

SARS-COV-2 Infection in Children and Pediatric Inflammatory Multisystem Syndrome

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Received: June 23, 2020; **Published:** July 10, 2020

Epidemiological studies have shown that children appear to be less affected by COVID-19. From the latest data, 2135 pediatric patients with COVID-19 were reported to the Chinese CDC [1]. Of the patients, 728 (34.1%) were identified as laboratory-confirmed cases, and 1407 (65.9%) were suspected cases. The median age of all patients was 7 years (interquartile range: 2 - 13 years). There was no statistically significant difference in the number of pediatric patients between boys and girls. Regarding the severity (including both confirmed and suspected cases), 94 (4.4%), 1088 (51.0%), and 826 (38.7%) cases were diagnosed as asymptomatic, mild, or moderate, respectively; and totally accounted for 94.1% of all cases. Only 1 child died.

According to the U.S. CDC [2], among nearly 150,000 cases of COVID-19 in the U.S. between February 12 and April 2, only about 2,500, or 1.7%, were in children.

Only 2.1% of all laboratory-confirmed COVID-19 cases reported to The European Surveillance System (TESSy) were in the age group between 0 and 14 years of age [3]. Since the outbreak began in Italy, there have been 1,919 SARS-CoV-2 coronavirus infections among children aged 0 - 9 (mostly with mild or symptom-free effects) of 0.8% of the total, while in the 10 - 19 age group they are 3,442, or 1.5% of the total. To date, there have been 4 deaths and no intensive care of patients in the 0 - 20 age group. In an Italian report [4], children younger than 18 years of age who had Covid-19 composed only 1% of the total number of patients; 11% of these children were hospitalized, and none died.

In general, coronavirus viruses are responsible for about one-five percent of viral pneumonia, and pneumonia is still the leading direct cause of infant mortality globally, with about 800,000 deaths per year among children aged 0 to 5 years (153,000 among infants under one month old), equal to one death every 39 seconds [5]. Pneumonia is a killer disease of childhood because children, along with the elderly and chronically ill, are the most vulnerable to acute respiratory infections. Infants and children under 2 years of age are particularly at risk, due to the physiological immaturity of the immune system. Immunodepressed children are at particularly high risk.

However, in the ongoing COVID-19 outbreak, there are far fewer infections among children and young people than in other epidemics.

The experience of these months has taught that Covid 19 disease among children is less aggressive and severe.

Why are children more resistant to Covid-19 infection? The concurrence of various factors is assumed, such as a lower density of the receptors which are necessary for the virus lock or their immaturity, which make it more difficult for the virus to enter the body; a less violent specific immune response in children, resulting in reduced inflammation of the lung; cross-protection from vaccinations.

In a recent study [6], the authors have proposed to give an answer to the data of the reduced severity of the disease among children who, on the other hand, are notoriously more susceptible to other infectious events, given the immaturity of the immune system, which,

however, has peculiar characteristics on which, probably, the protective effects against Sars Cov 2 depend. The main differences concern the B cells, which produce antibodies, secrete cytokines (in particular IL-10) which, as already said, are powerful anti-inflammatories. It is postulated that the child immune response might have the double function of exerting protection and reducing immune-mediated tissue damage particularly in the lung. In recent weeks, unfortunately, there have been some reports [7-13] of children who died from Covid-19 infection, but the fatal outcome would be due to the evolution of a vasculitis inflammation. At least 100 children in upstate New York are suffering from the rare and dangerous inflammatory syndrome, similar to Kawasaki syndrome, which is thought to be linked to the Covid-19 virus. This was announced by Governor Andrew Cuomo who spoke of at least three dead children, aged 5, 7 and 18 respectively. Half of the cases involve children between the age of 5 and 14. A new life-threatening inflammatory syndrome associated with COVID-19 has affected 230 children in Europe and the UK in 2020, and two children had succumbed to the condition: one in Britain and one in France [12]. The condition, known as paediatric inflammatory multisystem syndrome (PIMS), shares symptoms with toxic shock and Kawasaki disease including fever, rashes, swollen glands and in severe cases, heart inflammation.

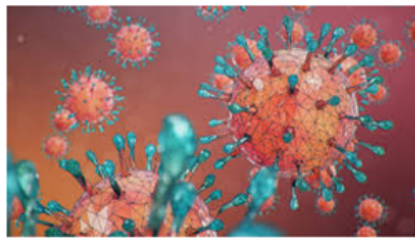
Affected children may require pediatric intensive care and input from pediatric infectious diseases, cardiology, and rheumatology. This rare syndrome shares common features with other pediatric inflammatory conditions, including: Kawasaki disease, staphylococcal and streptococcal toxic shock syndromes, bacterial sepsis and macrophage activation syndromes. It can also present with unusual abdominal symptoms with excessive inflammatory markers. The reports from the pediatric scientific societies hail from Bergamo [8] the most affected area with an incidence of Kawasaki syndrome 30 times higher than in the past, and from other cities of Northern Italian such as Genoa. In the United Kingdom, the Guardian has reported that the National Health System (NHS) has noticed a growth of cases in the last weeks that have led to the hospitalization of ICU children of different ages. The same occurs in Spain and in the United States.

Compared to the past, the observational data report that in two months, children and adolescents had systemic inflammation similar to Kawasaki syndrome, though often with incomplete symptoms or with some variant, reaching a number similar to what was totally recorded in several years.

The Rheumatology Study Group of the Italian Society of Pediatrics has decided to alert the Italian pediatric community about the possible onset of the Kawasaki disease in children affected by COVID-19 promoting a data collection of these cases in order to characterize the clinical manifestations, the therapies performed and the evolution still investigating the possible causal role of Sars-Cov-2 virus. Kawasaki syndrome is a rare syndrome whose annual incidence in Europe among children under the age of 5 is 1 per 6,500 - 20,500 [14]. It is a more frequent inflammatory condition under 5 years and presents with high fever that lasts for more than 5 days, oral mucositis, conjunctivitis, edema of hands and feet, lymphomegaly of the neck. A significant complication is represented by the development of aortic aneurysm which leads to the risk of heart attack at a young age. The most probable hypothesis underlying the syndrome is infectious even if it is not a spreading disease since it affects only immunologically predisposed subjects. The treatment of choice is the administration of high-dose vein immunoglobulins. The reason is not well known, but these generic antibodies quickly manage to stop the exaggerated inflammation and restore balance in the immune system of young patients. In case of no response to this treatment, cortisone and biological drugs have been proven useful. To this extent, we've been discussing on "classic" Kawasaki disease. In some Italian pediatric centers, in the midst of COVID-19 epidemic, it has been noticed that in a not negligible percentage of cases, the disease presented itself with a non-typical clinical picture and showed resistance to the aforementioned treatment as well as tendency to evolve towards a macrophage activation syndrome (particular picture linked to excess of inflammation) or a toxic shock syndrome, which required aggressive treatments and, not infrequently, hospitalization in the intensive care. This complication has some characteristics which are similar to the cytokine storm syndrome observed in many patients with COVID-19 pneumonia. In rare cases immunomodulatory or antiviral therapy is advised.

During these weeks of acute phase of the pandemic, in addition to the rare and more serious forms, some phenomena generically defined as "vasculitic" have been observed. In addition to the demanding systemic forms, more frequent cases of COVID-19 acrovasculitis are described, which seem to have a benign course since they resolve with complete healing in 14-20 days. However, it may be the only

symptom and therefore difficult to diagnose. It should be added that Covid infection in children can be suspected in the presence of gastrointestinal disorders associated with fever or exposure to Sars-Cov-2 positive people. In new recent study [15]. According to the authors, gastrointestinal symptoms would suspect a potential infection through the digestive tract, since the type of 'target' receptors of the virus, present in the lung cells, can also be found in the intestine. Sars-CoV-2 still hides many of its aspects, in terms of manifestation of acute and remote disease. Although it remains true that children appear more protected from infection, so as not to develop clear clinical symptoms in many cases, it is equally undeniable that the pieces in the knowledge puzzle increase every day, also on the pediatric front.



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Volume 9 Issue 8 August 2020

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