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Review

Covid-19 in children: A brief overview after three months experience

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Educational aims

The reader will come to appreciate that:

- Children may present non-specific viral infection symptoms.
- COVID-19 shows a milder clinical course in children than in adults.
- There is no clear evidence of SARS-CoV-2 vertical transmission.
- No excretion of SARS-CoV-2 in human breast milk has been reported.
- Underlying cardiovascular disease seems to be the most frequent comorbidity in severe COVID-19 pediatric confirmed cases.

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ABSTRACT

Severe Acute Respiratory Syndrome – Coronavirus – 2 (SARS-CoV-2) and its related Coronavirus Disease – 19 (COVID-19) has become a health emergency worldwide. The medical community has been concerned since the beginning of the outbreak about the potential impact of COVID-19 in children, especially in those with underlying chronic diseases. Fortunately, COVID-19 has been reported to be less severe in children than in adults. However, epidemiologic and clinical data are scarce. Children show unique features of SARS-CoV-2 involvement that may account for the low rate of infection and death in this age group. The purpose of this review is to summarize the most relevant evidence of COVID-19 in children highlighting similarities and differences with adults.

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INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic. COVID-19 is caused by SARS-CoV-2, a novel positive single-stranded RNA virus, belonging to the β Coronavirus genus (subfamily Orthoronavirinae, family Coronaviridae, suborder Cornidovirineae, order Nidovirales) [1], which emerged in December 2019 in Wuhan, China. SARS-CoV-2 shared 79.5% sequence identity with SARS-CoV and 96.2% with a SARS-like coronavirus in bats, suggesting a cross-species transmission [2].

All human coronaviruses (hCOVs – 229E, NL63, OC43, HKU1 SARS-CoV, Middle East Respiratory Syndrome – MERS-CoV) pri-

marily cause respiratory tract infections. Human coronaviruses 229E, NL63, OC43, HKU1 are commonly detected in 5% of hospitalized children with acute respiratory tract infections and in 8% of children in the ambulatory setting [3].

SARS-CoV and MERS-CoV, were responsible for the outbreaks in 2002 and 2012. Both infections were rarely reported in children, and milder than in adults [4].

PATHOGENESIS

SARS-CoV-2 enters the human cells via a clathrin-mediated endocytosis activated by the binding of the SARS-COV-2 Spike S protein with the angiotensin converting enzyme 2 (ACE 2) receptor [5].

ACE2 is expressed in several organs such as lungs, intestine, heart and kidney. The role of ACE2 is to convert angiotensin II into angiotensin (1–7), therefore regulating the homeostasis of renin-

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angiotensin system [6]. Data on rat models shows significantly decreased ACE2 expression with aging [7]. The analysis of genomics, epigenomics and transcriptomics data by Chen et al. [8] showed an age-dependent ACE2 expression decrease suggesting that the higher expression of ACE2 in children may have a protective role in the COVID-19 pathogenesis [8–10].

The interactions between SARS-CoV-2 and the host immune system seem to have a crucial role in the pathogenesis of the disease, partially explaining the lower disease severity in children. Similar to other respiratory RNA virus infections, the innate immune response is activated as soon as SARS-CoV-2 is detected by the immune system. In such early stages, type I Interferons (IFNs—IFN- α and IFN- β) seem to have a leading role not only due to their intrinsic antiviral activity, but also thanks to their capacity of stimulating the activation of immune cells (monocytes-macrophages, natural killer cells) and the production of chemokines and cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α). In addition, type I IFNs play a role in the initiation of adaptive immune response through the activation of dendritic cells and the promotion of the antigen presentation to CD4 T cells, and cross-presentation to CD8 T cells [9].

Based on SARS-CoV and MERS-CoV previous studies and initial findings on SARS-CoV-2, an abnormal immune response rather than the direct viral cytopathic effect appears to be responsible for the pathogenesis, especially in severe cases of infection. Specifically, it seems that a delayed IFN-I response compromises the initial control of the virus leading to a subsequent hyper-inflammatory state characterized by a massive production of cytokines by neutrophils and monocytes-macrophages resulting in a “cytokine storm” [10]. In COVID-19 severe cases, common findings are lymphopenia and massive pro-inflammatory cytokines production, such as interleukin (IL)-2, IL-7, granulocyte colony stimulating factor (G-CSF), interferon- γ inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1- α (MIP-1 α), and TNF- α . This cytokine storm leads to a hyper-inflammatory syndrome similar to that of the haemophagocytic lymphohistiocytosis (HLH) inflammatory state. This seems to cause pulmonary and extra-pulmonary immune-mediated damage leading to Acute Respiratory Distress Syndrome (ARDS) and respiratory failure in the context of multi-organ failure, ultimately leading to shock and death [12,13].

COVID-19 shows a much lower severity in the pediatric population. Children may have a more effective innate immunity activation, probably due to a higher incidence of viral infections, scheduled vaccinations (“trained immunity”) and to constitutionally higher number of lymphocytes, especially natural killer cells [11]. Nevertheless, cytokine storm has been observed in rare cases of critically ill children accompanied by decreased blood CD16+ and CD56+ lymphocytes and increased expression of IL-6, IL-10 and IFN- γ [12].

EPIDEMIOLOGY

As of May 28, 2020, 5,491,678 SARS-CoV-2 related cases (349,190 deaths) have been reported worldwide [13]. Pediatric cases account for a very small portion of the COVID-19 total cases [3]. Data reported by the European Center for Disease Prevention and Control (ECDC) on April 6, 2020, showed that only 1.1% of infected subjects were younger than 10 years old, while 2.5% were in the 10–19 years age group [14]. Age group distribution analysis reported by the Italian National Institute of Health (May 20, 2020) showed that out of 4244 pediatric cases with a microbiological diagnosis of infection, 566 (13.3%) were younger than 2 years old, 745 (17.6 %) aged 2–6 years old, and 2,933 (69.1%) 7–17 years old [15]. Data reported by the United States Centers for Disease

Prevention and Control (US CDC) on May 27, 2020 showed that 3.61% (47,857) of 1,324,111 COVID-19 cases were of children under 18 years. Of these, 5.7–20% were hospitalized and only 0.6–2% were admitted to an ICU. These data highlight the substantially lower percentages of infections in children than in adults [16].

On May 20, 2020, the Italian National Institute of Health reported an overall fatality rate of 13.7%, (median age of death: 81 years with a male/female ratio 3:2). Almost 2/3 of these patients were affected by three or more comorbidities such as arterial hypertension (68.3%), type 2 diabetes mellitus (30.1%) and ischemic heart disease (28.2%) [17]. On March 28, 2020, the US CDC preliminarily reported that patients with pre-existing conditions had a higher risk of COVID-19 severe outcomes [18].

Unlike in adults, COVID-19 risk of death is very low in the pediatric population. Fatalities in children are exceptional. On February 25, 2020, data from the China Center for Disease Prevention and Control (CCDC) showed a fatality rate of 0% in patients younger than 10 years and of 0.2% (one death) in patients aged 10 to 19 years [19]. As of April 8, 2020, ECDC reported 6 pediatric fatalities, worldwide [14]. The last Italian National Institute of Health update reported only one death under 10 years of age and no deaths in the 10–19 years age group [15].

ROUTES OF TRANSMISSION

The main route of transmission of COVID-19 appears to be through droplets ($\geq 5 \mu\text{m}$ diameter), mainly spread by coughing and sneezing. The droplets are capable of reaching limited distances ($< 1 \text{ m}$) [20].

The virus is estimated to remain viable in aerosols droplets for up to three hours. Nevertheless, as reported by the WHO, the airborne route of transmission appears relevant only in aerosol generating procedures such as cardiopulmonary resuscitation, intubation, extubation, bronchoscopy, induction of sputum, nebulization therapies, and non-invasive ventilation. Regarding the SARS-CoV-2 stability on surfaces, both direct and indirect contact transmission seem to be the major routes of infection. The virus has been detected for up to 48 hours on stainless steel and 72 h on plastic surfaces [21]. Fecal-oral transmission has been proven for other CoVs, but further investigation is needed for SARS-CoV-2. However, fecal viral shedding has been reported both in children and adults [22,24,25].

To date, no vertical transmission using clinical or laboratory evidence has been reported. SARS-CoV-2 has not yet been detected in the amniotic fluid, neonatal cord blood, nor in pharyngeal swabs of babies born from infected mothers. Furthermore, there is no evidence of virus excretion in human breast milk. Both vaginal delivery and breastfeeding are therefore recommended [23].

The transmission of infection by asymptomatic children is under investigation: in Italy, virological studies in nasal swabs of both symptomatic and asymptomatic subjects reported a similar viral load [24]. The transmission of infection by asymptomatic children and adults is considered to be less likely by the WHO but still possible, especially in the two days immediately preceding the onset of symptoms [25].

CLINICAL MANIFESTATIONS

In children SARS-CoV-2 infection is characterized by a broad spectrum of clinical manifestations that occur following 1–14 days of incubation (median 5–6 days) [26]. According to the study performed by Dong et al. (2143 children – 34.1% of them microbiologically confirmed cases), 50.9% had mild clinical condition and 38.8% had moderate disease. In most cases, symptoms were mainly

attributable to an upper respiratory tract infection or to mild pneumonia. Severe and critical patients were 5.2% and 0.6% of the group respectively, mostly infants. Asymptomatic children were 4.4% [27].

Lu et al. reported the most frequent symptoms among 171 children affected by SARS-CoV-2 as shown in Table 1 and Table 2. During hospitalization, oxygen saturation <92% was documented in 2.3% of children [28]. Pneumonia when present was generally mild and characterized by cough, dyspnoea and tachypnoea. Pediatric patients with pneumonia also may have developed central cyanosis [or SpO₂ <90%], severe respiratory distress (nasal flaring and pronounced chest retractions), inability to feed, lethargy and decreased level of consciousness or convulsions. ARDS, sepsis and septic shock in children were rare [29]. As previously described in other common pediatric viral infections [30], up to 40% of children with COVID-19 were shown to have a co-infection of as yet undetermined significance [31].

The natural history and clinical manifestations of COVID-19 are different in adults (Tables 1 and 2) [32,35,36]. Recent data from European countries showed that 32% of adult confirmed cases were hospitalized and 2.4% required admission to the intensive care unit [14].

Silent hypoxaemia, characterized by oxyhaemoglobin desaturation without signs and symptoms of respiratory distress, might be present in adults [34]. Many adults also report dysgeusia and anosmia, probably related to the neurotropism of the virus [35].

Recently, there have been several reports of children admitted to hospitals with a clinical picture resembling a combination of Kawasaki disease and toxic shock syndrome. A possible association with SARS-CoV-2 was suggested as RT-PCR or serology returned positive for COVID-19 in some of these children. Therefore, on 1 May 2020, the Royal College of Pediatrics and Child Health proposed the definition of pediatric inflammatory multi-system syndrome temporally associated with SARS-CoV-2 (PIMS-TS). To date, more than 200 suspected PIMS-TS cases are under investigation in Europe and North America. However, ECDC recently assessed the overall risk of PIMS-TS among children infected with SARS-CoV-2 and considered it to be low [36].

Asymptomatic infection in both children and adults has been reported [37,39–41]. Data from Lu et al. showed that 27 out of 171 children (15.8%) had no symptoms at diagnosis [28]. Further investigations are needed to confirm the real impact of asymptomatic COVID-19 infections in children to better understand transmission dynamics.

CHILDREN, COMORBIDITIES AND COVID-19

Pediatric data regarding SARS-CoV-2 infection in patients with underlying chronic conditions are limited. In the Xia et al. single center retrospective study, 2 out of 20 infected children had previ-

Table 1
Comparison of respiratory manifestations between children and adults.

	Child (N = 171) (Lu et al. [28])	Adult (N = 191) (Zhou et al. [32])	Adult (N = 55924) (WHO [33])
Dry cough	48.5%	79%	67.7%
Pharyngeal erythema	46.2%	–	–
Tachypnea	28.7%	29%	–
Rhinorrhea	7.6%	–	–
Nasal congestion	5.3%	–	4.8%
Sputum production	–	23%	33.4%
Shortness of breath	–	–	18.6%
Sore throat	–	–	13.9%
Hemoptysis	–	–	0.9%

Adapted from Lu et al. [28], Zhou et al. [32] and WHO Joint Mission in China [33].

Table 2
Comparison of non-respiratory manifestations between children and adults.

	Child (N = 171) (Lu et al. [28])	Adult (N = 191) (Zhou et al. [32])	Adult (N = 55924) (WHO [33])
Fever	41.5%	94%	87.9%
Fatigue	7.6%	23%	38.1%
Myalgia or arthralgia	–	15%	14.8%
Headache	–	–	13.6%
Chills	–	–	11.4%
Nausea or vomiting	6.4%	4%	5.0%
Diarrhea	8.8%	5%	3.7%
Tachycardia	42.1%	1%	–

Adapted from Lu et al. [28], Zhou et al. [32] and WHO Joint Mission in China [33].

ous cardiac surgery, 4 of 20 had arrhythmias and 1 of 20 had epilepsy [31]. In the Chen et al. study, 2 of 31 children (6.5%) had an underlying disease (asthma; duplicated kidney) [38].

According to US CDC, the most common comorbidities were chronic lung diseases (11.6%), cardiovascular diseases (7.2%) and immunosuppression (2.9%) [16].

Few data are available about SARS-CoV-2 infection in children with cystic fibrosis. From a recent multinational report, only one patient younger than 16 years old has been reported to have tested positive for SARS-CoV-2. However, no evidence of increased COVID-19 severity has been reported among adult cases [39,40].

To date, no data about SARS-CoV-2 infection in children with primary ciliary dyskinesia, bronchopulmonary dysplasia, neuromuscular disorders and other chronic conditions have been reported.

PREGNANCY AND THE NEONATE

Pregnancy and neonatal data are limited. In the Zeng et al. report, only 3 out of 33 neonates who were born from mothers affected by COVID-19 tested positive for SARS-CoV-2 through pharyngeal and anal swabs on day 2 after birth. These neonates had chest radiograph findings suggestive for pneumonia and were diagnosed with COVID-19 early onset. However, severe manifestations were only reported in one neonate, likely due to his severe prematurity associated with asphyxia and sepsis. The other two neonates showed only mild clinical symptoms such as fever and lethargy. All of them recovered [41].

A study on newborns born to SARS-CoV-2 infected mothers showed that perinatal COVID-19 maternal infection may have adverse effects on neonates such as fetal distress, premature labor, respiratory distress, thrombocytopenia and even death. However, no microbiological evidence of neonatal infection was available [42]. The first case of possible vertical transmission has been recently reported. Dong et al. described an asymptomatic infant delivered by cesarean section with COVID-19 negative RT-PCR swab and elevated IgM and IgG antibody levels two hours after birth. No RT-PCR testing of amniotic fluid or placenta was performed [43]. Therefore, it appears crucial to carefully monitor all the newborns with a maternal history of SARS-CoV-2 infection and to further investigate clinical manifestations of COVID-19 in the neonatal period.

DIAGNOSIS

Microbiological analysis

In children and adults, SARS-CoV-2 test is performed on biological samples obtained from a nasopharyngeal swab, tracheal

aspirate or bronchoalveolar lavage, according to the clinical status of the patients. A reverse transcriptase polymerase chain reaction (RT-PCR) assay identifies and amplifies unique sequences of viral RNA (N, E and RdRP genes) [44]. RT-PCR results are back in approximately 4 hours. Specificity approaches 100% [45]. The sensitivity range is wide: 32–93%, related to the types of clinical specimens: it seems to be higher in bronchoalveolar lavage, followed by sputum, nasal swabs, pharyngeal swabs, feces and blood [46].

The use of a nasopharyngeal swab rapid test has been emergently authorized by the FDA. The test identifies the target viral genes ORF1ab and S. Typically results are back in approximately one hour, which has crucial repercussions in the management of isolated patients [47].

In a Chinese study on 10 COVID-19 infected children, RT-PCR analyses were performed on both nasopharyngeal and rectal swabs: the latter persisted positive even after the former turned negative [22]. Therefore, if virus replication ability in the feces is confirmed, the paradigm of the pharyngeal swab as the only test to evaluate treatment effectiveness and importantly, the duration of patient isolation might change. This can have crucial transmission implications. Similar results were obtained from 74 COVID-19 confirmed positive adult patients, where rectal swabs were positive in 55% of patients and persisted positive for an average of 11.2 days (SD 9.2) after nasopharyngeal swabs turned negative [48].

Serological assay (ELISA) detects the presence of specific IgM and/or IgG antibodies against SARS-CoV-2 Rp3 nucleocapsid protein. Previous studies performed on SARS-CoV have shown that IgM antibodies can be identified after 3–6 days from symptom onset while IgG antibodies are detected after 8 days. Further investigations to validate the test and to define the timing of antibody responses are needed [49].

Laboratory tests

In children, routine laboratory blood tests alterations are infrequent and less specific. The white blood cell count may be normal or reduced. Lymphocytopenia is reported to be associated with severe pediatric cases. Normal or elevated C-reactive protein [CRP] serum levels are reported. Unless bacterial co-infection is present, serum procalcitonin is not elevated. In patients with severe disease, liver function tests can also be elevated (Table 3) [3,31].

Table 3
Comparison of laboratory findings between child and adult.

Laboratory tests (Unit)	Child (Lu et al. [28]) (N = 171) median (IQ)	Adult (Zhou et al. [32]) (N = 191) median (IQ)
White Blood Cell Count ($\times 10^3/\text{mm}^3$)	6.8 (5.5–8.2)	6.2 (4.5–9.5)
Lymphocyte count ($\times 10^3/\text{mm}^3$)	(2.2–4.4)	1.0 (0.6–1.3)
Hemoglobin (g/dL)	12.6 (11.8–13.5)	12.8 (11.9–14.0)
PCT (ng/mL)	0.05 (0.04–0.08)	0.1 (0.1–0.1)
C-Reactive protein (mg/L)	4.0 (1.3–8.0)	–
Lactate dehydrogenase (U/L)	246 (207–305)	300 (234–407)
Alanine aminotransferase (U/L)	15 (11–27)	30.0 (17–46)
Creatinine ($\mu\text{mol/L}$)	33.9 (26.1–42.7)	>133 (4%)
Blood Urea Nitrogen (mmol/L)	4.1 (3.3–4.8)	–
Fibrinogen (g/L)	2.1 (1.8–2.7)	–
D-Dimer (mg/L FEU)	0.2 (0.2–0.4)	1.6 (0.8–6.4)
Prothrombin time (s)	10.9 (10.6–11.3)	11.6 (10.6–13.0)
Thrombin time (s)	18.4 (17.7–19.2)	–

Adapted from Lu et al. [28] and Zhou et al. [32].

Unlike in children, an absolute lymphocyte count reduction is observed both in adults admitted to the ICU and those with less severe disease (non-ICU admitted adults) (median $0.8 \times 10^3/\text{mm}^3$; normal range $1.1\text{--}3.2 \times 10^3/\text{mm}^3$). Total white blood cells and absolute neutrophil counts are higher in the deceased patients than in survivors. Conversely, the number of lymphocytes appears to be lower in deceased adults.

D-dimer, serum urea and creatinine have been described to be more elevated in adult patients who died, especially in those with advanced disease stages (7 days or more after disease onset). In addition, there is evidence of substantial elevation in D-Dimer and lactate dehydrogenase [LDH] serum levels in ICU patients compared to others [50].

Cardiac troponins, myoglobin, CRP and IL6 have been reported to be higher in patients who died than in those who were discharged [51].

Imaging

Chest radiograph, lung ultrasound and High-Resolution Computed Tomography (HRCT) of the chest have been routinely used as imaging techniques in COVID-19 patients.

Chest radiograph typical findings include infiltration of the bronchovascular bundles, reduction of transparency and widespread patchy consolidation. Lung ultrasound usually shows thickening and irregularities of the pleural line, subpleural consolidations, converging B lines up to a white lung image in most severe cases, with disappearance of the A lines [52].

Chest HRCT reveals the presence of ground glass opacities, consolidation areas (multi-lobe and sub-pleural), local or bilateral patchy shadowing and reticular patterns with interstitial thickening, crazy paving and rarely nodules [35,53].

In children, although clinical features are more attenuated than in adults, HRCT alterations may be present. A study performed on 20 COVID-19 pediatric patients showed that unilateral lung lesions were present in the 30% of cases and bilateral lesions in the 50% of patients, even at the early stage of the disease. Subpleural lesions were present in all cases; 50% presented consolidation with a surrounding halo sign, considered a typical sign in pediatric patients; 60% ground-glass opacities; 20% reticular infiltrations; and 15% thin nodules. Residual fiber strips may be present during the convalescence phase [31].

In 171 HRCT obtained from children with COVID-19, Lu et al. reported a 32.7% prevalence of ground-glass opacities, 18.7% of local patchy shadowing, 12.3% of bilateral patchy shadowing and 1.2% of interstitial abnormalities; 27 out of 171 patients (15.8%) did not have any symptoms of infection or radiological findings of pneumonia [28] (Table 4).

THERAPY

Management of children affected by COVID-19 involves both support and pharmacological therapy and derives from experience in adults [54]. Antipyretic drugs are the mainstay of therapy for children with mild clinical picture, along with supportive care. Patients with respiratory distress or hypoxaemia benefit from respiratory support and low flow nasal oxygen. High-flow nasal oxygen and non-invasive ventilation can be considered in selected patients. In children with progressive respiratory failure and ARDS, invasive mechanical ventilation is indicated. If lung protective ventilation strategies fail, extracorporeal membranes oxygenation (ECMO) should be considered [29].

To date, no specific SARS-CoV-2 antiviral drug with proven efficacy in children is recommended [29]. Empiric therapy with lopinavir/ritonavir, nebulized IFN I or associations is reported [55].

Table 4

Comparison of CT findings between child and adult.

Abnormalities on high resolution CT of the chest	Child (N = 171) (Lu et al. [28])	Child (N = 20) (Xia et al. [31])	Adult (N = 191) (Zhou et al. [32])	Adult* (N = 975) (Guan et al. [53])
Seen	–	–	–	86.2%
Not Seen	15.8%	–	–	13.8%
Ground-glass opacity	32.7%	60%	71%	56.4%
Local patchy shadowing	18.7%	–	–	41.9%
Bilateral patchy shadowing	12.3%	–	75%	51.8%
Interstitial abnormalities	1.2%	–	–	4.4%
Fine mesh shadow	–	20%	–	–
Consolidation	–	50%	59%	–
Nodules	–	15%	–	–

Adapted from Lu et al. [28], Xia et al. [31], Zhou et al. [32] and Guan et al. [53].

* Data may include up to 9 patients aged 0–14 years old out of 975 total cases.

CONCLUSIONS

COVID-19 shows a milder clinical course in children than in adults. A significantly lower percentage of children develop a severe or critical illness and death is exceptional. Children may present non-specific viral infection symptoms suggesting the paramount importance of accurate differential diagnosis with typical pediatric clinical conditions such as upper respiratory tract infections, fever of unknown origin, viral or bacterial pneumonia, bronchiolitis, gastroenteritis, and asthma flares [56]. As in adults, underlying cardiovascular disease seems to be the most frequent comorbidity in severe pediatric COVID-19 confirmed cases. Further investigations are needed to assess SARS-CoV-2 infection impact on children.

DIRECTIONS FOR FUTURE RESEARCH

- Further investigations are needed to confirm the real impact of asymptomatic COVID-19 infections in children to better understand the transmission dynamics.
- Newborns with a maternal history of SARS-CoV-2 infection should be carefully monitored to further investigate the clinical manifestations of COVID-19 in the neonatal period.
- Preclinical and clinical studies focused on COVID-19 transmission, pathogenesis and host immune response are needed.
- Ongoing clinical trials encompassing specific antiviral and immunomodulating drugs will provide useful tools to fight SARS-CoV-2 pandemic.

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