% genomic similarity to (SARS-CoV) and 50% to MERS-CoV, causing severe respiratory illness and ARDS [10].

However, the pediatric population is less commonly affected by COVID-19. Published reports from different countries have mostly shown that pediatric patients represent a marginal proportion of COVID-19 cases, representing less than 2% of the reported ones. Moreover, they are less symptomatic and fatal as compared to the adult population. This is concordant to previous epidemic outbreaks of SARS-CoV and MERS-CoV in 2002 and 2012, respectively [11–14].

Methods

Search Process

For the literature review, we searched for all studies published between December 1, 2019, and April 15, 2020, using the PubMed search engine, SciELO database, and Google scholar. Search terms included (COVID-19 or SARS-CoV-2) AND (pediatric, children, newborn or infant). Two authors (F.A. and M.T.) reviewed all studies and further retrieved additional articles through reference searching. All case reports, case series and cohort studies describing the characteristics of children or youngsters less than 18 years of age with positive SARS-CoV-2 infection were included. Information of clinical symptoms and adverse events in positive infection was gathered. Duplicate case reports were identified and presented only once.

Clinical presentation, usual and atypical symptoms

Children infected with SARS-CoV-2 usually have mild symptoms; however, 15-35% can be asymptomatic [13,15].

The most commonly reported symptoms in children aged ≤9 years were fever (46%), cough (37%), headache (15%), diarrhea (14%), and sore throat (13%). In children aged 10–19 years, headache (42%), cough (41%), fever (35%), myalgia (30%), sore throat (29%), shortness of breath (16%), and diarrhea (14%) were the most frequent symptoms. Gastrointestinal symptoms may occur without respiratory symptoms. Other less commonly reported symptoms included rhinorrhea, nausea/vomiting, abdominal pain, and anosmia [16]. Cutaneous findings have been reported infrequently and are not well characterized; they include maculopapular, urticarial, and vesicular eruptions. Unusual symptoms in children and young adults are painful purple and red papules on fingers and toes, which has been termed “COVID toes,” as being the only manifestation of COVID-19 [17].

Severe disease requiring oxygen supplementation was reported in less than 3% cases, and <1% were to be critically ill. Current evidence suggests that children with certain underlying medical conditions and infants (age <1 year) might be at increased risk for severe illness from SARS-CoV-2 infection. Similar to adults, children with severe COVID-19 may develop respiratory failure, myocarditis, shock, acute renal failure, coagulopathy, and multiorgan system failure [18].

Children infected with SARS-CoV-2 are also at risk for developing a hyper inflammatory response, similar to adults with COVID-19. Moreover, in late April 2020, reports emerged of children having a different clinical syndrome resembling Kawasaki Disease and toxic shock syndrome. These patients often had evidence of previous exposure to SARS-CoV-2. Subsequent, to these initial reports from United Kingdom and Italy, similar cases were reported from Europe and the United States. Thereafter, this disease entity is currently referred in Europe as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection or multisystem inflammatory syndrome (MIS(-C)) in the USA [19–21].

The clinical and laboratory parameters of children who meet the criteria for MIS-C differ from those with Kawasaki disease. Patients who have MIS-C are usually older, have symptoms compatible with clinical shock, had involvement of the gastrointestinal and cardiovascular systems, lymphopenia, and also with remarkably elevated levels of inflammatory markers. Coronary artery aneurysms have been noted both in children aged <5 years (who were more likely to have presentations similar to those seen with Kawasaki disease) as well as in older children [22,23]. Another recently published cohort of 186 children who were presented with MIS-C had a mean age of

8.3 years; 70% had laboratory evidence of a SARS-CoV-2 infection *by* PCR and/or serum antibody testing. In this cohort, gastrointestinal (92%), cardiovascular (80%), hematologic (76%), mucocutaneous (74%), and respiratory (70%) symptoms were reported, with 80% cases required intensive care and 4 patients were succumbed to death [24].

Risk factors

Unlike adults, children rarely have comorbidities such as hypertension, cardiovascular disease, and diabetes [23]. The main reported risk factors for the pediatric population to be infected with COVID-19 were close contact with a family member with an infection and a history of travel or residence in an endemic area [24].

The few reported cases of pediatric patients who required ICU admission and those who died had different co-morbidities and underlying diseases such as hydronephrosis, leukemia, and intussusception. Until now, no study could identify the prevalence of co-morbidities in children infected with COVID-19 [21].

Laboratory investigation

Routine CBC

The white blood cell count is usually normal or reduced in the COVID-19 pediatric patients, with decreased lymphocyte count; progressive lymphocytopenia have been reported in severe cases [16,25].

The C-reactive protein is usually normal or increased. Procalcitonin is normal in the majority of the cases. Other laboratory investigations such as liver enzymes, muscle enzymes, myoglobin, and increased level of D-dimer might be elevated in severe cases [26].

Some laboratory markers differed significantly between mild and moderate clinical type of COVID-19 in pediatric patients, including decreased lymphocytes and high levels of creatine kinase MB, procalcitonin and D-dimer (16).

Etiologic detection

Laboratory diagnosis

Currently, nucleic acid detection using reverse transcriptase real-time polymerase chain reaction (Rt PCR) qualitative or quantitative (qPCR) are the most commonly used methods for the diagnosis of COVID-19 [27]. There are several available kits in the market, targeting highly conservative regions of the COVID-19 genome, which include RNA-dependent RNA polymerase (RdRp)/helicase (Hel) [28], spike (S), and nucleocapsid (N) [1,28–29]. Genes for confirmation and ORF1b [1,29] E enveloped gene [28,30] are more sensitive and used for rapid screening. E and RdRp genes are most commonly used commercially to detect SARS-CoV-2 in the majority of clinical laboratories [28,30–31]. There have been several international guidelines and regulations [26–32] for laboratory testing of SARS-CoV-2; the recommendations of these agencies along with local authority should be followed. The indication for the collection of sample, to detect COVID-19 nucleic acid from suspected, contacts and asymptomatic individual depends on the case definition and the current situation in each country. Nasopharyngeal and or opharyngeal swabs should be collected properly in a negative pressure using appropriate single viral transport media. Lower respiratory samples like bronchoalveolar lavage can be taken from critically ill patients in ICUs. If the test is not feasible immediately, the sample should be stored at 4 °C for not more 48-72 hours and subsequently kept at −70 °C to assure prevention of viral RNA degradation [26–32].

The sensitivity of COVID-19 nucleic acid detection varies depending on the type of sample collected. Various samples have been tested to detect SARS-CoV 19, mostly respiratory, which includes nasopharyngeal, oropharyngeal, and non-respiratory, mainly blood, feces and urine [33]. In the respiratory sample, the virus can be detected two days before symptoms and continue shedding infection for 12 to 24 days after symptoms [2,34]. Also, prolonged shedding of the virus has been observed in the stool of mildly symptomatic children up to 5 weeks [2]. The ability of a patient with prolonged shedding of the virus to transmit the infection, in the absence of clinical symptoms and radiological finding, is still not clear. However, some believe it might be due to the viral genome rather than the live virus, but this requires further studies [35]. It has been estimated that 44% of secondary cases acquired COVID-19 infection, while the index cases are in the pre-symptomatic stage [36–37].

In 205 clinically suspected COVID-19 patients, 1070 specimens were collected, the highest positive rate was from bronchoalveolar lavage fluid specimens (93%), followed by sputum (72%), nasal swabs (63%), pharyngeal swabs (32%), feces (29%), blood (1%), however none of the urine samples tested were positive [33]. The viral load of SARS-CoV-2 was higher in sputum than throat swab with a peak within 5-10 days after the onset of symptoms [37]. Another study showed overall sensitivity of PCR from nasopharyngeal or throat samples after 2-8 days is 71% cases [38]. However, another study showed lower sensitivity (53.3%) of Rt PCR from the oropharyngeal swab of patients with confirmed COVID 19 infection [39]. A large pediatric study in china showed that, laboratory confirmation of COVID-19 infection by PCR had been documented in 34% of cases with epidemiological, clinical or radiological evidence of the disease [16]. SARS-CoV-2 RNAemia has been reported in a small proportion of COVID-19 patients [40].

The negative Rt PCR result for SARS-CoV -2 does not always mean the absence of COVID-19 infection. Several factors might contribute to false-negative PCR in those patients. These include poor quality of the specimen due to inappropriate collection, transportation, handling or sample PCR inhibitors or viral mutation. Additionally, the collection of the specimen either very early or late hours of the infection [26]. This depends on the policy and protocol in the hospital and community. And measures to minimize the risk of transmission of the infection from those patients and implementation of isolation for 14 days if they are suspected, or extraction of another sample, preferably from the lower respiratory tract, should be carried out [41]. On the other hand, some patients who recovered from COVID-19 infection and discharged from the hospital might become positive again.

The molecular test is expensive and should be utilized efficiently in the setting of the pandemic. PCR should not be repeated on the confirmed case of COVID-19 infection until three days have passed without fever and respiratory symptoms and at least seven days after the onset of the symptoms. For asymptomatic SARS-CoV-2-infected persons, the tests to document virus clearance should be taken at a minimum of 14 days after the initial positive test. Two negative PCR result at an interval of at least 24 hours, can document viral clearance [42].

Rapid molecular detection of SARS-Co-2 would be a great option as most conventional PCR turnaround time range between 3 to 4 hours; also several tests are underdeveloped and need validation. Some of these tests are of a molecular basis while others are immunological detection of antigens from various samples, including saliva [43]. Future larger studies, on other sites in the pediatrics population would have a major impact in facilitating the diagnosis of COVID-19 infection.

Other viral respiratory pathogens [44] in 280 patients suspected to have COVID-19 positive were detected in 49% of patients in a study at the infectious diseases referral hospital in Marseille,

France. The patients turned to be SARS-CoV 2 negative but influenza A and B viruses, rhinovirus, metapneumovirus were the most commonly isolated virus in addition to other coronaviruses like HKU1 and NL63. On the other hand, in a study of pediatric in Madrid with confirmed COVID-19 infection, 5% had co-infections with other respiratory viruses [45].

Serological testing for SARS-CoV-2 has tremendous progress in recent past, which raised the possibility of using these tests for the diagnosis of COVID-19 in combination with nucleic acid testing after 5-8 days of onset of symptoms. In the studies with respect to sensitivity of nucleocapsid or Receptor binding domain (RBD) antigen to detect IgA, IgM and IgG by ELISA, it was found that, 90–98.3% of patients with COVID 19 can be diagnosed compared with only 53% in a single qPCR test [39,46–47]. Serological has a role in contact tracing, asymptomatic carrier, as well as in the determination of the burden of COVID-19 in the community [48].

The use of a chest CT scan along with Rt PCR [49–50] and serological tests [51] can improve the sensitivity for the diagnosis of COVID-19 infection [52].

The utility of inoculating human epithelial cell line for SARS-CoV 2 culture and isolation for the clinical diagnosis of COVID-19 is limited because it required a special bio safety level. And the long turnaround time make this test lose its clinical utility, and is not recommended in the routine diagnostic laboratory. However, it is commonly used for research and development of vaccine and new molecular immunoassays [26].

Viral whole genomic study sequencing in the recent year though the next generation has major clinical and epidemiological applications [28,51]. The initial sequencing of 2019-nCoV and phylogenic analysis showed that, it is within the subgenus Sarbecovirus of the genus Betacoronavirus, which more distant from SARS-CoV (about 79%) and MERS-CoV (about 50%). However, is closely related to other two bat-derived severe acute respiratory syndrome (SARS)-like corona viruses namely, bat-SL-CoVZC45 and bat-SL-CoVZXC21 [10,53–54]. The receptor-binding domain (RBD) that binds to Angiotensin Converting Enzyme 2 (ACE2) of SARS-CoV-2 is similar to SARS-CoV-1 with some amino acids variation in important residues [10,53–54]. Subsequently, during the early outbreak of SARS-CoV2, studies showed two distinct types due to a mutation in the Spike gene of SARS-CoV causing variation in their receptor sites. Also, this type of mutation in the Spike gene have been noticed previously during the outbreak of MERS-CoV [55–57]. Continuous monitoring of mutation and evolution of SARS-CoV 2 is important to detect any significant mutation in RBD. This intern will affect transmissibility and virulence [58–59].

Radiology

Radiological findings in children are different from adult patients. Chest X-rays and CT scans are often normal. Children might have viral pneumonia-like changes in chest imaging. Changes may be found on CT, even in asymptomatic patients. Common features in abnormal CT scans include mild, bilateral ground-glass opacities, but with less peripheral predominance as compared to adults [18,60].

Newborn cases

During the emergence of the pandemic of COVID-19, neonates are reported to acquire the infection postnatally. Few studies and case series of maternal COVID 19 had been reported with controversies and uncertainty about the vertical transmission and fetal effect. Recently two reports have published, evidence of IgM for SARS-CoV-2 in the neonatal serum at birth after delivery by c. section to infected mother with COVID 19. This may indicate a neonatal immune response to in-utero infection. The other laboratory findings were leukocytosis with raised inflammatory markers, especially interleukin-6.

The initial case report and case series from China suggested, no evidence of antenatal infection especially in cases, where all fluid samples were taken from the mother vaginal secretion, amniotic fluids, placenta and also breast milk was tested negative for SARS COV 2 [61–62].

With these controversies, Zhang L et al. had reported that, no significant effect of the virus infection on neonatal outcomes is observed with reference to premature birth, fetal distress, birth asphyxia and meconium-stained amniotic fluid [63].

During the delivery of infected pregnant women, all clinical guidelines indicated the need to have safe and protected deliveries to reduce the chance of intrapartum and postnatal transmission. Protocol emphasized on no skin contacts with the infected mother; and the need to isolated baby in a negative pressure room until the nasopharyngeal swab is negative. For the safety reason and after parents' agreement, the breast milk can be provided as expressed breast milk (EBM) or formula. For those neonates, who become symptomatic or the swab PCR turns to be positive should be admitted in a negative pressure isolation room with facility for intubation or airway management [64].

In neonatal confirmed cases with COVID 19, the presentation ranged from mild respiratory distress associated with thrombocytopenia accompanied by elevated liver enzymes to more severe respiratory failure disseminated intravascular coagulopathy and death [65].

Prognosis & Outcomes

At present, the epidemic of COVID-19 is ongoing and rapidly evolving. As of April 14, 2020, reported cases in the literature showed that, most pediatric COVID-19 patients have a good prognosis, and in mild cases, recovery takes 7 to 14 days after the onset of the disease [24].

Among an extensive analysis of 72,314 cases from China, there was a single death among 549 cases, in the age bracket of 10-19 years [66].

In Spain, 60% of confirmed COVID-19 infections in children required admission; among those, 10% were admitted to a pediatric intensive care unit (PICU) [67].

On the other hand, in the United States, 5.7%–20% of children were hospitalized with 0.58%–2.0% requiring PICU admission [68].

To gain a better understanding of children's COVID-19 infection outcome, more detailed information on clinical outcomes including discharge, ICU admission and death, needs to be further elucidated.

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None declared.

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