Coronavirus Disease 2019 in Children
Is It Really Mild?

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Abstract: Coronavirus disease 2019 pandemic has spread rapidly to the world. The disease can vary from mild cases to severe respiratory distress; this may increase rapidly and overwhelm the pediatric intensive care units. Lately, there have been various reports about a de novo multisystem inflammatory syndrome in children or pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 infection. We classified the disease into 2 spectrums: the acute phase in severely ill patients and the postinflammatory phase. Neither of them could be classified as mild because there is enough evidence that supports a wide range of complications. The goals of this brief review were to summarize available literature and to give some awareness about the current status of the coronavirus disease 2019 in the severely ill patients during the active phase and postinflammatory phase.

Key Words: COVID-19, SARS-CoV-2, multisystem inflammatory syndrome in children, Kawasaki-like syndrome, pediatric complications

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Key Points: We classified the infection into 2 spectrums: (1) the acute phase and (2) the multisystem inflammatory syndrome in children/pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 infection phase. Neither of them could be classified as mild because there is enough evidence that supports a wide range of complications, systemic and organ specific. Besides, there is no current specific management.

On December, 31, 2019, the Wuhan Municipal Health Commission[1] alerted about cases of pneumonia of unknown etiology in Wuhan city, Hubei province, China. Since then, coronavirus disease 2019 (COVID-19) pandemic, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly to the world.

Pediatric population usually manifests SARS-CoV-2 as mild and requires only symptomatic treatment,[2] relatively few pediatric COVID-19 cases were hospitalized (5.7%–20%), and only 2% were admitted to pediatric intensive care units (PICUs).[3] However, the disease can vary from mild cases to severe respiratory distress[4]; this may increase rapidly and overwhelm the PICUs.[5] Lately, there have been various reports about a de novo multisystem inflammatory syndrome in children (MIS-C); also called pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS).

There are limited data regarding the clinical characteristics and risk factors associated with a more severe illness in children. There are few reports about the postinflammatory phase of the COVID-19 in this specific population. The main goal of this brief review is to gather the available literature about the current status of the COVID-19 in the pediatric population, with a special consideration in severely ill patients in the acute phase and postinflammatory phase.

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METHODS

In this review article, we conducted a search on MEDLINE via PubMed with the MeSH terms: "COVID-19" OR "SARS-CoV-2" OR "2019 novel coronavirus" in combination with the terms: "children" OR "pediatric"; "de novo multisystem inflammatory syndrome in children"; "pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection." All of the included articles were published between January 1, 2020, and June 30, 2020. We also searched the official Web sites of the World Health Organization (https://www.who.int/), US Centers for Disease Control and Prevention (https://www.cdc.gov/), and European Centers for Disease Control and Prevention (https://www.ecdc.europa.eu/en). Finally, we made a secondary bibliographic research based on each article to further include studies or reports not priorly identified.

CLINICAL FEATURES OF ACUTE COVID-19

Most pediatric cases are asymptomatic or mild[2,6]; however, it is essential to report the cluster of patients who develop severe illness. According to a prediction made, the severe cases will require respiratory support and transfer to a PICU; this could overwhelm the national health system of any country.[5] The prevalence of severe and critical cases in children ranges from 1% to 8%,[7–10] but even rates as high as 50% have been reported.[11] Pediatric intensive care unit admission occurs only in a quarter of severe children patients,[12,13] and mortality reports are scarce.[8,9,13,14]

Infants (younger than 1 year) and adolescents were more likely to present severe outcomes,[8,15] became critically ill, and required hospitalization[15]; most PICU patients were 11 years or older.[12]

Comorbidities may predispose pediatric patients to severe illness; half of severe cases[14,15] and a quarter of critically ill cases[9] presented an underlying disease. Reported comorbidities were asthma, congenital heart disease, bilateral hydronephrosis, intussusception, neurologic, hematologic, and oncologic pathology.[10,15–17]

At admission, the most frequent symptoms were polypnea, cough, and fever (classical respiratory presentation of COVID-19).[14,15,18] Before PICU transfer, children tend to develop shortness of breath.[12]

Acute respiratory distress syndrome (ARDS) is the main complication reported in adults.[19,20] In pediatric patients, ARDS developed in 3 quarters of patients admitted to the PICU[12,21] and the main predictor was shortness of breath.[12,22] Almost all critically ill patients require respiratory support such as mechanical ventilation, bilevel positive airway pressure, or noninvasive ventilation short after PICU admission.[14,15,22] Oxygen saturation of less than 95% might predict the need of high-flow oxygen requirement after admission.[7] Some patients have required the use of the extracorporeal oxygenation membrane.[11]

Renal injury is rare in children, and 98% of pediatric cases presented normal renal function.[9] Acute kidney injury is more

common in the patients who required PICU, as shown by Chao et al[12] who reported acute kidney injury in 5 of 33 patients admitted to the PICU, of which 4 resolved with volume resuscitation; only 1 patient required renal replacement therapy for severe fluid overload associated with septic shock and multiorgan failure.

The characteristics of blood panels in COVID-19 severely and critically ill pediatric patients reported high markers of inflammation: C-reactive protein, procalcitonin,[9,12] leukocytes, interleukin 6 (IL-6), D-dimer,[18] and N-terminal pro-brain-type natriuretic peptide.[23,24] Other alterations such as hyponatremia and abnormal liver function demonstrated by increased alanine aminotransferase and high levels of serum lactic dehydrogenase have been reported but not associated with any outcome.[10,25] The total blood cell count usually remains normal despite the disease severity.[16,25]

THE MIS-C/PIMS-TS TIMELINE

On April 7, 2020, Jones et al[26] described the first case report of an infant diagnosed with Kawasaki disease (KD) who also tested positive for SARS-CoV-2.

Later, on April 27, 2020, the United Kingdom Pediatric Intensive Care Society[27] alerted about an increase of KD in children testing positive for SARS-CoV-2.

On May 1, 2020, the Royal College of Pediatrics and Child Health[28] published a case definition of the previous reports of Kawasaki-like disease naming all those cases as PIMS-TS.

On May 4, 2020, the New York City Health Department[29] also identified 15 pediatric patients with multisystem inflammatory disease potentially associated with COVID-19.

Subsequently, on May 6, 2020, Riphagen et al[30] reported a cluster of children with multiorgan involvement similar to KD shock syndrome, but most of them did not meet all the definition criteria for KD.

After these findings, in Italy on May 13, 2020, Verdoni et al[31] compared the incidence of KD before and after COVID-19 pandemic, which was 0.3 cases per month and 10 cases per month, respectively. The recently diagnosed children developed an atypical and more severe KD: hypotension, shock, and abnormal echocardiographic finding in 60% of their patients. Almost all patients were initially negative for SARS-CoV-2 polymerase chain reaction, but they tested positive for SARS-CoV-2 immunoglobulin G (IgG) antibodies and a third were also positive for IgM.

On May 14, 2020, the Center for Disease Control and Prevention labeled all these reports of suspected KD as MIS-C.[32] Until May 15, 2020, more than 300 children were under active surveillance because of suspected MIS-C/PIMS-TS in Europe and North America.[33]

The MIS-C/PIMS-TS Clinical Features

Although there are no specific reports about the age at which MIS-C/PIMS-TS is usually developed, some authors have found that the median age is 10 years.[11,34,35] These patients tend to be older and have no comorbidities nor respiratory failure as common as reported in active SARS-CoV-2 infection.[34,36]

In the literature, the most frequently reported clinical signs are as follows: cheilitis, cervical lymphadenopathy, meningism, unrelenting fever (38°C–40°C), limbic sparing conjunctivitis, prominent tongue papillae, and peripheral edema in the hands and feet.[11,26,30,37] On admission, gastrointestinal symptoms, described and diarrhea or abdominal pain, occur more frequently than respiratory symptoms.[37–39] Erythematous rashes are greatly described as one of the most common signs, being discovered in up to 52% of patients.[11,22,35] Among the complications found, the most severe was shock probably as a consequence of an unspecified arrhythmia or inflammatory capillary leak.[30,38,40]

Because of the mechanism by which MIS-C/PIMS-TS is produced, there are many inflammatory biomarkers that are usually at high levels, such as the following: C-reactive protein,[36] erythrocyte sedimentation rate, ferritin,[27] procalcitonin, leukocytosis with a predominance of neutrophils, lymphopenia, and anemia.[11,35,41]

It has been found that the proinflammatory cytokines play an important role and usually can be found greatly increased: IL-6, IL-1, IL-2, IL-7, IL-8, and IL-10.[21,22,38]

Clotting and cardiac markers are also described at abnormal levels, specially prothrombin time, D-dimer,[42] troponin I, and N-terminal pro-brain-type natriuretic peptide.[11,22,37,40] Other studies reported less common alterations such as hyponatremia, hypoalbuminemia,[26,40] thrombocytopenia, and hypertriglyceridemia.[15,22,41] Liver enzymes have been reported at unusual levels with moderate increases in serum alanine transaminases, γ-glutamyltransferase, and aspartate transaminases.[22,35,41]

Cardiovascular alterations in the setting of MIS-C are often measured by imaging, especially echocardiography. The main findings are left ventricular hypokinesis,[37] reduced ejection fraction,[31,34,37] left ventricular dysfunction (which resolved at discharge),[36] aortic regurgitation,[22] myocarditis,[34,36] pericarditis,[34] enhanced coronary vessel,[30,38,41] dilatation of the coronary arteries (mainly affecting the left main stem),[11,37,38,40] and coronary aneurysm.[11,31,37]

Besides the functional impairment, there are also electrical manifestations in the electrocardiogram, which manifests as nonspecific ST/T-wave abnormalities,[38] as well as first- and second-degree atrioventricular blocks with frequent supraventricular ectopic beats.[11] Other less common findings are dysrhythmias: nonsustained ventricular tachycardia,[11] sinus bradycardia,[38] and atrial fibrillation.[11]

The worldwide literature about the pathophysiology of MIS-C or PIMS-TS supports the main theory of an enhanced and delayed immune-mediated response[11,38] in the older pediatric population.[34,43] Xu et al[44] suggested that the mechanism by which inflammatory cytokines and cells gather in the endothelium is probably mediated via angiotensin-converting enzyme 2 receptors, causing an indirect lesion.[22]

Multisystem inflammatory syndrome in children usually arises within 3 to 5 weeks after the acute infection. Children were usually exposed to a previously infected family member.[39] Besides that, previous authors have further supported that theory with geographical evidence,[45] empirical management[43] (primarily targeting inflammatory cytokines such as IL-1 and IL-6), and serological testing.

In the cases who were initially negative to the SARS-CoV-2 polymerase chain reaction, serologic testing at the memento or within 3 to 5 weeks demonstrates high levels of IgG, followed by moderate increases in IgM and even IgA.[31,35,36,46] Such evidence supports the immune-mediated mechanism, but there is still unclear consensus on which is the optimal type of specimen, or diagnostic test, nor the correct testing sequence.[35]

CONCLUSIONS

In this brief review, we summarized the current literature about SARS-CoV-2 infection in the pediatric population. We classified the infections into 2 spectrums: the acute phase and the MIS-C/PIMS-TS phase. Neither of them could be classified as mild because there is enough evidence that supports a wide range of complications, systemic and organ specific. Besides, there is no current specific management.

Severely ill patients in the active phase have no specific group age, but they are usually younger than 1 years or adolescents, have a classical COVID-19 presentation with a predominance

of respiratory symptoms, have underlying diseases, and ARDS is the most frequently reported complication.

The main characteristics of MIS-C/PIMS-TS remain unclear, but the main theory about pathophysiology is a hyperinflammatory response due to a prior SARS-CoV-2 infection. The patients are usually older, complain of gastrointestinal symptoms, have no comorbidities, and develop cardiac alterations.

Further research is needed to comprehend why some patients present worse prognosis, what are the risk factors related with a hyperinflammatory response, and management options to counter it.

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