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)
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This document is the first update of the ESOT-ESCMID position statement about the management of the risk for COVID-19 in solid organ transplant recipients. The first statement was focusing on the need for additional vaccine boosters in these patients and provided initial highlights towards antiviral and prophylactic strategies in these patients. Six months later, in light of new evidences and of a different pandemic scenario, we felt important to provide an update addressing additional questions that may arise in patients and in healthcare professionals. In this document in particular, we aimed to deliver the content by using a language accessible to lay public and patients, in order to improve their awareness on the need to achieve as much as possible protection for the risk of COVID-19, based on the most currently available evidences.

1. Is there an easy way to know whether patients with solid organ transplantation are efficiently protected against COVID-19?

Recent studies have identified correlates of protection against COVID-19, i.e. tests that predict whether or not a patient is at risk of developing symptomatic COVID-19 after exposure to SARS-CoV-2. Neutralizing antibodies appear to be the most potent immune effectors to protect against disease, both in non-transplant patients and in SOTR (1,2). Neutralizing antibodies bind to the spike protein of the virus, thus blocking viral entry into target cells and helping to eliminate extracellular viruses. However, measuring the viral neutralizing capacity of a patient’s serum is not a routine assay, and the antibody titres are the only test available to clinicians. The results of the first vaccine studies showed a strong correlation between the antibody titres and the capacity of the serum to neutralize the virus. This made it easy to establish a threshold of antibody titer beyond which patients were protected. However this is no longer the case today. Indeed, it is now known that the antibody threshold that allows effective viral neutralization depends on the mode of previous exposure to the virus (vaccine or infection) and on the viral strain. In particular, while the ability of an immune serum to neutralize the omicron variant remains correlated with the antibody titre, it appears at a much higher titre than for the wild-type virus strain (3).

In practice, there are three situations. SOTRs who do not have anti-SARS-CoV-2 antibodies remain at very high risk of infection and should be prioritized for pre-exposure prophylaxis (see below). On the contrary, patients who, following different viral stimuli (vaccine or infection), have high antibody titres, can be considered as protected. Between the two, there is a grey area in which uncertainty must be dealt with.
2. Should booster doses be given to SOTRs, and if so, when?

There are contradictory data regarding the evolution of antibody titres. It has been demonstrated in health care workers that antibody titres decrease over time after vaccination with mRNA vaccines (4,5). In contrast, another study showed a stable titre of antibody six months after a second dose in SOTRs (6).

Considering that i) the data on the kinetics of long-term antibody titres in SOTRs are limited, ii) high antibody titres are required to protect SOTRs against variants of concern, iii) the third and subsequent booster doses are highly effective in increasing antibody titres in patients responding to vaccines (7–12), we consider it appropriate to give booster doses to SOTRs as early as 6 months after the last dose in order to maintain high antibody levels and optimal protection.

Data on the new mRNA vaccine formulations (containing mutated spike proteins) are still too preliminary for recommendations on their use to be made.

3. What is the place of preventive and curative treatments of COVID-19 in SOTRs?

Most of the monoclonal antibodies (Bamlanivimab + Etesevimab, Casirivimab + Imdevimab cocktails and Sotrovimab) that have been developed to prevent COVID-19 in immunosuppressed patients have no or reduced activity against the Omicron subvariants (13-14), which accounts for almost all cases in Europe at the time of writing (15). Only the tixagevimab/cilgavimab combination (EVUSHELD™) retains moderate neutralising activity against omicron sub-variants. Thus, the pre-exposure prophylaxis is now achieved through the administration of EVUSHELD™, at a dose of 600mg (330 mg of Tixagevimab and 300 mg of Cilgavimab). This treatment should be given as a priority to non-responders to vaccines. Patients who have received a first administration of 300mg should receive a second administration as soon as possible. This recommendation has been released by FDA in February 2022 (https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-revisions-evusheld-dosing). However, because not all national health authorities have validated this attitude yet, this strategy is not applicable everywhere in Europe. Of note, patients who have received monoclonal antibodies prior to any dose of vaccine should not be discarded. Indeed, a recent study showed that Bamlanivimab (a monoclonal antibody to SARS-CoV-2) had little effect on vaccine response in healthy subjects (16), suggesting that this strategy could also be applied in SOTRs to increase vaccine coverage.

Finally, the curative treatment Paxlovid™ (nirmatrelvir/ritonavir) is available but difficult to handle in SOTRs because of the major risk of interactions with immunosuppressive drugs. However there are currently recommendation on how to deal with drug-drug interactions that may allow a safe use of this drug (17-18). In addition, in some European countries another antiviral Lagevrio™ (Molnupiravir), is available and may be used as an alternative to Paxlovid™. Current ongoing studies should soon provide evidence on the best way to streamline the use of these different options.
References


