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PROTOCOL FOR THE USE OF KIDNEYS RETRIEVED FOR TRANSPLANTATION FROM COVID POSITIVE DONORS

1 - INTRODUCTION

The first case of SARS-CoV-2 infection was reported on December 31, 2019. Transmission of the infection occurs from human to human, mainly through droplets and/or aerosols from the respiratory tract of an infected individual. The infection manifests itself with flu-like symptoms and mainly affects the upper respiratory tract, but in many cases it also affects the lungs with consequent severe impairment of function and patient's death. In addition, the involvement of other organs has been documented in some patients which, however, cannot be attributed with certainty, directly to an active replication of the virus in these organs. *(Evidence of SARS-CoV-2 infection …. Through transplantation: Transpl. July 2021, 105, 7; 1405)*

Due to the fact that the essential prerequisite for the use of organs retrieved from deceased donors is the absence of known factors capable of transmitting serious infections and given that the SARS-CoV-2 infection is very contagious and has a rather high lethality rate, since the beginning of the pandemic there has been considerable concern about avoiding the transmission of SARS-CoV-2 from donor to transplant recipient.
Therefore, the competent health authorities and the scientific societies involved, immediately adopted resolutions defining as "not usable for transplantation" the organs of deceased donors with a positive or suspected history of SARS-CoV-2 infection, of which, at the time of death, the virological recovery from the disease for more than four weeks and the negativity of the SARS-COV-2 test within 48-72 hours prior to organ retrieval had not been ascertained (Prot 492/CNT 20 feb 20; prot 975/CNT 26 mag 20; Prot. 288/CNT 2021 24 feb 2021). Following the evolution of knowledge on the matter, the time interval from virological recovery was reduced to two weeks.
Moreover, both the enormous pressure exerted by the pandemic on the health systems of all the countries concerned, and the high rate of spread of the infection have led to a significant reduction in procurement and organ transplantation activities.

2- During the course of the pandemic, however, it was found that in transplants performed with organs retrieved from deceased donors who were subsequently identified as SARS-CoV-2 positive, the disease had been transmitted to lung recipients but there was no recorded case of transmission of the infection to kidney, heart and liver transplant recipients (*https://optn.transplant.hrsa.gov/news/Summary of Current Evidence….Organ Recovery from Donors…COVID-19)*

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Therefore, with the evolution of the pandemic and the acquisition of more consistent knowledge on the management of the SARS-CoV-2 infection, the competent health authorities and scientific societies have progressively reconsidered the possibility of using organs retrieved from donors who tested positive to SARS-CoV-2.

3- In Italy, on August 21, 2020 CNT's General Director, with the approval of the Council and CNT, taking note of the further knowledge acquired during the pandemic's first wave, issued a statement that said: "Organs from SARS-CoV-2 positive donors (in respiratory secretions from BAL or deep bronchial aspirate), or who have a positive history for COVID-19 without waiting 4 weeks after recovery, where "recovery" is defined as testing negative to the search for SARS-CoV-2-RNA in respiratory secretions (nasopharyngeal swab or BAL), can be offered for transplantation to SARS-CoV-2 positive patients who have developed acute organ failure due to infection and/or related drug toxicity, which causes a condition of clinical urgency (e.g. acute liver failure). **Therefore SARS-CoV-2 positive donors will not be considered *a priori* ineligible for organ donation"**.
Through subsequent notes, this provision was gradually updated in relation to what was emerging from the data available both from its application, from other countries' experience, and from the evolution of the pandemic itself. In Italy, in the 1 November 2020 - 21 November 2021 period, this resulted in the use of 21 SARS-CoV-2 positive donors which allowed 22 liver transplants and 3 heart transplants.
The data relating to the first 10 liver transplants were published in the American Journal of Transplantation (Romagnoli et al: *Am J Transpl DOI: 10.1111/ajt.16823*): no transmission of disease from donor to recipient was observed and patients, with a follow-up ranging from 75 to 239 days, are alive and with a functioning organ.

2 - DATA

1 - At 31 December 2019, the Italian register of dialysis and transplantation reports a prevalence of patients undergoing dialysis of 811 per million population which, compared to the resident population recorded by Istat's census on the same date, leads to a total of just over 48000 patients; of these, on the same date, the Italian National Transplant Center had 6499 patients wait-listed for kidney transplantation.*(https://ridt.sinitaly.org/2021/10/12/report-2019)*

2 - Since the first months of 2020, this population has heavily been affected by the SARS-CoV-2 pandemic. A survey conducted by the Italian Society of Nephrology research group on the Sars-CoV-2 infection, through specific questionnaires submitted in 365 nephrological centers, established that between **February and April 2020**, 2.2% of the 34960 hemodialysis patients surveyed, tested positive for SARS-CoV-2. The authors also reported a 0.86% incidence of SARS-CoV-2 on a sample of 25481 patients with follow-up kidney transplantation at the same centers, in the same period.
At the end of April, the mortality rate observed among the SARS-CoV-2 positive patients surveyed was 32.8% compared with a mortality rate of 13.3% observed in the general population over the same period.
(*Journal of Nephrology 33,725–736,2020*)

3 - Confirmation of the greater susceptibility to SARS-CoV-2 infection of transplanted patients or those awaiting transplant comes from a broader analysis conducted by CNT's data processing group by crossing the data from the Italian National Institute of Health integrated COVID-19 platform and

the data on the Italian Transplant Information System (SIT). This analysis found, in the 21 February - 31 December 2020 period, a cumulative incidence of SARS-CoV-2 positive subjects of 3.63% in the general population, 4.96% among solid organ transplanted patients and 6.4% among patients awaiting transplant (*F. Puoti, A Communication to the Italian Transplant Network General Assembly, Rome 16-17 November 2021*; *S. Trapani, F. Puoti, L. Masiero, et al.* **Impact of Sars-CoV-2 infection in solid organ transplant recipients: the reporting data at the end of a difficult year in Italy**. *Transpl International 2021. European Society for Organ Transplantation, Vol.34 (Suppl.1), POS424, p. 348*).

4 - With regards specifically to kidney transplantation, SIT data shows that in the 21 February - 31 December 2020 period, out of a total of 6113 wait-listed patients (ITT) for kidney transplantation, 590 (9.6%) tested positive to SARS-CoV-2 and, of these, 74 (12.5%) died after the infection.
Conversely, in the same period, out of a population of 26404 kidney transplant follow-up patients on the SIT, 1459 (5.5%) patients tested positive to SARS-CoV-2 and 195 (13.3%) died after the infection. 77.3% of these 198 (1.1%) re-contracted the SARS-CoV-2 infection.
(*F. Puoti, A Communication to the Italian Transplant Network General Assembly, Rome 16-17 November 2021*).

5 - In recent literature (research on PubMed on 30 November 2021) a considerable amount - in total 34 - of cases of kidney transplantation from a deceased SARS-CoV-2 positive donor are reported. All selected donors were positive to SARS-CoV-2 molecular tests in specimen collected at hospitalization and/or immediately prior to organ retrieval with upper respiratory tract swab or aspirate or deep respiratory tract wash.
No transmission of SARS-CoV-2 infection was found in any of the recipients.

6 – In cases where signs of viral replication were sought in a biopsy and/or autopsy kidney sample from patients who died of Covid-19, this research was negative or of uncertain interpretation.
(*Frelih M. et al. SARS-CoV-2 virions orubiquitous cell structures? Actual dilemma in COVID-19 Era. KidneyInt.2020;5:1608–1610.)*

7 - From the beginning of the pandemic to 21 November 2021, 67 potential SARS-CoV-2 positive organ donors who died of causes unrelated to the infection were reported to CNT's Operational Coordination.

3 – RATIONALE

The following considerations result from the above:

1 - In kidney transplants performed from the onset of the pandemic using, either involuntarily or deliberately, organs from deceased donors with a history of or tested positive to SARS-CoV-2, no transmission of infection was observed to the recipient.

2 - The risk of becoming infected with SARS-CoV-2 for patients awaiting kidney transplant, in the period February - December 2020, when vaccines were not available, was higher than for kidney transplanted patients; while the COVID-19 related mortality risk for wait-listed patients was comparable to that of transplant recipients.

3 - Among the patients on the waiting list there is a fair number of individuals with high seniority, high PRA, difficult to transplant due to blood group and/or HLA typing and with non-optimal clinical conditions (intermediate or high case mix).

4 - Since the vast majority of patients wait-listed for kidney transplantation is currently vaccinated and a substantial number of them caught the infection and have recovered, the risk of reinfection for these patients is very low. However, the data on the duration of the immunity induced both by the natural infection and resulted from vaccination show a progressive decline over time.

5 - We now retain an anti COVID-19 therapeutic background which allows us to counteract the infection, even if some of the monoclonal antibodies available are not effective against some of the variants currently circulating. The accessibility of antivirals with considerable efficacy against SARS-CoV-2 is able to potentially and effectively control the possible, although unlikely transmission.

6 - The data collected during the pandemic in Italy and those reported by operational CNT lead us to believe that a significant number of kidney transplants could be achieved in Italy with organs from a SARS-CoV-2 positive donor who died of causes other than the infection. Based on the elements described above, the use of kidneys from donors with active SARS-CoV-2 infection and who did not pass due to the infection, seems justified.
This protocol outlines an operating procedure proposition for using these kidneys.

4 – THE PROTOCOL

4.1 – Inclusion Criteria

A – Donor

The Ad Hoc Disease Transmission Advisory Committee of the United States' OPTN (*https://optn.transplant.hrsa.gov/news/summary-of-evidence-report-details-experience -with covid-19*) defined as:

1 – Donor with active COVID-19: a donor with a documented history of COVID-19 with less than 21 days from the onset of the symptoms and with a positive SARS-CoV-2 test in a respiratory sample or an asymptomatic subject without a history that helps determine the date of disease onset and with a positive SARS-CoV-2 test.

2 – Donor with mild COVID-19: a donor with a positive SARS-CoV-2 test in a respiratory sample with symptoms consistent with COVID-19 infection who did not require oxygen supplementation or inpatient hospitalization.

3 – Donor with severe COVID-19: a donor with a positive SARS-CoV-2 test in a respiratory sample with symptoms consistent with COVID-19 infection who required oxygen supplementation or inpatient hospitalization.

With reference to these definitions, we believe that, at least in a first phase, the only donors that should be taken into consideration are those *with positive SARS-CoV-2 tests in a respiratory secretion sample from BAL or bronchial suction at the time of retrieval and/or within 14 days prior*

to retrieval, who died of other causes, in the absence of clinical signs of COVID-19 disease.

B – Recipient

The following patients waitlisted for kidney transplantation are admitted to be transplanted with organs from donors with SARS CoV-2 infection as defined in the previous section:

- patients with documented recovery from the infection for no longer than 4 months or complete vaccination (3 doses) with the last dose administered not earlier than 4 months from the organ offer and with documented response by seroconversion and, if available, by virus specific cell-mediated immunity ;
- patients who signed, at the time of registration on the waiting list and, in any case before they were offered the kidneys from a donor with active SARS-CoV-2 infection, the informed consent for transplantation with an acceptable non-standard risk donor;
- patients whose clinical conditions make the risks associated with being waitlisted higher than those
  known so far, arising from the possible transmission of COVID-19 from a donor, according to the Transplant Centre's physicians. These may include patients:

  - in national urgency, due to depletion of vascular accesses;
  - included in the PNI program (National Hyperimmune Program);
  - in relative regional urgency;
  - with a long waiting period on dialysis;
  - with such a hyperimmunization condition that a long waiting period on the list is to be expected.

4.2 – Post-transplant monitoring

Monitoring must be focused, above all, at documenting/excluding any recurrence of the SARS-CoV-2 infection.
The data relating to delayed graft function, graft failure, the immunosuppressive therapy administered (dosage and time), infectious complications with relative diagnostics and specification of the treatment undertaken must be sent to CNT
- in the immediate post-operative period on a weekly basis
- when the patient is discharged
- at 1, 3, 6 months and 1 year
Any event occurring in the periods between the established follow-up must be reported to CNT and the national Second Opinion for Infectious Diseases by the physician responsible for the clinical management of the recipient.
In addition, the following investigations will be carried out and in the following time intervals for the monitoring of a possible SARS-CoV-2 infection:

	PRE-TRANSPLANT	POST-TRANSPLANT			
		DAY 7	DAY 14	DAY 21	DAY 28
Nasopharyngeal swab for SARS-CoV-2	X	X	X	X	X
BAL if intubated patient	X	X	X	X	X
Serological test for SARS-CoV-2*	X	X	X	X	X
Search for SARS-CoV-2 in other biological speciment (blood, biopsy, etc.)#	X	X	X	X	X
Search for SARS-CoV-2-RNA in biopsy of retrieved organ from donor and on perfusion fluid&	X	X	X	X	X

***** It is not necessary to acquire the result before transplant. Specify the type of serological test used and ideally always search for specific neutralizing antibodies

if indicated and if validated diagnostic tests are available

& The result will be acquired *a posteriori* and does not affect the transplant. It is essential to report to CNT any adverse event that may occur in the recipients of these organs and to monitor the recipient even after the first month after transplantation in order to assess any possible negative impact in the medium and long term.

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