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Coronavirus Disease 2019 in Children: An Invisible Threat Which We Cannot Ignore*

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The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus which emerged in December 2019 in Wuhan, Hubei Province, China. This highly pathogenic virus has rapidly spread around the world resulting in a global pandemic called coronavirus disease 2019 (COVID-19) (1). Although some subjects with SARS-CoV-2 infection may remain asymptomatic, the clinical picture is generally associated with upper respiratory tract infections, with flu-like signs and symptoms including fever, persistent dry cough, fatigue, and headache (2). However, some patients (mostly adults) may suffer severe forms characterized by lower respiratory tract infections, pneumonia, dyspnea, multiple organ failure, and even death (3). Sadly, as of April 6th, COVID-19 has already caused over 1.3 million confirmed positive cases and over 74,000 deaths worldwide. Italy has suffered the highest lethal toll so far, with over 16,000 deaths (1, 4). Interestingly, newborns and children seem to be relatively spared of severe symptoms of COVID-19, even though the reasons for such phenomenon remain unclear (5, 6).

Nonetheless, severe cases may occasionally occur also in the pediatric population and few deaths have been reported from China and elsewhere (7).

*See also p. 662.

Key Words: child; coronavirus disease 2019; intensive care; severe acute respiratory syndrome coronavirus-2

Dr. Biban received funding from Chiesi Pharmaceutical and Getinge.

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DOI: 10.1097/PCC.0000000000002431

In this issue of *Pediatric Critical Care Medicine*, Ong et al (8) provide a comprehensive narrative review on the impact and implications of COVID-19 in children, focusing on the management of those most severely affected, as well as providing some practical suggestions for pediatric intensive care clinicians to prepare should COVID-19 become more virulent in children. We are still in the early stages of understanding this disease in children and appropriately the authors raise a number of issues which warrant further extensive research. Indeed, the scientific community is committed to better understanding of the clinical course of children with COVID-19, particularly of those who may need intensive care. However, very scant data are available on specific interventions which may improve outcomes in the sickest children. Current information are mostly derived from the adult experience and several important questions pertaining to critically ill children remain unanswered.

HOW MANY CHILDREN WITH COVID-19 INFECTION MAY REQUIRE INTENSIVE CARE?

In adults, about 5% of subjects infected by SARS-CoV-2 require admission in ICU (9). Among hospitalized patients, the frequency of ICU admission may increase up to 25–30% (2). Conversely, we have little information on severely and critically ill children with COVID-19. According to the largest series reported so far, by Dong et al (7), only two children out of 2,143 required intensive care. Thus, the frequency of critically ill children could have been about 0.4% if considering confirmed positive cases only, or 0.6% if considering the whole population, including suspected and confirmed cases.

In another small series, reporting on eight severe pediatric cases with coronavirus in Wuhan, only two patients were mechanically ventilated and none died (10). Even if the overall frequency of severe cases was not reported, by analyzing a

population of 171 children with proven SARS-CoV-2 infection, enrolled nearly in the same period and in the same hospital (11), it could be estimated an frequency of about 1.2% of children requiring invasive mechanical ventilation.

In Italy, until April 2, 2020, only 84 out of 1,078 subjects (7.8%), less than 18 years old and with laboratory-confirmed SARS-CoV-2 infection, were hospitalized. Admission rate varied from 11.5% to 3.9% in the age subgroup 0–1 years and in the subgroup 7–17 years, respectively (12). Even though official reports were not available at the time of writing, unpublished data from the Italian PICU Network (TIPNET) indicate that less than five children did require intensive care interventions, such as invasive mechanical ventilation, at least so far. Thus, from a rough estimate in excess, one could expect an frequency of critically ill children as low as 0.4–0.5%, comparable to the figures reported by Dong et al (7). However, the situation may be different in low- and middle-income countries where social distancing is difficult and malnutrition, tuberculosis and HIV infection is more common.

WHAT ABOUT RISK FACTORS AND SPECIFIC BIOMARKERS TO EARLY PREDICT OR IDENTIFY MOST SEVERELY ILL CHILDREN WITH COVID-19?

Early detection of children who are likely to deteriorate and suffer critical illness would be useful for clinicians, as a prompt admission to ICUs would allow advanced monitoring and potentially useful treatments.

In adults, patients who required ICU care are generally older and more likely to have underlying comorbidities, including hypertension, diabetes, cardiovascular disease, cerebrovascular disease, or malignancy (2, 9). At present, no obvious risk factors for children have been identified. Plausibly, pediatric subjects with severe comorbidities should have a higher risk for more complicated COVID-19 courses, but evidence to confirm such an assumption are still lacking.

Similarly, laboratory findings do not seem to be helpful in discriminating children most severely affected by COVID-19, as a consistent pattern of altered laboratory values has not been identified yet (13). For instance, severe and persistent lymphopenia has not emerged as a specific marker for a complicated COVID-19 course in children, differently from adults (2, 11, 13). Similarly, other markers do not seem either specific or predictive of adverse outcome in children (13).

ARE THERE SPECIFIC THERAPEUTIC INTERVENTIONS FOR CRITICALLY ILL CHILDREN WITH COVID-19?

Many antiviral and other agents are being used in adult patients with COVID-19, including remdesivir, lopinavir/ritonavir, tocilizumab, chloroquine, and even traditional Chinese therapy. Although several clinical trials are being conducted, results are unavailable and current data situation does not allow firm recommendations for any particular treatment. At present, management is as per best supportive care for any respiratory disease. Similar considerations may be applied to children as well, with the awareness that conducting clinical intervention trials could be even more difficult in this population, given the paucity of severe cases observed so far.

The authors must be congratulated on being able to provide very useful information for clinicians who must deal with critically ill children with COVID-19, particularly for those who are still in an early organizational phase. In addition, Ong et al (8) identified several knowledge gaps between evidence and practice in the management of the sickest pediatric patients with COVID-19 which is a good start in our collaborative efforts.

Several large collaborative pediatric studies are on the horizon, as intensivists from all over the world are responding in an unprecedented way and working together as a scientific community to find smart solutions to fight against this dreadful virus while waiting for a safe and effective vaccine. Finally, not to be forgotten, leader groups should play an essential role for actively supporting our colleagues and other healthcare providers working in low- and middle-income countries (14), where pediatric populations may be more vulnerable to this pandemic.

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