

Management of the COVID-19 outbreak in a pediatric hemato-oncology department
Early experience in protecting immunocompromised patients in Lombardia, Italy

As of **March 14**, at 4 p.m., according to the **WHO dashboard**, updated every 15 minutes, **142,320 cases of COVID-19 infection in 129 countries** have been confirmed **worldwide**, yielding **5,391 deaths**.

On the same date, the ISS reported **19,441 cases in Italy**, the second exposed country in the list, after China, including **1,674 healthcare professionals**. Overall **1,235 deaths** have been reported. Cases are defined by positive molecular tests analyzed in specific regional laboratories, designated by the Health Authority. In the cases reported above, symptoms were absent in 6%, mild in 53%, unspecified in 10%, severe in 26%, life-threatening in 4%. The proportion of patients admitted to Intensive Care Units (ICU) has been 10% in the last two weeks.

Lombardia is, by far, **the most affected Region** in Italy, with **9,820 cases** (median age 65 years, range 0-101), more than half of the National cases, including **1,089 healthcare professionals**. Most cases are concentrated in the Bergamo area, where all **medical residents** do work as attending physicians.

In the **Ospedale San Gerardo in Monza**, a general hospital with 700 beds, activities almost suddenly changed over the past 6 weeks. Most resources have been involved in the management of the emergency. Previous **departments** have been rapidly **switched into new COVID-19 dedicated units**. Most patients accessing the **Emergency Room (ER)** carry symptoms compatible with COVID-19. Very few other medical and surgical emergencies walk through the waiting areas. Similarly, in the pediatric Emergency Room accesses per day decreased to approximately 10%. People are scared to access hospitals due to the possibility of viral transmission.

Patients undergoing specific **swabs** are transferred in a dedicated area of the hospital, from which they are transferred to one of the new ongoing COVID-19 units in case of positivity, or to a COVID-19-free area, in case of negativity. Symptomatic patients with a negative test may undergo a second swab if there is a strong clinical suspicion; temporarily a second swab is required before ruling out the infection.

The first SARS-CoV-2 positive pediatric patient entering our General Pediatric Unit was a 4-month old infant transferred last night for a clinical pattern consistent with bronchiolitis. Actually very few infants and children with no comorbidities have been admitted with COVID-19 elsewhere in Lombardia, and no deaths have been reported so far.

In such a glooming scenario, **no positivities have been detected in hemato-oncological or transplanted pediatric patients so far**. Furthermore, to the best of our knowledge, **no pediatric hemato-oncological cases have been reported in Italy**.

Since the beginning of the outbreak, the **absence of information from China regarding immunosuppressed patients, hemato-oncology and transplanted patients**, in particular, was striking indeed.

From the pediatric perspective, it could be assumed that the disease might have a mild course in **childhood**, nevertheless the very few swabs performed in oligosymptomatic patients scarcely investigated the pediatric population. The **early discontinuation of school activities**, in Lombardia first, then throughout the Country, might have **limited the transmission** in children and young adults. Whether the SARS-CoV-2 spared the pediatric population or the infection occurred with mild symptoms only is still controversial.

The reasons for the absence of reports regarding **immunocompromised** patients is a matter of debate. A possible explanation is that such patients had been rarely infected by the SARS-CoV-2. As a matter of fact, these patients usually experience **social isolation per se**, therefore they might have been early spared since the earliest phases of the outbreak. Such a concept could hold also for another protected fragile category of patients; to the best of our knowledge, COVID-19 has been confirmed in a single 28 year-old patient with cystic fibrosis (personal communications). This occurred 48 hours ago, so that the clinical course could not be described.

Us all, as **pediatricians**, have been relatively **preserved** in someway, therefore some of us **volunteered** to work within the COVID-19 units. At this time COVID-19 workers are separated from the team taking care of immunosuppressed patients.

Within each Department, the creation of a staff dedicated to specific COVID-19 related issues might be considered:

- crisis unit meetings with the hospital director and the key people leading the emergency management: intensive care, infectious disease, emergency room and laboratory directors
- continuous reviewing of WHO, CDC, national authorities websites, Lancet, New England Journal of Medicine, Journal of Infection Diseases, plus general literature searches - (Editors should be aware of how grateful we all are for the timely availability of COVID-19 literature!)
- remote patient management
- PPE provision to plan
- SOP and flow-chart writing,
- relationships with other Departments within the hospital
- donor search coordinator to reschedule transplantation
- physician shift remodeling according to new COVID-dedicated units.
- psychologists should be dedicated to support heart-care professionals working in the COVID-19 dedicated areas, as **physical discomfort and psychological distress** are challenging, due to the burden of managing severely ill patients kept in isolation
- research, if possible

Our **Pediatric Department** includes three wards, Hematology, Transplant, and General Pediatrics, and two outpatient units, one taking care of Hematology and Transplant patients and the other one of pediatric patients, subdivided into multiple sections, including inborn errors of metabolism and genetic diseases. Some of the adopted procedures within the Hematology and Transplant Units were listed here below.

Hematology and Transplant OPD:

- access was limited to the necessary visits, which excluded chemotherapy maintenance, long-term patients in follow-up and most of benign hematology patients, unless judged as urgent, as aplastic anemia, thalassemia, severe anemia, and so on
- patients whose visit had been delayed were managed by phone, in order to check on clinical conditions, biochemistry, when performed elsewhere, and sometimes require the intervention of the primary pediatrician
- sickle cell patients, as well known, are at highest risk when they miss clinical controls and cautions should be used
- only one parent for each kid was allowed to walk in the OPD, unless procedures or conferences/consents required the second parent
- facial surgical masks were worn by health-care professionals, patients and parents at all time
- no volunteers were allowed (child-life specialists, and so on)
- hand washing and alcoholic gel use was intensified and frequently reminded
- patient isolation was even more careful
- employees at the reception have been specifically instructed
- a simple leaflet explaining the characteristics and the risks of the infection was distributed at the reception and to the many families asking for clarification by mail
- a patient flow during and after OPD opening hours was hung to doors and walls in order to differentiate the “clean” and the “dirty” dedicated pathways to access the hospital
- many signs clarify that relatives are not admitted to visit with the admitted patients in the wards, with very few exceptions.

Specific SARS-CoV-2 **swabs** are performed in children when admission was required due to respiratory symptoms and at least 2 out of the following 3 features were present: fever, cough, contact with confirmed or suspected cases.

Also pediatric patients undergoing swabs are transferred in a dedicated area of the General Pediatric Unit with negative pressure; in case of a negative results they are moved to the appropriate unit (i.e. clean Gen Ped or Hem-One Units), whereas in case of a positive result patients remain in the dedicated rooms, up to a C-PAP stage. In case of rapid deterioration deeming intubation, patients would be transferred to a

Pediatric ICU. Symptomatic patients with a negative swab undergo a second swab after 24 hours to rule out the infection. Nevertheless, indications keep changing.

Stem Cell Transplantation Units

Considering transplantation postponement in most non-malignant diseases, apart from life-threatening disorders, is mandatory.

The chances that hematopoietic stem cell donations from unrelated donors could be jeopardized by SARS-CoV-2 related events is not negligible, including COVID-19 involving donors or their family, operating theatre closure in donor centers or anesthesiologists unavailable to assist the harvest procedure, being busy with COVID-19 patients or even being sick themselves. Furthermore, couriers could be put on hold or quarantined in airports towards or from the donor center.

Therefore the transplant Authority in Italy highly recommended to start the conditioning regimen after the stem cells were already collected, transferred, cryopreserved and available to the recipient unit. Stem cell products have been exceptionally cryopreserved in the collection center, when transportation issues became clear after the cell harvest took place.

Last, according to the Authority, all donors should undergo SARS-CoV-2 swab on the same day of donation, regardless of the timing of its result. Such restrictions do not apply to related donors, even though issues regarding the operating theatre and the anesthesiologist availability should be preliminarily evaluated.

Shortage of intensivists and bed unavailability should be considered upon each transplantation planning.

Shortage of blood products is likely to occur, despite the fact that National Authorities specifically mentioned blood donations as a valid reason to circulate, despite the restrictions applied to the red-areas, which include the whole country since March 11.

Hemato-Oncology Units

Slight changes only were adopted in the Hematology Unit. Surprisingly, new leukemia diagnoses frankly dropped. Expected delayed diagnoses will be expected, so that diseases might be diagnosed at a more advanced stage, when higher hyperleukocytosis, CNS involvement or deeper cytopenia will have occurred.

Chimeric antigen receptor T cells

The same issues related with transplant product couriers might apply to CAR-T product delivery, when cells were manipulated elsewhere. What is most cumbersome is the possible unavailability of ICU beds and physicians. Furthermore, the hypothesis that tocilizumab, electively used to manage post-CAR-T cytokine release syndrome,

might be extensively used in the COVID-19 treatment (studies would be desirable!) is an additional issue. On the other hand, it is well known that candidates to CAR-T are mainly patients with refractory diseases for whom the risk of a postponement could be fatal.

Conclusions

These lines were written with the purpose to share issues encountered in the first few weeks of the SARS-CoV-2 outbreak in Italy.

Many of us had thought that media had caused what had been defined a “infodemia”, which spread panic worldwide. Expected death rates, after the Chinese experience, have been compared to those yielded by influenza yearly, to minimize its impact. Immunologists and epidemiologists will investigate the role played by the absence of immunity towards this new viral strain, its speed of transmission, the multiple patterns of the disease, which do not allow to recognize and isolate oligosymptomatic cases, the clinical course of the infection, mainly in the elderly, in making the COVID-19 pandemic an unprecedented one in the recent times. Did anything similar happen during the colonization of the New World after 1492, when Native Americans had no immunity to many of the deadly diseases brought there?

None of us was prepared for this SARS-CoV-2 outbreak or could have imagined its consequences. The purpose of these lines is to alert colleagues to be promptly prepared for the emergency.

According to Remuzzi and Remuzzi projections, more than 2,500 additional ICU beds should be implemented within one week in Italy for COVID-19 patients; accordingly, 20,000 additional doctors and nurses and 5000 additional ventilators should be provided to Italian hospitals.

As the WHO clearly stated, all countries could still change the course of this pandemic infection. As most European Countries are few weeks behind Italy, in terms of SARS-CoV-2 outbreak, our emergency measures should also be a priority for them. In case this report could allow somebody not to say “if only I would have known in advance...”, it will have met its aim.

Estote parati. Which, in Latin, means: be ready!

References to complete.

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