
***POSITION STATEMENT ON MEASURES TO
REDUCE THE RISK OF COVID-19 IN SOLID
ORGAN TRANSPLANT RECIPIENTS BY
USE OF VACCINATION, IMMUNE TESTING,
AND PUBLIC HEALTH POLICIES***

ON BEHALF OF THE EUROPEAN SOCIETY FOR ORGAN TRANSPLANTATION (ESOT) AND THE
ESCMID STUDY GROUP FOR IMMUNOCOMPROMISED HOSTS (ESGICH)



ESGICH

ESCMID STUDY GROUP
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This document represents a position statement by which the European Society of Organ Transplantation (ESOT) and the ESCMID Study Group for Immunocompromised Hosts (ESGICH) aim to provide guidance to clinicians involved in the care of solid organ transplant recipients regarding the management of the risk for SARS-CoV2 infection in the current pandemic scenario, and to advocate for public health policies directed towards protection of this particularly frail population. With the support of the Centre for Evidence in Transplantation, a panel of experts from both societies reviewed the current literature focusing on the effectiveness of immune response following SARS-COV2 vaccination, the interaction with immunosuppressive medication, and the role of antiviral therapies in this context.

The document has been structured by specific questions developed according to the Population Intervention, Compare and Outcome (PICO) format. Recommendations have been developed following a Delphi-like process among the panel of experts.

Because of the rapid evolving evidence, recommendations are subject to periodic update, and despite our effort to report the most current supporting studies, we acknowledge the possibility that at the time of the issue of this statement, some recommendations may be outdated by upcoming studies. Nevertheless, we believe that this position statement is filling a gap in the need for specific guidance and advocacy to mitigate the risk of COVID-19 in solid organ transplant recipients.

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Solid organ transplant recipients (SOTR), which are at significantly higher risk of severe disease and mortality when infected by SARS-Cov2, were prioritized worldwide for vaccination campaigns against SARS-CoV-2. However, because this vulnerable population was excluded from all phase 3 clinical trials conducted on the COVID-19 vaccines currently available in the EU, most of the available evidence comes from observational “real life” studies. The latter suggest that COVID-19 vaccination with mRNA vaccine is safe in SOT recipients, with no excess risk of acute rejection and an incidence of adverse events similar to that reported in the general population (mild injection site pain, 61%; fatigue, 38%; headaches, 32%; myalgias, 15%; chills, 9%; and fever, 4%) (1). On the other hand, several independent studies have reported a significantly lower response rate of SOT recipients to the standard 2-dose scheme of vaccination (2-4). Thus, concerns on the clinical response to vaccination and about the need to monitor and optimize vaccine response in the SOT population have been raised.

1. Does the third dose of SARS-CoV2 provide clinical efficacy in SOTR as compared to patients receiving two?

SOTR naïve for the virus have lower antibody response rate to COVID-19 vaccines as compared with the general population (5). It has been reported that only 4-48% of SOTR have detectable IgG after the second dose of COVID-19 vaccine (6). Antibody response appears to be negatively influenced by antimetabolite therapy, older age, high body mass index, and short delay (< 1 year) after transplantation (7). In addition, antibody response rate was different according to the kind of transplant, with liver recipients showing the higher rate of response and renal transplant and thoracic organ recipients showing the least (8). The lower antibody response following two-dose vaccination is mirrored by a lower clinical efficacy than general population, with about 30% hospitalization rate in breakthrough infections (9), although vaccinated SOTR do show a significantly lower risk of SARS-CoV2 infection than unvaccinated ones (10).

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In this scenario, randomized studies show that a third dose of vaccine showed improved efficacy in increasing the rate of antibody response up to 55% 4 weeks after the injection, even if the third dose was a vector-based vaccine (11, 12).

- *Because of an inadequate protection following the two-dose vaccination scheme, it is recommended that all SOTR receive a third dose of either mRNA-based or vector-based SARS-CoV2 vaccine.*

2. Is there evidence that monitoring immune response to SARS-CoV2 vaccination in SOTR has any clinical utility as compared with no monitoring?

Which of the cellular or the humoral adaptive immune effectors are the most important in conferring protection against COVID-19 after mRNA vaccination (i.e. “mechanistic correlates of protection”) is not yet entirely clear. Recent reports have however clearly demonstrated the importance of neutralizing antibodies (13), in particular in vaccinated SOTR (14). Neutralizing antibodies act by binding to the spike protein of SARS-Cov-2, thereby eliminating extracellular viruses and preventing their entry in host’s cells: absence of antibody response after vaccination identify patients with no protective immunity against SARS-CoV2 infection (15).

Measuring the neutralizing capacity of patient’s serum requires specific *in vitro* assays that are not routinely accessible in the clinical practice. However, high titers of anti-spike (or RBD) IgGs, measured by conventional enzyme-linked immunosorbent assays (ELISA), correlate well with serum neutralizing capacity and vaccine efficacy against symptomatic COVID-19. An additional major advantage of binding antibody assays is that their results can be converted to the WHO international standard (NIBSC code 20/136) and expressed in binding antibody unit (BAU)/ml, making individual results comparable across the various platforms and laboratories (16).

- *We recommend to use the titer of anti-spike (or RBD) IgG in specific cases to estimate the level of protection of SOTR against severe COVID-19.*

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- *Despite the lack of clear consensus regarding the threshold of BAU/ml conferring protection, there is consensus that absence of any detectable antibody response indicates lack of effective protection against severe COVID-19 and may identify patients needing additional protective strategies.*

3. Do SOTR receiving additional doses of vaccine achieve more protection from COVID-19 than those receiving three doses?

Some SOTR do not develop adequate antibody titers after 3 doses of vaccine. Recent studies suggest that a 4th dose of mRNA vaccine is well tolerated and allows inducing antibody response in 45 to 60% in these non-responders to 3 doses (15, 17-19).

Although no data are available in the transplant population, the currently dominant Omicron variant has shown significant immune-escape abilities in the general population receiving two vaccine doses. This immune escape is mitigated by a third dose in the general population and it can be speculated that a fourth dose may elicit increased protection against Omicron variant in SOTR.

- *We suggest the administration of additional booster vaccine doses in SOT recipients that do not have sufficient antibody titers to be protected from the dominant virus variant in circulation.*

4. What is the interaction between immunosuppressive therapy and efficacy of SARS-Cov2 vaccine response in SOTR?

The reduced response to SARS-Cov2 vaccine in SOTR has been discussed previously. Patients on transplant waiting list show a slightly reduced response to vaccination as compared to healthy population, but significantly better than transplant recipients (20, 21). In a single small observational study, anti SARS-CoV2 antibody titer in kidney recipients vaccinated prior to transplant persisted higher than recipients vaccinated after transplant (22).

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The response rate to COVID-19 vaccination is lower for patients in their first months after transplantation, especially for those that received T or B cell-depleting agents as induction therapy or as treatment for rejection (23, 24).

In addition, steroid, high dose mycophenolate mofetil and belatacept in maintenance regimen have also been associated with a lower rate of vaccine response (23). Although tempting to speculate that a reduction of maintenance immunosuppression would improve the response to vaccine, there is currently no data demonstrating this theory. Furthermore, it is controversial to what extent the advantage in reducing immunosuppression to favor vaccine response is counterbalanced by the risk for rejection or donor specific antibody onset.

- *We recommend that all transplant candidates receive full cycle of SARS-Cov2 vaccine before transplant*
- *Administration of SARS-Cov2 vaccine within the first 3 months after transplantation or lymphocyte depleting therapies has limited efficacy and it is advisable to postpone vaccination*
- *Despite the convincing evidence showing that immunosuppressive drugs, including high dose of mycophenolate derivatives, belatacept, steroids and lymphocyte depleting agents, limit the immune response to the COVID-19 vaccination, the net benefit in reducing or withdrawing these drugs to favor the response to SARS-CoV2 vaccination is still under investigation, and cannot be currently recommended in this context. Nevertheless, in SOT recipients with absence of detectable response to previous vaccine dose, over one year from transplantation with stable graft function and no recent episode of rejection or de novo DSA onset, a reduction or withdrawal of these immunosuppressive drugs before additional vaccine dose can be evaluated, taking into account the epidemiological risk of severe COVID-19 and the individual risk of rejection.*

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5. Do SOTR additionally treated with passive immunization achieve greater protective immunity against SARS-CoV2 when compared with SOTR receiving vaccination only?

A fraction (estimated up to 20%) of SOT recipients do not develop any detectable antibody response after the intensified 3-dose regimen of mRNA vaccine (25). They appear unlikely to respond to a further booster dose and might instead benefit from passive transfer of anti-SARS-CoV-2 monoclonal antibodies as primary prevention strategy with Tixagevimab-Cilgavimab, recently approved for pre-exposure prophylaxis (15, 26). However, there is uncertainty regarding the sensitivity of OMICRON variant to Tixagevimab-Cilgavimab, while it appears sensitive to Sotrovimab which is available for treatment and not approved for prophylaxis (27-29).

- *Pre-exposure prophylaxis with monoclonal antibodies can be considered to prevent severe COVID-19 in patients with no detectable antibody response after 3-dose regimen of SARS-CoV2 vaccine. Administration of these antibodies however prevents the response to any subsequent SARS-CoV2 vaccine for a time period of at least six months.*
- *Caution should be taken into account regarding the potential resistances of emerging variants against approved antibodies*

6. Do SOTR require specific public health measures to contain the risk for COVID-19?

In relation to the higher risk of severe outcomes after SARS-CoV 2 infection and the limited response to vaccination, SOTR represent a fragile population, exposed to a higher risk of mortality and morbidity due to COVID-19. Studies investigating the impact of lifestyle measures or public health policies on the risk for COVID-19 consequences in these patients are limited but support the concept that behavioral preventive measures do have a protective effect (30). In this context current public health policies to contain SARS-Cov2 pandemic

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vary widely across different countries, and in the majority of cases there is no specific recommendation for SOTR. We believe that health authorities at different levels need to develop specific recommendations and implement measures to protect these patients.

- *We strongly recommend that regardless of the rules implemented for the general population, SOTR continue to wear masks and keep social distancing every time they need to convene in a crowded open space or in any indoor gathering. We also recommend frequent hand washing.*
- *We recommend that hospital administration provide support to identifying clean paths and safe procedures to avoid contact of transplant patients with hospital areas at high risk of SARS-CoV-2 transmission.*
- *We recommend that healthcare systems identify preferential paths to facilitate early treatment with monoclonal antibodies and novel antivirals for transplant patients with SARS-CoV-2 infection”*

The scope of this statement is to provide guidance and support to the transplant community in protecting transplant recipients from SARS-CoV2 adverse consequences. However, the evidences supporting this statement are rapidly evolving, therefore recommendations will be frequently revised according with the most updated literature. We welcome comments from ESOT membership, including suggestions, additional questions, and advice for new upcoming papers to be considered for future updates.

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