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DR. LORENZO D'ANTIGA (Orcid ID : 0000-0001-7150-3148)

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Coronaviruses and immunosuppressed patients. The facts during the third epidemic

Lorenzo D'Antiga

Paediatric Hepatology Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII Bergamo, Italy

Corresponding author: Lorenzo D'Antiga, MD

Paediatric Hepatology, Gastroenterology and Transplantation

Hospital Papa Giovanni XXIII

Piazza Oms 1, 24127 Bergamo Italy

Tel ++39-0352673856, Fax ++39-0352674959

E-mail: *ldantiga@asst-pg23.it*

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Abstract

Following the outbreak in China, the Lombardy region of Italy has become one of the areas of highest incidence of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). As the outbreak grew to a pandemic, many centres worldwide raised the concern that immunocompromised patients may be at high risk of developing a severe respiratory disease called COVID-19. Unlike common viral agents (such as Adenovirus, Rhinovirus, Norovirus, Influenza, Respiratory Syncytial Virus), Coronaviruses have not shown to cause a more severe disease in immunosuppressed patients. For this family of viruses the host innate immune response appears the main driver of lung tissue damage during infection.

More importantly, reviewing the mortality and morbidity reports published on Coronaviruses outbreaks such as Severe Acute Respiratory Syndrome (SARS) that emerged in 2002, Middle East Respiratory Syndrome (MERS, still ongoing) and more recently COVID-19, no fatality was reported in patients undergoing transplantation, chemotherapy or other immunosuppressive treatments, at any age. Risk factors for poor outcome include advanced age, male sex and presence of comorbidities (obesity, diabetes, heart disease, lung disease, kidney disease).

The Hospital Papa Giovanni XXIII in Bergamo, is located in the "red zone" of the Italian outbreak, and hosts the main paediatric hepatology and liver transplantation centre of Italy. Our preliminary experience, in agreement with recent data from China, shows that, among patients in the follow-up for cirrhosis, transplantation, autoimmune liver disease, chemotherapy for hepatoblastoma, none developed a clinical pulmonary disease, despite some tested positive for SARS-CoV-2.

The experience made so far on Coronaviruses outbreaks suggests that immunosuppressed patients are not at increased risk of severe complications compared to the general population, both children and adults. Despite the resource consumption of SARS-CoV-19 epidemic, it is important to circumvent the risk that this pandemic indirectly increases mortality and morbidity of commonly treatable diseases.

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As of March 14, 2020, infection by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), known to cause Coronavirus disease 2019 (COVID-19), has been reported in 142.539 subjects worldwide, with 5.393 fatalities (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200314-sitrep-54-covid-19.pdf?sfvrsn=dcd46351_6). Following the outbreak in China, the Lombardy region of Italy has become one of the areas with highest incidence. The most recent update provided by the Italian Ministry of Health on March 14 2020 declared that as many as 21.157 Italian subjects were diagnosed with COVID-19, including 17.750 who tested positive to the nasopharyngeal swab (http://www.salute.gov.it/portale/nuovocoronavirus/). In Lombardy approximately a thousand new cases are reported every day. Following these outbreaks, concern has been raised for the risk that immunocompromised patients may face during SARS-CoV-2 pandemic.

The Hospital Papa Giovanni XXIII in Bergamo is one of the main hospitals of Lombardy, is located in the "red zone" for the Italian outbreak, and hosts one of the largest European centres for pediatric liver transplantation. We therefore considered advantageous to review available data, and report our preliminary experience with these patients, to offer suggestions on appropriate measures to be taken for the management of children on immunosuppressive treatment.

The number of transplanted patients, both children and adults, is steadily increasing, and so is the burden of patients immunosuppressed for variable reasons, including cancer. Immunosuppressive medications have effects on humoral, cell-mediated immunity and neutrophil function, increasing the risk of severe infections caused by viral agents, such as Adenovirus, Rhinovirus, Norovirus, Influenza, Respiratory syncytial virus (1). Influenza is associated with a more complicate course in children <5 years, adults >65 years of age, persons with co-morbidities. Patients receiving immunosuppressive therapy are at risk for more severe or complicated influenza induced disease (2). This does not seem to be the case for infections caused by the Coronavirus family to date.

The majority of viruses that have caused recent epidemics, with high lethality rates in people, are zoonoses originating from bats. Many of these viruses, including Coronaviruses, implicate the host response as an important contributor to the disease process; in this respect dysregulated and excessive innate immune responses appear particularly important drivers of tissue damage during infection. It has been postulated that the reason why bats are the natural, healthy reservoir of these viruses may reside in their immune tolerance (3-4). These aspects may be relevant when it comes to infection of an immunocompromised host, potentially protected by a weaker immune response against the infection.

In late 2002 occurred an outbreak of severe acute respiratory syndrome (SARS) caused by a novel Coronavirus, which was subsequently named SARS Coronavirus (SARS-CoV). SARS was characterised by an atypical acute, community-acquired pneumonia. The epidemic ended in July 2003, leaving behind a total of 8096 patients infected and 774 fatalities (9.5%) in over 30 countries. Based on WHO data, the case fatality ratio was estimated to be less than 1% in persons aged 24 years or younger, 6% in persons aged 25 to 44 years, 15% in persons aged 45 to 64 years, and greater than 50% in persons aged 65 years and older. Risk factors included household contact with a probable case of SARS, increasing age, male sex and the presence of co-morbidities (5). Overall 48 children under 12 years of age were diagnosed with SARS. Most of them had mild symptoms (fever, cough, rhinorrhoea), and none

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required oxygen supplementation. Overall SARS in children was self-limited and indistinguishable from symptoms reported with other common respiratory viruses (6). Although transplant patients were expected to have poor outcomes if they acquired SARS, at the end of the outbreak no such case had been recorded.

Middle East respiratory syndrome (MERS) is another lethal zoonosis caused by the Coronavirus named MERS-CoV, causing death in 35% of infected subjects. As of February 28, 2018, 2182 cases of MERS-CoV infection (with 779 deaths) in 27 countries were reported to WHO, most occurring in Saudi Arabia. Risk factors for poor outcome in people with MERS-CoV infections include advanced age, male sex and presence of comorbidities (obesity, diabetes, heart disease, lung disease, kidney disease). Immunosuppressed status was not found to be a risk factor (7).

Reviewing the mortality and morbidity reports published on SARS, MERS and more recently on COVID-19, no mention is made on immunosuppression as a risk factor for mortality, and no fatality is reported to be linked to transplantation, chemotherapy or other conditions requiring immunosuppressive treatment, at any age. A recent discussion has appeared in the literature on the possible risk of severe COVID-19 in cancer patients. The few cases presented again appeared to be associated with the known risk factors for severe disease in the general population, rather than to factors related to cancer or its management (8).

Our preliminary experience in Bergamo (where approximately 700 children have received a liver transplant, 3 in the last two months) shows that, among around two hundred transplant recipients at our centre, including ten current inpatients, one hundred with autoimmune liver disease, three under chemotherapy for hepatoblastoma (inpatients), none have developed clinical pulmonary disease, despite three tested positive for SARS-CoV-2 . Considering the infection is currently endemic in our area, other immunosuppressed children are likely to be carriers of the virus, but none was reported to our clinics or to our daily shared-care phone consultation because of pneumonia.

Noteworthy, during the SARS outbreak, the liver transplantation centre of Hong Kong suffered the effect of the shift of resources to SARS patients and the fear of severe disease in transplanted patients. The centre performed no transplants for 6 months, the patients were afraid of attending the follow up clinics, but no case of severe pneumonia was recorded. This affected the quality of care of transplanted patients and liver transplant candidates (8).

In conclusion available data on Coronavirus past and present outbreaks suggest that immunosuppressed patients are not at increased risk of severe pulmonary disease compared to the general population. Children under the age of 12 do not develop Coronavirus pneumonia, regardless of their immune status, although they get infected and can therefore spread the infection. Risk factors for severe disease remain old age, obesity and its complications, other co-morbidities and male sex. Although the surveillance on this particular group of patients should continue, during Coronaviruses outbreaks there are no reasons to postpone life-saving treatments such as transplantation or chemotherapy for cancer, both in children and in adults.

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