After the First Wave of COVID-19: Reflections From Italy

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The coronavirus disease 2019 (COVID-19) was first described in China in December 2019 and declared a pandemic by the World Health Organization in March 2020. Italy was the first European country to be severely affected. By May 20, more than 227,000 confirmed SARS-CoV-2 infections were registered and more than 31,000 people had died, a much higher case-fatality rate (13.6%) than reported for China (2%–3%).[1] There was also concern of a more severe COVID-19 burden in Italian children, as compared with China where children (<18 years) accounted for only 2.4% of confirmed infections, most of them asymptomatic or with mild disease, and fatalities in children were only anecdotally reported.[2] In Italy, there are an estimated 1 million children with comorbidities and each year about 11,000 children and adolescents (0–19 years) progress to terminal illness (Italian Society of Pediatrics). Italy has limited availability of pediatric (non-neonatal) intensive care beds with regular bottlenecks prior to the pandemic, and so a more severe course in Italian children could potentially overwhelm pediatric care facilities with disastrous consequences.

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EPIDEMIOLOGY

During the first month of the epidemic in Italy, children accounted for only 1% of total cases identified with SARS-CoV-2 infection. The proportion has since steadily increased to 2% by mid-May, with 4244 confirmed cases. There have been 4 SARS-CoV-2-related deaths in children in Italy, all with comorbidities.[1] These data are likely to underestimate the actual burden of infection in children. In the initial weeks of the epidemic, caregivers did not bring their children to health services, including those with moderate signs of respiratory tract infections, and testing was concentrated on symptomatic patients in all age groups. Further, the incubation period in children can be as long as 24 days and severe disease – especially in comorbid patients – may develop only during or after the third week of illness.

The role of children in the spread of the pandemic remains unclear. In general, they tend to be less symptomatic despite having a similar viral load in upper respiratory tract specimens as adults and shedding virus for up to 21 days. There is also evidence that children may shed SARS-CoV-2 RNA for a longer time in feces,[3] but it is not yet clear if this correlates with persistent infectiousness of SARS-CoV-2 by the fecal–oral route in the convalescent phase. New evidence supports a role for different expression of angiotensin-converting enzyme 2 receptors in the observed lower prevalence of COVID-19 in children.[4] Early experience suggests that, in marked contrast to other infectious respiratory viruses such as influenza, but similar to SARS-CoV-1, most children seem to acquire the infection through household contacts and thus are not a major driver of transmission.[5] This issue of current uncertainty is critically relevant for decisions relating to the re-opening of schools and child-care facilities.

CLINICAL FEATURES

The last account (dated May 20, 2020) from the Italian Ministry of Health[1] reports that 2062 female and 2179 male children under 18 years had confirmed infection and that 2.9% of these children were hospitalized. Infants (<12 months) were overrepresented among the infected cases (13.3%) and even more among the hospitalizations (29.3%). Clinical data from the first 2 large Italian cohorts[6,7] of infected children are reported in Table 1.

The Italian Registry of SARS-CoV-2 infection in children was established at tertiary-level infectious diseases pediatric centers and pediatric wards by the Italian Society of Pediatric Infectious Diseases and the Italian Society of Pediatrics. Preliminary data until April 10, 2020, have been published that describe the clinical features of 168 confirmed COVID cases in children, most of whom (67.9%) were hospitalized. A high proportion (19.6%) of these children had known comorbidities, including lung diseases, congenital malformations, neurologic and metabolic disorders, cancer and immunosuppression. The high proportion of infants (39.3%) and especially newborns (8.9%) may partly

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TABLE 1. Demographic and Clinical Characteristics of Children With COVID-19 in Italy

Demographic and Clinical Characteristics at Presentation	CONFIDENCE N = 100	SITIP-SIP N = 168
Study period	March 3–27	March 25–April 10
Median age in years	3.3	2.3
Infants < 1 year (n)	40	66
Female (%)	43	44
Known co-morbidity (%)	27	19.6
Fever >37.5°C (%)	54	82.1
Cough (%)	44	48.8
Rhinitis (%)	22	26.8
Diarrhea (%)	9	13.1
Shortness of breath/dyspnea (%)	11	9.5
Sore throat/pharyngitis (%)	4	5.4
Nausea/vomiting (%)	10	5.4
Conjunctivitis (%)	NR	3.6
Chest pain (%)	NR	2.4
Abdominal pain (%)	4	NR
Fatigue (%)	9	1.8
Non-febrile seizures (%)	0	1.8
Febrile seizures (%)	0	1.2

Modified from references 6 and 7 (Italian SITIP-SIP Pediatric Infection Study Group and CONFIDENCE study). Some overlap between the cohorts cannot be excluded

NR indicates not registered.

reflect parents and clinicians being particularly concerned of a more severe disease course in the youngest age group.

A low proportion of hospitalized children (12.5%) developed severe acute respiratory illness, and 2 of this cohort required intensive care admission and mechanical ventilation – a preterm newborn and a child with congenital heart disease. Chest imaging has not been deemed necessary in all cases, but interstitial pneumonia was diagnosed in 23.6% of hospitalized children. Blood count alterations, such as raised or lowered neutrophil, lymphocyte and/or platelet counts, have all been noted. Highly elevated erythrocyte sedimentation rate, C-reactive protein and procalcitonin may resemble sepsis, but can be due to a SIRS-like syndrome and need to be recognized and treated accordingly. In this first large cohort on SARS-CoV-2-infected children in Europe with a high proportion of comorbidities, no fatalities occurred.

Furthermore, worldwide 140 children with cancer and SARS-CoV-2 infection have been reported (among them 45 from Italy), 8 needed intensive care (Italy 1) and 1 died (Italy 0). However, in a large routinely tested cohort from all pediatric hematology–oncology centers in Lombardia, half of the infected had their antineoplastic treatment modified (chemotherapy reduced or delayed, surgery postponed).[8]

COVID-19 is a novel disease, and robust data on short- and long-term courses and outcome are still lacking. Thus, a high level of suspicion for yet undescribed but important complications is warranted. In fact, new evidence from pediatricians in Italy shows vasculitic/thrombophilic involvement that is not only limited to the skin[9] but is also systemic, leading to a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) resembling an atypical Kawasaki (shock) syndrome.[10] It is particularly concerning that 4 of 10 affected children in the most recent report also show meningeal signs and EEG changes. Which of the SARS-CoV-2-associated conditions are truly caused by the virus directly and which are only anticipated in susceptible children through a triggering function of the virus remains to be seen.

NEONATAL INFECTION

The possibility of mother-to-child transmission through delivery or breast-feeding has not yet been clearly established. While a newborn whose mother had COVID-19 pneumonia had SARS-CoV-2 infection identified from a nasopharyngeal swab taken immediately after birth, testing for SARS-CoV-2 using real-time C-reactive protein on placental tissues, umbilical cord blood, amniotic fluid and vaginal swabs have been negative. Moreover, to date, no maternal milk sample has been found to be positive for SARS-CoV-2.

Outcomes in SARS-CoV-2 positive neonates are considered generally good. No death has been reported among infected neonates, though one 15-day-old neonate with viral sepsis has been described. In an Italian case series with 7 SARS-CoV-2-positive pregnant women, 2 neonates were SARS-CoV-2-negative at birth and day 3 of age, but one of them was found positive at 2-week follow-up.[11] Another Italian center had 6 infected newborns, only 2 needing treatment for respiratory distress and receiving chloroquine. The authors emphasize that neonates of mothers with COVID-19 in pregnancy need long-term follow-up, even if they tested negative at birth.

Among the available consensus documents regarding management of pregnant women with COVID-19 and their neonates, some discrepancies can be observed. The Chinese expert consensus on perinatal and neonatal management for the prevention and control of COVID-19 does not recommend mother–infant close contact after birth. On the other hand, the World Health Organization and the United Nations Children's Fund underline that breastmilk is the best source of nutrition for infants, and considering also the generally mild course in infants and young children, they support breast-feeding, skin-to-skin contact and rooming-in, if the mothers' clinical condition allows it. The American College of Obstetricians and Gynecologists, The Royal College of Obstetricians & Gynecologists and Italian Society of Neonatology endorsed by the Union of European Neonatal & Perinatal Societies suggest that in the case of asymptomatic or pauci-symptomatic mothers with SARS-CoV-2 infection, rooming-in is feasible and breast-feeding is supported, under strict measures of infection control such as hand hygiene and face mask use while breast-feeding.[12]

ANTIVIRAL TREATMENT

In the Italian cohort,[6] 29.2% of children received experimental treatments for SARS-CoV-2 infection, including lopinavir/ritonavir, hydroxychloroquine and/or azithromycin. A systemic steroid was administered only in 1 case. An exhaustive review of treatment for pediatric SARS-CoV-2 infection is beyond the purpose of this reflection, and a more complete review of what is in the pipeline can be found elsewhere.[13] Until now, no antiviral treatment has proven efficacy – neither in prevention nor in therapy of symptomatic/severe COVID-19 in children.

Though the protease inhibitor lopinavir/ritonavir and various forms of chloroquine had some conceptual and in vitro evidence, the available clinical data demonstrate no benefit in the treatment of COVID. Furthermore, their extensive inappropriate use and the accompanying shortage for patients on these drugs for other conditions (HIV, rheumatic illness) may do additional harm. Remdesivir is an investigational drug, a nucleotide analogue developed for the treatment of Ebola virus, but in vitro studies suggested a possible efficacy against other betacoronaviruses (SARS-CoV-1 and MERS-CoV). The drug was made available under "compassionate use" for pregnant women and children, even if pharmacokinetics studies in

childhood are not yet published. Liver toxicity as a major adverse event is reported.

For the time being, FDA and EMA suggest that, whenever antivirals are considered, they should be prescribed in clinical trials – and those trials need to include children upfront, as dedicated pediatric trials alone will hardly reach numbers necessary to make relevant conclusions. Furthermore, the generally favorable outcome of SARS-CoV-2 infection in infants and children, even in those with underlying diseases, should limit antiviral treatments in mild/moderate illness, as stated by the USA Pediatric Infectious Diseases Society and the Italian Pediatric Infectious Diseases Society.[14] Supportive care (ie, various forms of oxygen administration, venous thromboembolism prevention with low-molecular-weight heparin, immunomodulation with methylprednisolone and/or high-dose intravenous immunoglobulins) is the mainstay of treatment, while biologicals are not routinely used. The PIMS-TS and similar forms can be treated adapting the existing Kawasaki guidelines.

INDIRECT CONSEQUENCES AND IMPACT ON SOCIETY

While severe disease, sequelae and death directly due to COVID may be rare in children, the secondary or indirect consequences could be far-reaching and more important. These include increased challenges to provide prompt and effective prevention and care for all childhood illness, including severe forms of infectious diseases, and the consequences of prolonged (and possibly recurrent) school closures and social distancing. Early experience shows increasing numbers of children who delay seeking health care from routine vaccines to surgery. In March 2020, consultations in some Italian Pediatric Emergency Rooms declined by over 80%. Anectodal reports of late presentations with advanced and sometimes fatal conditions include severe diabetic ketoacidosis, severe anemia due to leukemia, pleural effusion associated with lymphoma, repeat severe convulsions associated with invasive bacterial infection, hypovolemic shock due to pyloric stenosis, prolonged obstruction with abdominal tumor and painful crises due to sickle cell disease. Most explained their delayed presentation to health services being due to fear of getting infected in the hospital.[15]

CONCLUSION

The present pandemic, in all probability not the last, appears to be relatively merciful to children and their doctors. However, the next may not. Therefore, we should take the opportunity to study all aspects of this pandemic on child health, health systems and even societies, to increase effective prevention efforts, timely preparedness and careful resilience all over the world. Furthermore, we want to stress the importance of Pediatric Infectious Diseases not only as an academic subspecialty but also as a clinical branch with a need for adequate units equipped with isolation rooms, trained nurses and, most important, as a culture – in every sense!

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