Acta Biomed 2020; Vol. 91, N. 2: 172-176 DOI: 10.23750/abm.v91i2.9586

Novel coronavirus infection and children

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Summary. *Background and aim:* Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Its outbreak in many states of the world, forced the World Health Organization (WHO) to declare a pandemic. Currently, COVID-19 has infected 1 991 562 patients causing 130 885 deaths globally as of 16 April 2020. The aim of this review is to underline the epidemiological, clinical and management characteristics in children affected by COVID-19. *Methods:* We searched Pubmed, from January to April 2020, for the following search terms: "COVID-19", "children", "SARS-COV2", "complications", "epidemiology", "clinical features", focusing our attention mostly on epidemiology and symptoms of COVID-19 in children. *Results:* Usually, infants and children present milder symptoms of the disease with a better outcome than adults. Consequently, children may be considered an infection reservoir that may play a role as spreader of the infection in community. (www.actabiomedica.it)

Key words: COVID-19, SARS Cov-2, children, symptoms

Background

In the last few months, some cases of pneumonia of unknown aetiology were identified worldwide. The first cases were detected in Wuhan, China.

Collecting the samples of these patients, scientists have discovered a new coronavirus (COVID-19) that is now known as the cause of the disease named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). By 16 April 2020, 1 991 562 cases have been confirmed and 130 885 deaths have been reported globally (2). Transmission takes place through respiratory droplets or contact with symptomatic cases. Transmission from asymptomatic cases, especially children, seems to have also an important role (3). Moreover, SARS-CoV-2 RNA has been detected in stool of some patients, so faecal-oral transmission could be possible (4).

The most common symptoms in adults are fever, dry cough, sore-throat, myalgia, fatigue and in severe cases (usually older patients with comorbidities) acute respiratory distress syndrome (ARDS) with lung failure or severe coagulation dysregulation as a result of an uncontrolled inflammation (5). According to the experience of Wuhan, children usually present milder symptoms.

Pathogenesis

The initial viral replication occurs in mucosal epithelium of upper respiratory tract and later in lower respiratory tract and gastrointestinal mucosa. COVID-19, like others coronavirus, uses a specific receptor to infect human cells. This receptor is angiotensin-converting enzyme 2 (ACE2) and it's a functional receptor that is widely expressed in many organs, especially in lungs, but also in heart, kidney, vascular endothelium and intestine (6).

Severe complications of COVID-19 infections are ARDS with consequently lung failure, immune disfunction and coagulation disorders. The rapid viral replication may cause massive epithelial and endothelial cell death, stimulating the production of pro-inflammatory cytokines and chemokines. This 'cytokine storm' with an uncontrolled inflammation is considered a leading cause of fatality (7).

Clinical manifestations

Current data show that children with SARS-COV2 usually belong to cluster family cases. Infected children may appear asymptomatic or present mild symptoms like cough, fever, nasal congestion. In addition, gastrointestinal symptoms such as diarrhea, nausea, vomiting, abdominal discomfort are more frequent in children than in adults.

Despite mild respiratory symptoms with interstitial pneumonia, radiographycally assessed, only few cases have needed intensive care because of respiratory complications (8).

A recent study analysed 44,672 laboratory-confirmed cases across China and reported that only 416 (0.9%) were less than 10 years of age and 549 (1.2%) between 10 and 20 years of age. According to this study, children usually have a good prognosis and they recover within 1-2 weeks after the onset of the disease (9).

Data provided by The Centers for Disease and Control in USA are stackable. Only 5.7% of children have been hospitalized because of the appearance of dyspnoea. According to this report, children aged < 1 year and children with comorbidities have presented the highest percentage of complications. The most common underlying conditions have been cardiovascular disease, chronic lung disease especially asthma and immunosuppression. However, compared with the adult cases, the severity of children's COVID-19 cases has been milder (10).

At variance, in Spain around 60% of children affected by COVID-19 have been hospitalized for mild symptoms and 9.7% of these patients have requested intensive care because of the comparison of respiratory complications. Only one patient had recurrent wheezing as previous condition. No patients died. The Spanish series agrees with those previously published except for the number of admissions. This probably depends on the fact that the percentage of children tested have been higher than in other countries and it could be associated with different hospitalization criteria (11).

Children usually are asymptomatic or with few accompanying symptoms. Fever and mild cough are common symptoms at onset of the disease. Other symptoms at presentation include sore throat, nasal congestion and rhinorrhea, diarrhea. For mild case, fever is brief and resolved rapidly. Usually children do not need admission in hospital. Only a small percentage of all the patients have been in need of intensive care and usually they have been children with comorbidities or children aged < 1 year (12).

On the basis of these studies and clinical experience, COVID-19 vertical transmission hasn't been detected but further studies are needed. The infection of 2019-nCoV during pregnancy seems less serious compared to infection of SARS-COV and MERS-COV with no cases of maternal death, or perinatal death (13-15). Usually, neonates have evolved favourably. There are no contraindications to breastfeeding if mothers observe proper hygiene rules (16).

Diagnosis

In adults, it is usually possible to find a decreased lymphocyte count and increased liver enzymes and muscle enzymes. Many patients present elevated C-reactive protein levels and erythrocyte sedimentation rates, and normal procalcitonin levels. With the worsening of the disease, it is possible to find also a high D-dimer level with a dysregulation of the coagulation. Unfortunately, there are limited data on children in literature. According to a study published by Brandon MH et al., only few infants experienced lymphopenia. Usually in children the leukocyte count is normal and CPR and procalcitonin sometimes are elevated. The lack of significant lymphopenia may depend on the relative immaturity of the children's immune system (17,18) (Table 1).

Currently, the better method to detect RNA the virus through RT-PCR is to collect samples from

Table 1. Laboratory findings in children. Unlike adults, children usually don't present lymphopenia and the leukocyte count is normal. In a small percentage of children, it is possible to find increased CRP and LDH[17,18].

Laboratory tests	
Leukocytes count	Usually normal. Lymphopenia is uncommon in children.
CRP	Normal or increased
LDH	Normal or increased
Liver and cardiac function	Usually normal
Coagulation function	Usually normal

throat swabs (better using nasopharyngeal swab in children), sputum, or lower respiratory tract secretions. Another important technique for COVID-19 diagnosis is using imaging technology (CT scan or chest X-ray). In fact, chest images show a characteristic distribution with interstitial changes which are initially in the lung periphery and further deteriorate to small nodular ground glass opacities (19,20) (Figure 1).

In infants and children, it may be also useful to make lung ultrasound to avoid radiation and to obtain images directly at patient bedside. Lung ultrasound clearly document signs suggestive for interstitial-alveolar damage showing bilateral, diffuse pleural line abnormalities, subpleural consolidations, white lung areas and irregular vertical artefacts (21) (Figure 2).

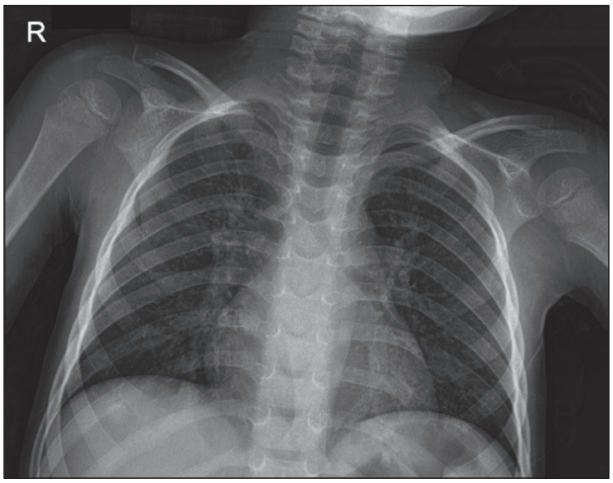

Figure 1. Chest X-ray of a 4-year old patient with Covid-19, admitted for high fever and dry cough. Reticular interstitial densities and bilateral lung involvement are shown.

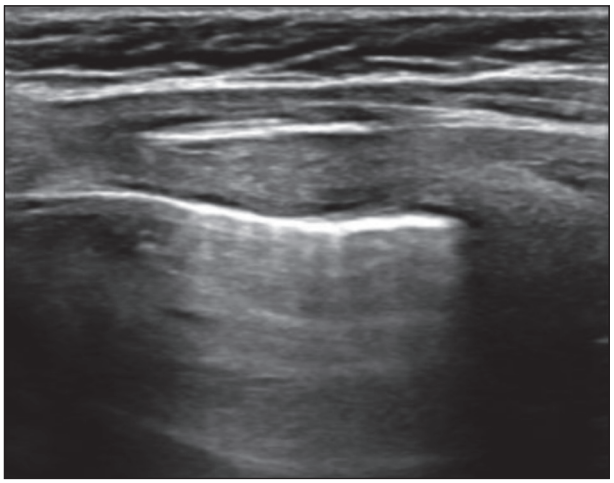

Figure 2. Lung Ultrasound of a 6-year child with Covid-19 and admitted for fever and cough. Vertical artifacts, named B lines, are shown, with increased thickness of pleural line.

Severity of infection

On the basis of the Chinese experience, the severity of COVID-19 disease in children is defined by clinical features, laboratory testing and chest radiograph into 5 groups (22) (Table 2).

Management and treatment

Actually, there aren't any drug trials specific for the children and adolescents.

According to the Chinese management protocol, the recommended treatment is usually supportive. In severe cases, when there is a respiratory involvement characterized by dyspnoea, central cyanosis and an oxygen saturation of less than 92%, they suggest to start oxygen therapy and antibiotics for bacterial superinfections (23).

Table 2. Severity of Covid-19 infection in children. This classification has been formulated on the basis of Chinese data and experience to standardize prevention and management of 2019-nCoV infections in children[22].

Severity of infection	Clinical and radiological features
Asymptomatic	No clinical symptoms and signs, normal chest imaging, with positive 2019-nCoV nucleic acid test.
Mild	Symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose and sneezing. Some cases may have nausea, vomiting, abdominal pain and diarrhoea.
Moderate	Pneumonia with fever and cough (mostly dry cough, followed by productive cough) without hypoxemia. Some cases may have no clinical signs and symptoms, but chest computed tomography shows typical lung lesions.
Severe	The disease progresses with dyspnoea and central cyanosis. Oxygen saturation is <92%.
Critical	Children and particularly adolescents and young adults can progress to respiratory failure and shock or other organs failure (encephalopathy, acute kidney injury, heart failure, coagulation dysfunction) .

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The antiviral treatment and gamma globulin treatment are currently disputed (24).

Conclusion

COVID-19 infections remain undiagnosed in children because they often present mild symptoms. Fortunately, according to literature only a small proportion of children become critically ill. Children represented 2% of diagnosed cases in China (25), 1.2% of cases in Italy (26), and 1.7% of COVID-19 positive cases in the US (27).

The prognosis seems to be good with a recovery in 12-14 days for the majority of the reported cases worldwide. Only a death has been reported in a study of Lu X and Zhang, because of a secondary intussusception in a 10 month old child (28). Another report has showed that of the 2135 paediatric patients included in the study, only 1 child died (14-year-old boy from Hubei province) and most cases were mild (12).

Children are often exposed to viral infections so it is possible that they have higher levels of antibody against virus than adults. Another possible explanation is that children may be protected against SARS-CoV-2 because ACE-2 is less expressed at a younger age. Moreover, children's immune system is still developing and may respond to pathogens differently from adult immune system.

Despite all, asymptomatic cases may have a lower transmission rate but remain a great source of infection.

The determination of the potential cluster transmission is very important for an epidemiological survey and to develop adequate measures for a better pandemic control.

Paediatricians are responsible for testing patients on the presence of signs and symptoms compatible with COVID-19, in order to protect vulnerable people, such as elderly and people with comorbidities.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Received: 18 April 2020
Accepted: 20 April 2020
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