The Effects of SARS-CoV-2 on Transplant Patients

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Abstract

The COVID-19 pandemic has had a profound effect on the entire human race. It is easy to look over the fact that people with certain health challenges are more severely impacted than others. While a significant amount of research explains how COVID-19 affects the general population and how to prevent infection among these individuals, there has been a lack of information relating to the effects of the SARS-CoV-2 virus on the smaller population of transplant patients. Specifically, what is the pathogenesis of the SARS-CoV-2 virus in these patients, and do the COVID-19 vaccines protect these people from infection? This study will attempt to uncover the answers to these questions by utilizing current peer-reviewed research done on transplant patients with and without COVID-19. In addition, an interview will be conducted with a healthcare provider who cares for transplant patients. This research will provide a critical evaluation of the existing research to identify any gaps in the current understanding of this topic. This will also provide healthcare providers with useful information on how to manage SARS-CoV-2 infection in transplant patients.

Key Words: SARS-CoV-2, Transplant Patients, Pathogenesis, Vaccine

Introduction—Research Question

At the height of the COVID-19 pandemic, scientists searched for a solution to stop the spread and protect the millions of people who were at risk of dying from the disease. Countless hours of research led to the discovery and subsequent mass production of vaccines in under a year. While these efforts were instrumental in slowing the spread of COVID-19 and saving the lives of those affected, one group was left in the dark. Due to the lowered immune status of Solid Organ Transplant (SOT) recipients, it was unclear how this patient population would react to infection with SARS-CoV-2. In addition, it was uncertain how these patients would respond to a vaccine. Information regarding this population continues to lack. Although research is slowly emerging, physicians are still unsure how to care for these individuals after the emergence of the SARS-CoV-2 virus. For the general population, vaccine recommendations have been clearly defined, whereas recommendations for the SOT population have been left rather ambiguous.

Transplant patients must comply with stringent immunosuppressant drug therapy for the remainder of their lives to prevent rejection of the transplanted organ. These drugs cause SOT patients' immune systems to be severely depressed. This not only increases their risk of contracting illness but also increases their risk of having a severe reaction. This research paper will attempt to understand the pathogenesis of SARS-CoV-2 in Solid Organ Transplant patients, and therefore discern how this virus affects SOT patients differently than the general population. In addition, the efficacy of the COVID-19 mRNA vaccine in SOT patients will be examined. The results of this research will allow for a review of the current CDC recommendation for immunosuppressed individuals. Overall, this paper asks, is there a correlation between immune status and mortality rates for SOT recipients infected with COVID-19, and will the SARS-CoV-2 vaccines protect them from contracting the virus and prevent severe disease?

Physician Interview and Case Experience Regarding COVID-19 Guidelines

A primary objective of conducting research regarding transplant patients and COVID-19 was to provide healthcare workers with more information to properly treat these patients. In an interview conducted with a family physician, they stated that the number one area of study still lacking regarding COVID-19 was that of the transplant patient population. While the instructions for the prevention and treatment of COVID-19 in the general population are well-defined, the immunosuppressed population does not have the same comfort. When asked about vaccination recommendations for their patients, the physician strongly supported getting vaccinated if "at risk"; which includes patients with "comorbid conditions, obesity, asthma, heart disease, diabetes, and immunosuppression". In addition, they recommended that anyone coming into contact with a transplant patient, including family and friends, should be vaccinated. Because of the lack of information regarding the efficacy of SARS-CoV-2 vaccines, the interviewed physician normally instructs their transplant patients to first ask their transplant team of doctors before getting vaccinated to check for contraindications. When asked about future improvements regarding care for transplant patients, the physician stated that there must be better communication between specialists and primary care providers. Increased communication ensures that the patient is being cared for accurately from the perspective of the transplant team as well as the family physician. The following case study describes one of the physician's transplant patients and their experience with COVID-19.

A 65-year-old woman presented to her family physician for a wellness exam. The patient has a history of polycystic kidney disease and received kidney transplantation in 2014. She is on lifelong immunosuppressants to prevent the rejection of the transplanted organ.

She explains that her transplant team through Beaumont Hospital immediately suggested that she receive a COVID-19 vaccine when they were released in 2020 after the pandemic began. She was initially hesitant due to fear of an abnormal reaction to the mRNA vaccine because of her depressed immune system and transplantation status.

The patient proceeded to get three SARS-CoV-2 vaccines, as requested by her transplant team. However, antibody tests showed less than optimal antibody response to vaccination. For this reason, she does not wish to receive any further vaccinations. However, the patient also stated that she was exposed twice to COVID-19 but never got sick. The patient continues to wear a mask in public and is very careful in general in preventing illness.

Finally, she mentioned that the COVID-19 pandemic has made her feel forgotten and ignored due to the lack of information about Solid Organ Transplant patients and COVID-19.

This case study illustrates a real example of a transplant patient's experience with COVID-19. The uncertainty throughout the process and lack of knowledge not only discouraged the patient from continuing with vaccination but also made her feel overlooked by the medical community. This highlights the importance of increased research on the pathogenesis of COVID-19 in transplant patients and the efficacy of the vaccine. More information will allow family physicians and transplant teams to better guide these patients in prevention and treatment. In addition, definitive research and recommendations regarding the SOT population will prevent the spread of misinformation that leads to untrusting and nervous patients who are afraid to get vaccinated.

Overview of COVID-19 in the General Population

Among the general population, once the SARS-CoV-2 virus is transmitted, the viral spike glycoprotein on the surface of the virus will bind to the host cell via angiotensin-converting enzyme 2 (ACE2) (Cowan & Smith, 2021). This binding will allow the viral genome to enter the cell and begin replication (Cowan, & Smith, 2021). The virus may spread to the lower respiratory tract and infect alveoli type II cells causing apoptosis and therefore lung damage (Cowan, & Smith, 2021). This infection initiates a cascade of immune responses that lead to some of the symptoms seen in COVID-19 infection.

Within the innate immune system, the two major events that occur in COVID-19 patients are the overproduction of cytokines and the overstimulation of the complement system. Most cytokines, including interleukin (IL) -6, normally operate to regulate the functions of the immune system. However, infection with COVID-19 will result in the excessive production of proinflammatory cytokines such as IL-6, IL-8, tumor necrosis factor (TNF), interferon-gamma, and IL-17 (Paludan & Mogensen, 2022). This "cytokine storm" results in the excessive inflammatory response seen in COVID-19 patients, causing viral sepsis and multisystemic immune dysregulation. A normal response to the SARS-CoV-2 virus is characterized by the presence of anti-inflammatory, prophagocytic, antigen-presenting macrophages in the lungs whereas critical COVID-19 is characterized by the presence of hyperinflammatory macrophages (Paludan & Mogensen, 2022). In addition, this disease also causes abnormal stimulation of the complement system. This pathway normally acts to opsonize and destroy pathogens. Because this system uses inflammatory mediators to aid in the destruction of foreign particles, chronic activation of complement can cause excessive inflammation and tissue damage in the host. Systemic activation of the complement system has been correlated with respiratory failure in hospitalized patients (Paludan & Mogensen, 2022).

In the adaptive immune system, T cells play a major role in combating COVID-19 or in some cases, worsening the viruses' effects. T cells, including CD4+ and CD8+ T cells, normally act by secreting cytokines that will recruit other leukocytes that destroy microbes or directly kill infected cells through apoptosis. It remains uncertain if the symptoms of COVID-19 are caused by a suboptimal T cell response or an excessive T cell response. Researchers found that patients with severe COVID-19 disease showed a markedly decreased cytotoxic T-cell response compared to those with moderate disease (Chen & John Wherry, 2020). Alternatively, some data have suggested the presence of an overaggressive CD8+ T cell response, increased expression of natural killer cells, and increased cytotoxicity (Chen & John Wherry, 2020). Within the adaptive immune system, B cells are also a prominent factor. B cells have many functions in the immune system including producing antibodies that bind to microbes to neutralize them. However, in response to infection with SARS-CoV-2, it is known that intense antibody responses are "likely to cause severe cytokine release syndrome and may be associated with increased risk of death" (Jordan, 2021). It is clear from this information that the overstimulation of the immune system plays a key role in worsening COVID-19 disease. There should be a balance of the immune system in which it is not hyperactive or depressed. Figure 1 illustrates these immune responses occurring in the alveolar cells of the lung (Paludan & Mogensen, 2022). The image depicts three types of lung alveoli: an uninfected alveolus, a mild COVID-19 infection, and a critical COVID-19 infection. In the critical infection, the image shows extensive damage due to a hyperactive immune system leading to excessive cytokine expression.

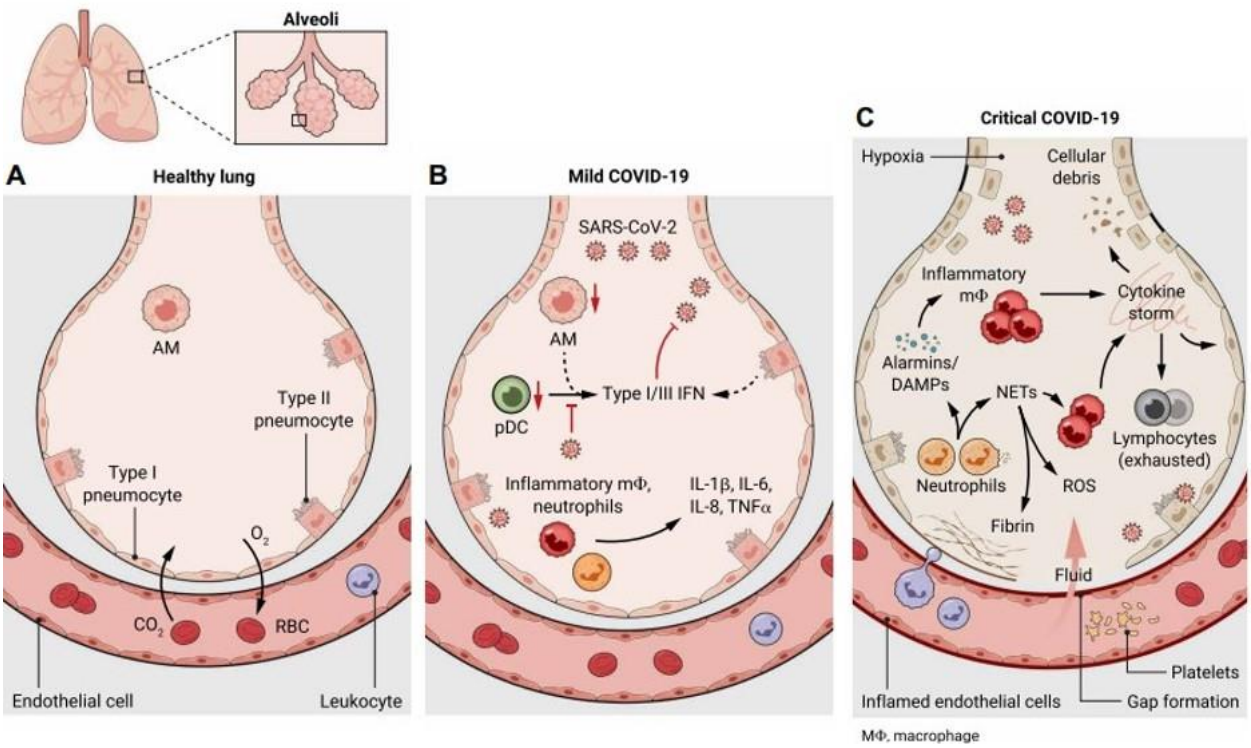

Figure 1. Overview of COVID-19 pathogenesis. Adapted from "Innate Immunological Pathways in COVID-19 Pathogenesis," by S. R. Paludan, and T. H. Mogensen, 2022, January 7, *Science Immunology*, Volume: 7, p. 2. Copyright 2022 by The Authors.

Transplant Patients and Immunosuppression

Patients with organ failure are often left with one option, transplantation. For example, when an individual suffering from chronic alcoholism no longer has a functioning liver, they can replace their liver with that of a healthy, well-matched organ donor. Because our immune systems are designed to fight against any foreign objects in the body, many actions need to be taken to ensure successful organ transplantation. The key component of transplant surgery is immunosuppression. The goal of immunosuppressive therapy is to ensure the survival of the transplanted organ by preventing acute and chronic rejection (Tönshoff, 2020). There are many different types of immunosuppressants with different mechanisms of action including "depleting lymphocytes, diverting lymphocyte traffic, or blocking lymphocyte response pathways"

(Tönshoff, 2020). Patients are put on immunosuppressant drugs before their surgery and for the remainder of their lives. However, the extent of immunosuppression "required long-term is very low compared to the levels required within the first weeks" (Tönshoff, 2020). Although it is true that some patients may be able to stop immunosuppressant drugs for long periods of time without rejection of the transplanted organ, these are very rare cases (Tönshoff, 2020). From this information, it can be concluded that patients with suppressed immune systems, caused by these medications, are at greater risk for infection. Therefore, they are more at risk for infection with SARS-CoV-2.

Current Vaccination Recommendations

The role of immunosuppressants in solid organ transplant patients is vital to successful transplantation and can potentially be lifesaving. However, due to this suppression, these drugs can also negatively impact the immune system's primary role in fighting infections. These individuals are therefore at a much higher risk of COVID-19-related complications (Giannella et al., 2021). There has been little research regarding the effect of COVID-19 on these organ transplant recipients in comparison to the general population. Furthermore, data is still being collected to determine vaccination recommendations for this population. Regardless, the CDC has a COVID-19 vaccine recommendation for moderate to severely immunosuppressed people. The guideline depends on the age, degree of immunosuppression, as well as which vaccine that individual will be receiving. In most cases, the CDC is recommending 4 doses of the COVID-19 vaccine. For example, an immunosuppressed individual 18 years or older, receiving the Pfizer-BioNTech vaccine is recommended to get three primary series doses, and one booster dose two

months after the third dose (Centers for Disease Control and Prevention, 2022). The research presented in this paper will aim to either support or oppose this vaccine recommendation.

Literature Review—The Pathogenesis of SARS-CoV-2 in Solid Organ Transplant Recipients

The deprived state of the immune system in a Solid Organ Transplant (SOT) recipient makes them more vulnerable to severe infection with SARS-CoV-2. Data regarding the pathogenesis of this virus within an immunosuppressed patient is still emerging. It may be beneficial to assess the immunology of other viruses, such as influenza, in the immunosuppressed individual to gain some insight into how SARS-CoV-2 may be functioning. One study published by the American Journal of Transplantation evaluated the Hemagglutinin antibody (HI) response to influenza infection in transplant patients. This review concluded that seroconversion (the period during which the body begins to produce detectable quantities of antibodies) occurred in only 32.8% after Influenza A infection and 29.7% after influenza B, four weeks after infection (Hirzel et al., 2019). This differs greatly from the general population as it is known that immunocompetent individuals are 82-95% likely to seroconvert after infection with influenza (Hirzel et al., 2019). From this information, it is reasonable to infer that infection with SARS-CoV-2 will also result in decreased antibody production in SOT patients.

Similarly to B cell response, T cell response in SOT patients infected with the influenza virus may also be comparable to T cell response during infection with SARS-CoV-2. One study measuring CD4+ and CD8+ T cell levels among SOT recipients after infection with influenza showed an adequate initial T cell response and a significant increase when measured 28 days after initial diagnosis (L'Huillier et al., 2020). Another study showed that a CD4+ T cell response occurred in 42.9% of seroprotected patients and 58.3% of patients who had negative serology

(Baluch et al., 2011). In addition, 85.7% of seropositive patients had a CD8+ T cell response as well as 75% in negative serology patients (Baluch et al., 2011). This information explains that there is a strong T-cell response in influenza-infected SOT patients regardless of antibody production. From these studies, it can be concluded that SOT patients with SARS-CoV-2 may also show an adequate T-cell response. In fact, one study stated that "T-cell mediated anti-SARS-CoV-2 response generally did not differ from immunocompetent patients" (Dęborska-Materkowska & Kamińska, 2021).

Although information presented has suggested that SOT recipients are at higher risk for acquiring COVID-19, there has been no evidence to link immunosuppression to higher mortality rates. One multicenter cohort study of critically ill adults with COVID-19 showed that a mortality rate of 43% in immunocompetent individuals did not differ much from a mortality rate of 40% in SOT patients (Dęborska-Materkowska & Kamińska, 2021). This could be due to the decreased inflammatory response from the immune system caused by immunosuppressive therapies among SOT recipients. Earlier it was discussed how infection with SARS-CoV-2 causes increased release of pro-inflammatory cytokines. This excessive inflammatory response has been positively correlated with the severity of COVID-19 symptoms (Dęborska-Materkowska & Kamińska, 2021). However, in an immunosuppressed individual, this response is not as strong due to decreased activation of cytokines. Therefore, it can be postulated that immunosuppressive therapy in SOT recipients will prevent some of the severe symptoms of COVID-19 by inhibiting a hyperactive immune system. It is this decreased inflammatory phase that will prohibit the progression to severe lung disease, which is often the cause of death in COVID-19 patients (Giannella et al., 2021).

It is more likely that comorbidities associated with SOT recipients are responsible for high-risk factors in the immunosuppressed population. Common comorbidities among transplant patients include diabetes mellitus, hypertension, and heart disease (Wu et al., 2005). According to the Centers for Disease Control and Prevention, each of these conditions is associated with an increased risk of severe disease with COVID-19 (2023). Furthermore, recent studies comparing non-SOT patients who have the same comorbidities as SOT patients have failed to determine immunosuppression as a risk factor for higher mortality rates (Giannella et al., 2021). Therefore, concluding that it is more likely to be an underlying condition rather than decreased immune function that causes severe disease.

Literature Review—The Efficacy of the SARS-CoV-2 Vaccines in Solid Organ Transplant Patients

The approved mRNA-based vaccines (Moderna and Pfizer-BioNTech) in circulation today have shown to be greatly effective in preventing the acquisition of the SARS-CoV-2 virus. In fact, these vaccines are roughly 100% efficient in preventing severe disease leading to hospitalization and death among the general population (Giannella et al., 2021). However, when discussing the immunocompromised it is important to recognize that they will experience reduced immunogenicity to vaccines. This reduced response is the result of having a depleted immune system. In an immunocompetent host, the COVID-19 gene-based vaccine will deliver the genetic instructions to the host's cells. This genetic material instructs the cell to make the SARS-CoV-2 spike protein to which the host can mount an antibody response (Abbasi, 2020). Evidence of the efficacy of the SARS-CoV-2 vaccine in an immunocompromised individual is only beginning to accumulate. There is still a great amount of research that needs to be done to

determine if immunocompromised transplant patients will benefit from receiving a COVID-19 vaccine.

The two primary COVID-19 vaccines available, Moderna and Pfizer, are mRNA vaccines (Centers for Disease Control and Prevention, 2022). These mRNA vaccines operate by giving the vaccinated individual's immune system the instructions to make the spike protein that is found on the COVID-19 virus surface. The body will then be able to make these spike proteins which the immune system will use to produce antibodies that will protect against future infection (Abbasi, 2020). Therefore, the vaccine is not introducing a live virus into the host and the vaccine cannot cause infection with COVID-19. In fact, all approved COVID-19 vaccines, including vector vaccines and protein-based vaccines, do not contain live replicating viruses and are acceptable for transplant recipients (Giannella et al., 2021).

To gain some insight into how an immunocompromised host may respond to these mRNA SARS-CoV-2 vaccines, it may be beneficial to examine how these individuals have responded to vaccines in the past. Previous experience administering influenza vaccines to solid organ transplant (SOT) patients has shown that cell-mediated immune responses are lower as compared to the general population (Giannella et al., 2021). The antibody production rate with influenza vaccines among the SOT population is low, between 34% and 52% (Giannella et al., 2021). Regardless of this decreased immune response, the influenza vaccine has still been effective in protecting against severe disease (Giannella et al., 2021). This may be due to the evidence suggesting that the influenza vaccine still elicits a sufficient T-cell response in SOT patients (Giannella et al., 2021). Such research may indicate a similar suboptimal antibody response in SOT recipients receiving the SARS-CoV-2 vaccine and an equally effective result in protecting against the disease. However, the influenza vaccine is a protein-based vaccine rather

than mRNA-based. Therefore, it is unknown how the immune system of an immunocompromised individual will react to an mRNA vaccine especially because no other approved vaccines in circulation have used this mRNA technique (Abbasi, 2020). Data is still needed to determine the extent of reduction in SARS-CoV-2 vaccine effectiveness.

Data is only beginning to emerge regarding the efficacy of SARS-CoV-2 vaccines among SOT recipients. Among the first studies being conducted, one researched breakthrough infection after vaccination in SOT recipients. It was found that the rate of infection postvaccination in SOT patients was only 0.6% (Giannella et al., 2021). However, this is much higher than the postvaccination rate of infection in the general population which was only 0.05% (Giannella et al., 2021). Although the vaccine is less effective in protecting against breakthrough infection in SOT patients as compared to the general public, the vaccine is still highly protective in both populations. This is proven by such low postvaccination infection rates. Because the vaccine is assuredly safe for use among SOT patients, vaccination seems to be in these patients' best interest. Also, increased doses compared to the general population may be recommended due to the fact that the vaccine elicits a less effective antibody response in SOT recipients.

Conclusion

The COVID-19 pandemic presented a plethora of challenges that continue to cause disorder in the lives of many today. The unbelievable efforts of front-line workers and medical researchers allowed for the quick release of information and resources. The public was constantly being informed of new knowledge that was discovered regarding the understanding and prevention of COVID-19. This not only allowed the public to adequately protect themselves but also provided a sense of comfort during such an unprecedented time. However, one group of

individuals did not share the same sense of security. Transplant patients continue to be deprived of knowledge regarding how to protect themselves from COVID-19. This is due to the lack of definitive information and recommendations for this particular group. The personal experience of the transplant patient in the case study mentioned previously presented the need for further information. The patient stated that they felt forgotten and frightened by the lack of data being released. While the rest of the population has started to move on from the COVID-19 scare, the transplant population continues to confront the dangers of COVID-19 every day.

The research provided in this paper aims to allow for a better understanding of the effects of COVID-19 in solid organ transplant patients which will allow healthcare providers to better manage and prevent infection in these individuals. A literature review regarding the pathogenesis of SARS-CoV-2 in SOT recipients used data obtained from transplant patients with influenza to gain insight into how a SOT patient may respond to COVID-19. Research showed that SOT patients with influenza produced a smaller amount of anti-influenza antibodies as compared with the general population (Hirzel et al., 2019). However, the T-cell response to the influenza virus did not appear to be impaired and was similar to the T-cell response of an immunocompetent individual (Hirzel et al., 2019). It was inferred that a similar suboptimal antibody response yet normal T-cell response would be seen in transplant patients with the SARS-CoV-2 infection. One study supports this data stating that transplant patients showed a lower prevalence of anti-SARS-CoV-2 antibodies yet “no difference between SOT and non-immunocompromised convalescents regarding the distinct SARS-CoV-2 reactive T cell response” (Dęborska-Materkowska & Kamińska, 2021). In addition, no correlation was found between transplant status and mortality rates if infected with SARS-CoV-2. This was attributed to the decreased

immune response in SOT patients and therefore decreased inflammatory response which causes severe disease with COVID-19 (Giannella et al., 2021).

A similar approach was used to examine the efficacy of SARS-CoV-2 vaccines in SOT recipients. Data from transplant patients who had received the Influenza vaccine showed that the vaccine elicited a decreased antibody production rate and a normal T-cell response as compared to the general population. However, because the influenza vaccine is protein based whereas the SARS-CoV-2 vaccines are mRNA-based, more research is needed to determine how a SOT patient will respond. New studies emerging are showing that COVID-19 post-vaccination infection among the SOT population is extremely low. Therefore, it appears that the SARS-CoV-2 vaccines are effective in preventing severe disease with COVID-19 in SOT recipients, although not as effective as in the general population.

This research leads to the conclusion that it is in the best interest of solid organ transplant patients to get vaccinated against COVID-19. The current CDC recommendation for immunosuppressed individuals of 4 doses is supported by the research presented. In addition, due to the decreased antibody response to the vaccine, SOT patients should continue to get booster vaccines as they become available. Because the research presented was solely a literature review, further research is needed to fully understand the immunology of SARS-CoV-2 as well as the efficacy of the SARS-CoV-2 mRNA-based vaccine in transplant patients. Research including patient studies must ensure the mRNA-based vaccine is not contraindicated in SOT patients due to either transplant status or certain immunosuppressive drugs. Definitive research will not only aid in the treatment and prevention of COVID-19 in these patients today but will also aid in future research regarding emerging diseases and will allow for better preparedness.

The information compiled in this research paper will provide a resource for healthcare providers to find the recommended guidelines and supporting facts. Rather than having to consult multiple resources, physicians will be able to read all the information needed within this paper. The provided infographic below presents the key points and can be easily distributed as a resource.

SOT PATIENTS AND COVID-19

Guidelines for prevention and treatment

IMMUNE RESPONSE TO SARS-COV-2

SOT recipients may elicit a decreased antibody response but a normal T-cell response to infection with SARS-CoV-2

EFFICACY OF THE SARS-COV-2 VACCINE

It is assumed that the vaccine will elicit a decreased antibody production rate and a normal T-cell response but early studies are showing low rates of post-vaccination infection

IMMUNE STATUS VS MORTALITY RATES

Immunosuppression is not a risk factor for higher mortality rates. Comorbid conditions commonly associated with these patients are more likely the cause of severe disease.

VACCINE RECOMMENDATIONS

SOT patients should receive 4 doses of the SARS-CoV-2 vaccine and continue to get booster vaccines as they become available

REFER TO THE PAPER "THE EFFECTS OF SARS-COV-2 ON TRANSPLANT PATIENTS" FOR FURTHER INFORMATION

SOT: SOLID ORGAN TRANSPLANT

By :
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