

COVID-19 – Impact on Childhood Haematology Patients

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There is little doubt that the consequences of the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic on healthcare, infrastructure as well as on our socio-economic life will be severe and long-lasting. The high infectivity of this “new” virus, a high frequency of asymptomatic carriers, the lack of herd immunity and a range of rare presentations, including fatal cytokine storms, are posing major challenges.¹

Fortunately for our young patients, severe COVID-19 disease mainly affects adults and otherwise healthy children and young

adults appear to be relatively spared. Reports on COVID-19 disease showed that less than 1% of the cases were in children younger than 10 years of age.² Lu et al reported on the spectrum of illness from SARS-CoV-2 infection in 171 children. In contrast with infected adults, most infected children appeared to have a milder clinical course. During the course of hospitalization, only 3 children required intensive care support and invasive mechanical ventilation; all 3 had coexisting medical problems (hydronephrosis, leukemia receiving maintenance chemotherapy and intussusception). There was one death, a 10-month-old child with intussusception who developed multi-organ failure and died 4 weeks after admission. Asymptomatic infections were reported in 15.8% of infected children.³ A nationwide case series of 2135 pediatric patients with COVID-19 reported to the Chinese center for disease control and prevention showed that more than 90% of all patients had asymptomatic, mild, or moderate disease. Younger children, particularly infants, were relatively more vulnerable to SARS-CoV-2 infection. The proportions of severe and critical cases were 10.6%, 7.3%, 4.2%, 4.1%, and 3.0% for the age groups <1, 1 to 5, 6 to 10, 11 to 15, and ≥16 years, respectively.⁴

A Kawasaki-like multisystem inflammatory syndrome in children has recently been reported in a number of countries associated with the SARS-CoV-2 pandemic.^{5,6} Others reported a COVID-19 post-infectious cytokine release syndrome that had features similar to Kawasaki Disease and Toxic Shock Syndrome.⁷ Interestingly and possibly related to this inflammatory picture, variations in NK cell and perforin function which are associated with virally induced HLH may also influence the severity of the clinical course and mortality rates of SARS-CoV-2 infections.⁸ Whittaker et al described a case series of 58 children from England with a wide spectrum of presenting symptoms and signs and disease severity, ranging from fever and inflammation to myocardial injury, shock, and development of coronary artery aneurysms who met the criteria for the newly defined pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (PIMS-TS) which differed from other pediatric inflammatory entities.⁹

In contrast to children in general, data on the clinical manifestations of SARS-CoV-2 infections in pediatric hematology patients are scarce and anecdotal. An 8-year-old child undergoing myelosuppressive chemotherapy for T-cell acute lymphoblastic leukemia in a Wuhan hospital developed respira-

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HemaSphere (2020) 4:5(e465). <http://dx.doi.org/10.1097/HS9.0000000000000465>.

Received: 23 June 2020 / Accepted: 7 July 2020

tory failure, eventually requiring mechanical ventilation.^{3,10} A 1-year-old girl with acute myeloid leukemia receiving chemotherapy at the Meyer Children's Hospital in Florence, Italy, developed temperatures and increased bilateral reticular marking on chest X-ray but fortunately fully recovered without needing any airway support.¹¹ Hrusak et al made a flash survey on COVID-19 incidence and severity among children on anticancer treatment.¹² Reports from 25 countries worldwide, covering a population of approximately 10,000 children and young people on anti-cancer therapy, identified only nine children that tested positive for SARS-CoV-2. Eight of the nine cases had asymptomatic to mild disease and one had just been diagnosed. This consortium is currently collecting additional and more detailed long-term data on COVID-19 incidence in children and adolescents with cancer as well as information on the testing policies of the participating centers. At the Memorial Sloan Kettering Cancer Center (MSK) pediatric cancer patients were screened for 1 month (March 10 to April 12, 2020) for SARS-CoV-2. Of the 20 patients that tested positive only one required noncritical care hospitalization for COVID-19-related symptoms. Three other patients without significant COVID-19 symptoms were admitted for concomitant fever and neutropenia, cancer morbidity, or planned chemotherapy. All other pediatric patients were managed at home.¹³ In Italy, data were collected in the 6 pediatric hemato-oncology centers in Lombardia over the first 8 weeks of the pandemic (February 20 to April 15, 2020). Twenty-one cases of COVID-19 infection were identified. Fifteen of these patients were on treatment, and six were in follow up after elective discontinuation of treatment. Only two patients experienced complications: one, with a diffuse intrinsic pontine glioma and respiratory impairment, developed pneumonia requiring respiratory support; another, with refractory Hodgkin lymphoma and prior mediastinal irradiation developed atypical bilateral pneumonia with mild symptoms.¹⁴ Cases of Kawasaki-like disease or HLH have so far not been reported in pediatric oncology patients.

The situation is similar for children with benign hematological disorders. The UK national hemoglobinopathy panel reported 195 cases of COVID-19 of which only 20 were children. 10.5% of adults required intensive care for airways support compared to none of the children.¹⁵ In France, the PICU at the Hôpital Necker-Enfants malade reported four children with sickle cell disease and COVID-19; all required noninvasive airways support and all made full recovery.¹⁶ Data on patients with primary immunodeficiencies are also scarce, even more so in the pediatric population. Whilst initially there were significant concerns that this population may be extremely vulnerable to SARS-CoV-2, many may, conversely, be at lower risk. There are some data suggesting that patients with lymphopenia, for instance in untreated patients with HIV, may have a less severe clinical course because they lack T lymphocytes, which may reduce the risk of acute respiratory distress syndrome and other hyper-inflammatory states.¹⁷ One systematic review of children and adults receiving immunosuppression reported sixteen relevant articles, which identified 110 immunosuppressed patients including children, with cancer, following transplantation and with immunodeficiency. It concluded that immunosuppression may be associated with a more favorable outcome as compared with other comorbidities.¹⁸ This is supported by a recent study in adults that did not identify chemotherapy as a risk factor for mortality from COVID-19 disease.¹⁹ In contrast, Liu and colleagues followed the systemic review with a meta-analysis and concluded that immunosuppression and immunodeficiency were associated with increased risk of severe COVID-19 disease

with the vast majority of patients being adults often with additional co-morbidities.¹⁰ This underlines the difficulty on obtaining good quality information on COVID-19 in pediatric patients at the present time. Based on the current available information, there may be more concern for patients whose immunodeficiency predisposes to hyper-inflammation, such as hemophagocytic lymphohistiocytosis or chronic granulomatous disease. Until more definite information becomes available, a counsel of prudence and shielding this vulnerable population would seem reasonable, as adopted by many national and specialist society guidelines.

Together, these reports suggest that children with hematological disease, including children receiving anti-cancer chemotherapy and children with inborn errors of the immune-system, may have a mild or asymptomatic course of COVID-19; however, children with comorbidities, including immune suppression and malignancy, can have severe disease²⁰ and too few hematology patients have so far been affected to assess the definitive risk of SARS-CoV-2 infection on this patient population.

We still have a lot to learn a lot about COVID-19 in our patient population and many open questions remain, including:

- What are the biomarkers predicting the course and outcome of COVID-19 in children and young people with hematological disorders?
- How will our patients respond to a SARS-CoV-2 vaccine once such a procedure becomes available? What should a proper vaccination program look like when the child is receiving immunosuppressive treatment or following a stem-cell transplantation?
- Are there genetic variants that underlie susceptibility to COVID-19 and, if so, are they linked to tumor predisposition and treatment response? So far, the COVID Human Genetic Effort (<https://www.covidhge.com/>), an international consortium that aims to discover monogenic inborn errors of immunity underlying severe forms of COVID-19 in previously healthy individuals does not consider children with malignancies.

How has the SARS-CoV-2 pandemic affected the treatment of pediatric hematology patients?

An important and widely discussed potential risk for cancer patients is delayed diagnosis and treatment during this SARS-CoV-2 pandemic. Delayed diagnosis could be due to a decreased access of young patients to their health care provider and/or avoidance of families to seek medical advice because of the fear of infection. Delays in therapy may occur due to delay or cancellation of “non-essential” treatments, including cancer surgery, or imaging and stroke risk screening in sickle cell disease. Hematopoietic stem cell transplant activity has been curtailed, with many services treating only urgent cases. Furthermore, accessing unrelated donors has become more difficult, as they may be unavailable to donate because of illness or isolation – testing for SARS-CoV-2 and awaiting negative results has further slowed down the normal process. Current recommendations are to receive stem cells and freeze them before commencing conditioning, which may impair engraftment and immune reconstitution, especially in case of unfavorable donor-recipient weight disparity, when the number of cells in the graft is expected to be suboptimal.

As far as we know, experience has been different in different countries throughout Europe. While in Lombardia, Italy, a dip had been observed in newly diagnosed pediatric cancer

patients,¹⁴ no such reduction has been seen in referrals in other countries such as the Austria, Israel or the Netherlands. Even in Lombardia, this dip was in part due to fewer out-of-region and international referrals.

In addition, it has been speculated whether social distancing and home isolation might actually lower the incidence of B-lineage ALL, as was observed after the SARS epidemic in 2003.²¹ Alternatively, spreading of SARS-CoV-2 in naive populations, as has been described for other viruses such as the AH1N1 swine flu virus,²² could be linked to small outbreak clusters of B-precursor ALL in kindergartens and schools. Future studies will need to provide further insight into the epidemiological consequences of this pandemic on the incidence of ALL.

Although most pediatric hematologists have anecdotal experience of individual patients that presented late, on a whole there does not seem to be significant barrier of children accessing health services for diagnosis and treatment in Europe. The important message that families with ill children need to seek medical advice and that general practitioners should continue to refer patients with a differential diagnosis of cancer, has come across. Treatment of pediatric hematology patients has continued, albeit under significantly more difficult circumstances.

The time and resources used to develop guidelines on isolation of children under treatment (with and without symptoms/SARS-CoV-2 positivity), screening guidelines (for patients with and without symptoms, before anesthesia), reorganizing outpatients clinics (eg, implementation of social distancing, video consultations), setting up clinical pathways to prevent SARS-CoV positivity²³ or treat COVID-19 patients have been tremendous. This has been further complicated by the plenitude of advice and recommendations, sometimes conflicting, even at local level. Whom, when and how often to screen? Which personal protective equipment to use by patients and health care professionals in which situation and when? What is an aerosol-generating procedure?

Whatever we have done has been associated with a low incidence of SARS-CoV-2 infections in our patients. All efforts and measures will need to be carefully assessed and looked at in the context of potential future pandemics. What have we learned? And what can we do better or more efficiently next time round? We will also need to carefully look now how this whole pandemic has affected our young patients, their parents and siblings to provide adequate multidisciplinary team support: social isolation, including lack of visits from close relatives and friends during long hospital stays, anxieties caused by the pandemic or discomfort from repeated COVID testing in young children, their guardians and staff.

What is clear is that pediatric hematology research has come to a standstill. Researchers have been unable to go to their labs. Clinical trials have been put on hold as safety of trial participants has been the first priority. Charities are seeing or expecting a significant drop in fundraising. The largest charity in Europe funding cancer research, Cancer Research UK, expects a drop of 20% to 25% in their fundraising income (<https://www.cancerresearchuk.org/about-us/cancer-news/press-release/2020-03-30-cancer-research-uk-estimates-25-per-cent-drop-in-fundraising-in-come-due-to-coronavirus>) and expects to make difficult cuts in research funding. Governmental agencies will also struggle to fund research in the context of a shrinking economy, the necessity to fund packages to stimulate the economy and a decreased tax income and, understandably, research funds will be shifted toward research on SARS-CoV-2 infections. Our voice and, even more importantly, the voice of the different parent organizations active in the pediatric hematology space will be crucial to lobby

governments to keep research for our young patients on the agenda; and as a community, even more than ever, we need to support our different charities in raising awareness and money.

Conclusion/Summary

As health care professionals, we need to provide patients and families but also health care providers in primary secondary care with clear information. Access to medical care for diagnosis and treatment of childhood cancer and other hematological disorders is paramount and the risk of hematological disease clearly outweighs the risks of SARS-CoV-2 infection in our patient population. International consensus guidance on prioritizing diagnosis and treatment for pediatric cancers during the COVID-19 pandemic have recently been published.²⁴

Fortunately, the spread of SARS-CoV-2 in our patient population has been limited, the course of disease has been mild in many children affected, even if severely immunocompromised, and, with an incredible effort from our multidisciplinary teams, we have been able to provide good care for our patients throughout this first phase of the pandemic. The medium- and long-term effects of the COVID-19 pandemic on society, including funding of health care and research, and the direct and indirect effects of the COVID-19 pandemic on our patients, however, remain to be carefully monitored. In times of challenging socio-economic decisions that are likely to affect both health care and research, it will be important to ensure that adequate resources and funding will be available for the treatment of our patients and for innovation and research. Working closely together with all the different stakeholders active in the pediatric hematology space (including parent/survivor groups, charities, research funders, governmental organizations, insurance providers and pharma) will be crucial to keep the needs of our patients on the agenda.

For further information see:

<https://ehaweb.org/covid-19/>

<https://siop-online.org/covid-19-resources-and-guidance/>

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