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COVID-19 in Italian pediatric patients: the experience of a tertiary children's hospital

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Short title

SARS-CoV-2 infection in 43 Italian children

Keyword

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Coronavirus disease (COVID-19) caused by the novel SARS-CoV-2 has spread worldwide since its onset in Wuhan in December 2019. In Italy COVID-19 rapidly increased in February 2020 and by 12 May 2020, 2.0 % of the confirmed cases were under 18 years and 3.7% of those had been hospitalized (1). This case series report reviews the demographic characteristics, clinical course, laboratory findings, radiologic features and treatment of children admitted with COVID-19 to a tertiary care hospital in Italy.

The study included the children with COVID-19 admitted between the March 15- May 6 2020 at the Bambino Gesù Children's Hospital. Diagnosis of SARS-CoV-2 infection was defined by the detection of virus RNA through real-time polymerase chain reaction on naso-pharyngeal swab. Family cluster was defined as the presence of a family member (mother, father, household) with certain or suspected diagnosis of SARS—CoV-2 infection at the time of the admission in the hospital.
The institutional ethics board approved the study and written, informed consent was provided by the parents.

In total 43 patients were identified with a median age of 7 years. Patients' characteristics are presented in Table 1. Thirty-eight on forty-three children belonged to a family cluster. In 14/38 (37%) of cases the family member was a health care worker.
The symptoms at the admission are reported in Table 1.
On 43 patients, 5 children (12%) developed new symptoms during hospitalization including: respiratory symptoms requiring supplemental oxygen for three days in a 7 years-old-boy, mild diarrhoea with spontaneous resolution of ileal thickening detected on ultrasound in a 12-years-old girl, conjunctival hyperemia without SARS-CoV-2 detected on ocular surface in a 6 years-old-boy and the hyperinflammatory syndrome in 15-and-14 years old boys. These two patients were admitted with fever and cough at the onset of the disease; after two days and three weeks from the admission respectively, they developed abdominal pain, diarrhoea, high fever associated to lymphopenia, high levels of inflammatory indexes (C - reactive protein, ferritin, D-dimer) and a progressive mild heart failure. The transfer to the PICU was necessary. The clinical course and treatment of these two patients will not be discussed in this brief report.
Patients laboratory findings at the admission are presented in Table 1.

During the hospitalization lymphopenia and neutropenia were observed in 16/43 (37%) and 11/43 (26%) of patients, respectively. The C-protein remained negative in 32/43 (74%) children. Transient and self-limited thrombocytopenia (112 x 10^9/L) was detected in the child who presented the respiratory deterioration, as described above.

The imaging was performed in 15/43 (35%) cases with suspected lower respiratory tract infections (Table 1). Chest X ray was performed in 14/43 (33%) patients while only 5/43 (12%) children were subjected to chest CT scan. In 2/43 (5%) children over the age of 12 years the CT scan showed more extensive lung involvement than the X-ray, with ground glass opacities: one monolateral and one bilateral. Brain magnetic resonance imaging identified pneumonia in a patient without respiratory symptoms after afebrile seizures extended to the chest.

In our cohort ten patients were treated with different combination of medications (table 1).

Because of the co-administration of drugs that potentially could prolong QT, routine ECGs were performed every 48-72 hours. In all these patients the QT interval remained in the normal range.

A 15-years-old girl, affected by a connective tissue disorder in therapy with Hydroxychloroquine (HCQ) and Mycophenolate, was treated with a combination of HCQ and lopinavir-ritonavir. We observed bradycardia (HR 50-60 bpm) likely related to drug-drug interaction between the two drugs (HCQ and lopinavir-ritonavir). The heart rate returned to the normal rate after discontinuation of lopinavir-ritonavir.

In general, our data suggest that SARS-CoV-2 infection in children may be mild or atypical compared to adult patients, strengthening the hypothesis that pediatric cases may be underdiagnosed and misdiagnosed. Multiple hypothesis have been proposed to justify the different clinical presentation of COVID-19 between adults and children; still today there is no a univocal explanation. Noteworthy, although a small percentage is reported, pediatric patients may develop a hyperinflammatory syndrome that needs to be carefully evaluated for a prompt treatment. Notably, adults have a much higher prevalence of increased C-reactive protein, suggesting a much milder immunological response and less immune-mediated tissue damage in children (3). In our study, we did not find a correlation between the lymphocyte count and the course of the disease. One asymptomatic child with COVID-19 had pneumonia, which suggests specific paediatric imaging criteria so that lower respiratory tract infections are detected. The treatment strategy for children with COVID-19 is based on adult experience. The combination therapy with azithromycin and hydroxychloroquine is supported by the evidence, albeit of small size, that hydroxychloroquine

86 treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients
87 and that its effect is reinforced by azithromycin (4). Antiviral treatment has been used in only one
88 immunocompromised patient but data on its efficacy in children with COVID-19 are missing (2).
89 Pending on a pediatric clinical trial we included lopinavir-ritonavir in our guidelines.
90
91 In our experience, and according with the literature (5) although children are just as susceptible to
92 COVID-19 as adults, they appear to have a milder clinical course. We observed that the major
93 pattern of viral transmission was intra-family therefore the risk of family cluster transmission from
94 children harboring virus and the impact to community-based epidemic prevention should be taken
95 into consideration in policy making for epidemic control.
96
97

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CONFLICTS OF INTEREST

We have no conflicts of interest

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Table 1 Demographic, Epidemiological and Clinical features on admission

Characteristics	**Value n (%)**
Median age	7 years
Range	8 days to 17 years
< 1 month	4/43 (9)
1 month – 6 years	13/43 (30)
6-12 years	15/43 (35)
≥ 12 years	11/43 (26)
Boys	24/43 (56)
Epidemiological history	
Contact with a confirmed/suspected case of COVID-19	38/43 (88)
Related to a family cluster	38/43 (88)
Family healthcare worker	14/38 (37)
Underlying diseases	
Previously healthy	33/43 (77)
Neurological disorder	4/43 (9)
Cardiovascular disease	1/43 (2)
Other *	5/43 (12)
Clinical symptoms	**n (%)**
Fever	27/43 (63)
Cough	18/43 (42)
Diarrhoea/vomiting	10/43 (23)
Headache	7/43 (16)

Dyspnoea	5/43 (12)
Nasal congestion	5/43 (12)
Arthralgia	4/43 (9)
Myalgia	3/43 (7)
Febrile seizure	2/43 (5)
Sore throat	2/43 (5)
Anosmia	2/43 (5)
Abdominal pain	1/43 (2)
Seizure	1/43 (2)
Laboratory values	**Value Mediana (IQR)**
White blood cells (10^9/L)	6.56 (5.30-9.98)
Lymphocytes (10^9/L)	2.66 (1.79-4.34)
C- reactive protein (mg/dl)	0.08 (0.04-0.46)
Radiological findings	**N (%)**
Chest X ray	14/43 (33)
Interstizial abnormalities	11
Local patchy opacities	2
Bilateral patchy opacities	1
Chest Computer Tomografy	5/43 (12)
Interstizial abnormalities, Local patchy opacities, Bilateral patchy opacities, Tree in bud	1
Ground glass opacity	2
Chest MRI	2/43 (5)

Local patchy opacities, Ground glass opacity	1
Medication **	**n (%)**
Hydroxychloroquine + Azithromycin	7/41 (17)
Hydroxychloroquine	2/41 (5)
Hydroxychloroquine + lopinavir-ritonavir	1/41 (2)

*(prematurity, neonatal respiratory distress, urogenital tract malformation)** the treatment of the two patients with the hyperinflammatory syndrome is not included