Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic

TO THE EDITOR:

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 centers worldwide raised the concern that immunocompromised patients may be at high risk of developing a severe respiratory disease called coronavirus disease 2019 (COVID-19). Unlike common viral agents (such as adenovirus, rhinovirus, norovirus, influenza, and respiratory syncytial virus), coronaviruses have not been shown to cause a more severe disease in immunosuppressed patients. For this family of viruses, the host immune response appears to be the main driver of lung tissue damage during infection. More importantly, in reviewing the mortality and morbidity reports published on coronavirus outbreaks—such as severe acute respiratory syndrome coronavirus (SARS-CoV), which emerged in 2002; Middle East respiratory syndrome coronavirus (MERS-CoV), which is still ongoing; and, more recently, COVID-19—no fatalities were reported in patients at any age who were undergoing transplantation, chemotherapy, or other immunosuppressive treatments. Risk factors for poor outcome include advanced age, male sex, and presence of comorbidities (obesity, diabetes, heart disease, lung disease, or kidney disease). The Hospital Papa Giovanni XXIII in Bergamo, Italy, is located in the "red zone" of the Italian outbreak, and it hosts the main pediatric hepatology and liver transplantation center of Italy. Our preliminary experience, in agreement with recent data from China, shows that among patients in the follow-up for transplantation, autoimmune liver disease, and chemotherapy for hepatoblastoma, none developed a clinical pulmonary disease, despite some testing positive for SARS-CoV-2. The experience so far on coronavirus outbreaks suggests that immunosuppressed patients are not at an increased risk of severe complications compared with the general population, both in children and adults. Despite the resource consumption of the SARS-CoV-2 epidemic, it is important to circumvent the risk that this pandemic indirectly increases mortality and morbidity of commonly treatable diseases.

As of March 14, 2020, infection by the SARS-CoV-2, known to cause COVID-19, was reported in 142,539 patients worldwide with 5393 fatalities.[1] 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 patients were diagnosed with COVID-19, including 17,750 who tested positive to the nasopharyngeal swab.[2] In Lombardy, approximately 1000 new cases are reported every day. Following these outbreaks, concern has been raised for the risk that immunocompromised patients may face during the SARS-CoV-2 pandemic.

The Hospital Papa Giovanni XXIII in Bergamo, Italy, is one of the main hospitals of Lombardy, is located in the eye of the cyclone of the outbreak, and hosts one of the largest European centers for pediatric

Abbreviations: COVID-19, coronavirus disease 2019; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

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liver transplantation. We therefore considered it advantageous to review the available data, to report our preliminary experience with these patients, and 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 various 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, and respiratory syncytial virus.[3] Influenza is associated with a more complicated course in children <5 years, adults >65 years of age, and persons with comorbidities. Patients receiving immunosuppressive therapy are at risk for more severe or complicated influenza-induced disease.[4] 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 immune responses appear to be 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.[5,6] 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, an outbreak of severe acute respiratory syndrome occurred that was caused by a novel coronavirus, which was subsequently named SARS-CoV. SARS-CoV was characterized by an atypical acute, community-acquired pneumonia. The epidemic ended in July 2003, leaving behind a total of 8096 patients infected and 774 (9.6%) fatalities in over 30 countries. On the basis of World Health Organization data, the case fatality ratio was estimated to be <1% in persons aged 24 years or younger, 6% in persons aged 25-44 years, 15% in persons aged 45-64 years, and >50% in persons aged 65 years and older. Risk factors included household contact with a probable case of SARS-CoV, increasing age, male sex, and the presence of comorbidities.[7] Overall, 48 children under 12 years of age were diagnosed with SARS-CoV. Most of them had mild symptoms (fever, cough, or rhinorrhoea), and none required oxygen supplementation. Overall, SARS in children was self-limited and indistinguishable from symptoms reported with other common respiratory viruses.[8] 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 is another lethal zoonosis caused by the coronavirus named MERS-CoV, causing death in 35% of infected patients. As of February 28, 2018, there have been 2182 cases of MERS-CoV infection (with 779 deaths) in 27 countries reported to the WHO, most of which have occurred in Saudi Arabia. Risk factors for poor outcomes in people with MERS-CoV infections include advanced age, male sex, and presence of comorbidities (obesity, diabetes, heart disease, lung disease, and kidney disease). Immunosuppressed status was not found to be a risk factor.[9]

Reviewing the mortality and morbidity reports published on SARS-CoV, MERS-CoV, 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 for patients 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.[10]

Our preliminary experience in Bergamo (where approximately 700 children have received a liver transplant, 3 of which occurred in the last 2 months) shows that among approximately 200 transplant recipients at our center, including 10 current inpatients, 100 with autoimmune liver disease, and 3 under chemotherapy for hepatoblastoma (inpatients), none have developed clinical pulmonary disease, despite 3 testing positive for SARS-CoV-2. Considering that the infection is currently endemic in our area, other immunosuppressed children are likely to be carriers of the virus, but none have been reported to our clinics or to our daily shared-care phone consultation because of pneumonia.

It is noteworthy that during the SARS outbreak, the liver transplantation center of Hong Kong suffered the effect of the shift of resources to SARS patients and the fear of severe disease in transplanted patients. The center performed no transplants for 6 months, and the patients were afraid of attending the follow-up clinics, though no case of severe pneumonia was recorded. This

affected the quality of care of transplanted patients and liver transplant candidates.[11]

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

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