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OBM Transplantation

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Review

Introduction to COVID-19 Vaccines and Kidney Transplant Recipient

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Academic Editor: Maurizio Salvadori

Special Issue: Safety and Effectiveness of COVID-19 Vaccine in Kidney Transplant Recipients

OBM Transplantation
2025, volume 9, issue 1
doi:10.21926/obm.transplant.2501236

Received: August 03, 2024
Accepted: February 16, 2025
Published: February 24, 2025

Abstract

COVID-19 has presented considerable health hazards, particularly for immunocompromised persons, such as kidney transplant recipients. This population experiences increased susceptibility due to the immunosuppressive treatments necessary to avert organ rejection, potentially resulting in a diminished immune response to immunizations. The implementation of COVID-19 vaccinations has been essential in alleviating these dangers. Studies demonstrate differing levels of vaccine efficacy among kidney transplant recipients, underscoring the necessity for customized vaccination approaches. This assessment appraises the safety, effectiveness, and immunological responses of COVID-19 vaccinations in kidney transplant recipients, highlighting the significance of educated vaccination policies. Comprehending these processes is crucial for enhancing COVID-19 protection in this high-risk population and guiding continuous public health initiatives.

Keywords

COVID-19; vaccines; kidney transplant recipients; immunosuppression; safety; efficacy; antibody response; guidelines

1. Introduction

The COVID-19 pandemic has profoundly affected worldwide health systems, necessitating the swift creation and distribution of vaccines to mitigate the virus's transmission [1]. Individuals with impaired immune systems, especially kidney transplant recipients (KTRs), have raised critical inquiries about the efficacy, safety, and optimal timing of COVID-19 vaccinations [2]. Recipients of kidney transplants generally administer immunosuppressive drugs to avert organ rejection. Although these treatments safeguard the transplanted kidney, they may also hinder the body's capacity to generate a vigorous immunological response, rendering this population especially susceptible to severe consequences from COVID-19. Health authorities prioritized these patients for vaccination due to their heightened risk of serious disease [3, 4]. Comprehending the distinct problems and factors for KTRs regarding COVID-19 immunization is essential for safeguarding their health, promoting informed decision-making, and improving the overall efficacy of vaccination initiatives in this vulnerable population [5]. This context establishes the foundation for examining certain vaccine types, suggested immunization regimes, and the current research focused on the immunological responses of kidney transplant recipients to COVID-19 vaccinations.

2. Overview of COVID-19 Vaccines

In order to prevent the global pandemic caused by the new coronavirus known as SARS-CoV-2, many vaccinations against COVID-19 have been developed and approved for use in emergencies. These vaccines have shown promising results in clinical trials, demonstrating high levels of efficacy in preventing severe illness and death from COVID-19. However, there is limited data on the effectiveness of these vaccines in immunocompromised populations, such as transplant recipients, who may have a weakened immune response to the vaccine. Therefore, further research is needed to determine the optimal vaccination strategies for this vulnerable population and to ensure their safety and protection against COVID-19. Several different platforms, such as mRNA, viral vector, and protein subunit technologies, are utilized in producing these vaccines. Each platform is engineered to stimulate the immune system's ability to identify and eliminate the virus.

2.1 mRNA Vaccines (e.g., Pfizer-BioNTech, Moderna)

Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) vaccines are examples of mRNA vaccines. These vaccines consist of genetic material that encodes the spike protein of SARS-CoV-2. Once within the body, mRNA delivers cellular instructions for the production of spike proteins, which subsequently elicit an immune response leading to antibody production. Clinical trials have demonstrated that the medication is remarkably efficient in avoiding symptomatic COVID-19 infection, with reported effectiveness rates exceeding 90% [1, 3].

2.2 Viral Vector Vaccines (e.g., Johnson & Johnson, AstraZeneca)

The Johnson & Johnson (Janssen) vaccine and the AstraZeneca (AZD1222) vaccine, known as viral vector vaccines, are examples in this category. These vaccines use a virus that is not harmful to the recipient, known as an adenovirus, to transfer genetic material that contains instructions to build the spike protein. This elicits an immunological response to the spike protein, akin to how mRNA vaccines impact the immune system. Clinical investigations have demonstrated the efficacy of these immunizations in averting severe cases of COVID-19, hospitalization, and death [6, 7].

2.3 Protein Subunit Vaccines (e.g., Novavax)

The Novavax (NVX-CoV2373) vaccine is an example of a protein subunit vaccine. This vaccine contains pure proteins derived from the spike protein of SARS-CoV-2. Additionally, an adjuvant is included in these vaccinations in order to strengthen the immunological response. According to [8], efficacy trials have demonstrated that the vaccine is highly efficient in preventing symptomatic COVID-19 infection, with efficacy rates comparable to mRNA vaccines. To determine whether or not these vaccination platforms are safe and effective, they have all been subjected to extensive testing in clinical studies. Inducing protective immunity against SARS-CoV-2 is the objective of all authorized COVID-19 vaccines, even though the precise mechanisms of action and dose regimens may differ. Essential details about COVID-19 vaccines are shown in Table 1.

Table 1 Important details about COVID-19 vaccines, including their names, types, storage requirements, dosage, and primary efficacy.

S. No.	Vaccine Name	Type	Storage Requirements	Dosage	Primary Efficacy (%)	Manufacturer
1	Pfizer-BioNTech	Messenger RNA	-80 to -60°C	2 doses (3 weeks apart)	~95%	Pfizer/BioNTech
2	Moderna	Messenger RNA	-25 to -15°C	2 doses (4 weeks apart)	~94%	Moderna
3	Johnson & Johnson (Janssen)	Viral vector	2 to 8°C	1 dose	~66%	Johnson & Johnson
4	AstraZeneca	Viral vector	2 to 8°C	2 doses (4 to 12 weeks apart)	~76%	AstraZeneca
5	Sinovac (CoronaVac)	Inactivated virus	2 to 8°C	2 doses (2 to 4 weeks apart)	~51%	Sinovac
6	Sinopharm (BBIBP-CorV)	Inactivated virus	2 to 8°C	2 doses (3 to 4 weeks apart)	~79%	Sinopharm
7	Novavax	Protein subunit	2 to 8°C	2 doses (3 weeks apart)	~90%	Novavax
8	Sputnik V	Viral vector	2 to 8°C	2 doses (3 weeks apart)	~91.6%	Gamaleya Research Institute

Notes: Percentages of effectiveness may differ in the real world due to variables not included in clinical trials. To keep vaccines effective, certain storage conditions are required. Emerging variations and new evidence may cause vaccination recommendations to change.

3. Optimal Timing of Vaccination

The recommended timing for administering the COVID-19 vaccine in individuals who have undergone kidney transplantation is as follows.

3.1 Timing of First Dose

According to [9], recipients of kidney transplants should wait at least three months following the transplant surgery before receiving their first dose of the COVID-19 vaccination. Before receiving immunization, it is recommended that patients who have received other organ transplants wait one month after the transplant. During this period of delay, the immune system is allowed to recuperate to a level where it is more likely that the vaccine will be successful [10].

3.2 Timing of Second Dose

According to the recommended vaccine schedule, the second dose should be administered approximately three to four weeks after the initial dose [11].

3.3 Timing of Additional Doses

According to [11], patients who are immunocompromised to a moderate to severe degree, including those who have received a kidney transplant, are advised to take a third dose at least one month after the second administering dose. To provide the highest possible level of protection, it is now suggested that transplant patients receive a fourth dose. An investigation is still being conducted to determine the most appropriate timing for further doses beyond the fourth [12].

3.4 Timing for Those with Prior COVID-19 Infection

Those who have received a kidney transplant should still get vaccinated against COVID-19, even if they have had the virus in the past. Before getting vaccinated, kids should wait until they have completely recovered from the COVID-19 virus they contracted. In conclusion, recipients of kidney transplants should wait three months following the transplant before beginning the COVID-19 vaccine series. Following that, they should adhere to the recommended dose schedule for the type of vaccine they are receiving. It is recommended that additional doses be taken after the fourth, but studies are still being conducted to determine the ideal timing. Even for those who have had a previous infection with COVID-19, vaccination is essential.

4. Immune Responses of Kidney Transplant Recipients to Various Vaccines

KTRs encounter distinct obstacles with vaccination owing to the immunosuppressive drugs required to avert rejection of the transplanted kidney. These medications hinder the immune system's capacity to respond adequately to immunizations. This overview details the immunological responses of KTRs to various vaccines, highlighting both the reduced responses and prospective measures to improve vaccine efficacy in this demographic.

4.1 Influenza Vaccination

Influenza immunization is essential for kidney transplant recipients because of their heightened vulnerability to severe influenza. Nonetheless, the immunological response to the influenza vaccine in kidney transplant recipients is frequently diminished. Research indicates that the immunological response to influenza vaccines is typically reduced in KTRs relative to healthy individuals, mainly attributable to the influence of immunosuppressive agents such as calcineurin inhibitors and corticosteroids. The diminished efficacy may lead to a decreased incidence of seroprotection; yet, vaccination continues to mitigate the severity of sickness in individuals who do not attain complete immunity. Pre-transplant immunization is frequently advised to enhance immune responses following transplantation [13-15].

4.2 Pneumococcal Vaccination

Pneumococcal infection continues to be a significant cause of morbidity and mortality in kidney transplant recipients, so immunization is strongly advised. The immunological response to the pneumococcal vaccine is often compromised in this population. The polysaccharide and conjugate forms of the pneumococcal vaccine provoke diminished responses in kidney transplant recipients relative to healthy controls. Nonetheless, research indicates that pneumococcal immunization can provide protection, especially when given promptly post-transplantation and utilizing a two-dose regimen. Improved responses may be attained by refining immunosuppressive protocols or administering elevated vaccination dosages [16-18].

4.3 Hepatitis B Vaccination

Hepatitis B immunization is essential for kidney transplant recipients, especially those who have not been vaccinated or are at elevated risk of exposure. Immunosuppressive medications diminish the immune system's capacity to respond adequately to the hepatitis B vaccine. Research indicates a markedly reduced seroconversion rate in kidney transplant recipients compared to healthy individuals. To enhance the response, increased vaccination dosages or numerous booster administrations may be necessary. Alternative vaccination regimens or adjuvants may be employed in certain instances to augment immunogenicity [19, 20].

4.4 Human Papillomavirus (HPV) Vaccination

Recipients of kidney transplants face an elevated risk of HPV-associated malignancies, such as cervical, anal, and oropharyngeal cancers, attributable to their extended immunosuppressive therapy. Nevertheless, research indicates that kidney transplant recipients exhibit a markedly diminished response to the HPV vaccine, rendering them less likely to get sufficient protection. It was determined that although kidney transplant recipients exhibited reduced seroconversion rates post-HPV vaccination, immunization remained advisable due to the prolonged risk of HPV-associated malignancies in this demographic. Strategies to enhance vaccination efficacy encompass administering greater doses or several administrations of the vaccine [21].

4.5 COVID-19 Vaccination

The COVID-19 pandemic underscored the distinct limitations of vaccination in immunocompromised groups, particularly KTRs. Despite diminished responses to the COVID-19 vaccine in kidney transplant recipients, characterized by decreased neutralizing antibody levels and attenuated T-cell responses, these individuals continue to derive advantages from vaccination. Research indicates that although KTRs may exhibit reduced seroconversion rates, the vaccine protects against severe illness, hospitalization, and mortality. Research suggests that the timing following transplantation, the kind of immunosuppressive treatment, and supplementary booster dosages can enhance the immune response. Current guidelines recommend vaccination for all kidney transplant recipients, particularly highlighting the importance of booster doses [11].

4.6 Tuberculosis (TB) Vaccination (BCG)

The Bacille Calmette-Guérin (BCG) vaccination for tuberculosis has not been extensively researched in kidney transplant recipients; nonetheless, the immunosuppressive medications administered to these individuals are expected to attenuate their response to the vaccine. Specific investigations have highlighted the potential risk of disseminated BCG infection in immunocompromised people. Consequently, the BCG vaccine is typically contraindicated for kidney transplant recipients, especially those undergoing immunosuppressive treatment [22].

4.7 Meningococcal Vaccination

Meningococcal illness represents a significant infection risk for kidney transplant recipients, particularly those with comorbidities or undergoing immunosuppressive treatment. The immunological response to meningococcal vaccination may be inadequate in KTRs, with studies indicating diminished seroconversion rates in this demographic. Nonetheless, vaccination still provides some degree of protection, and it is advised, especially for kidney transplant recipients with a heightened risk of exposure (e.g., travel to endemic regions or close interaction with patients in high-risk categories) [23].

5. Negative Effects of Immunosuppressive Treatments on Vaccination

Immunosuppressive therapies are crucial for KTRs to avert rejection of the donated organ. Nonetheless, these therapies, which frequently comprise corticosteroids, calcineurin inhibitors (e.g., tacrolimus), antimetabolites (such as mycophenolate mofetil), and mTOR inhibitors (e.g., sirolimus), may adversely impact vaccination responses. The principal issue is that immunosuppressive medicines attenuate the immune system's capacity to generate a vigorous immunological reaction to vaccines, potentially resulting in diminished vaccine efficacy and, in certain instances, inadequate immunity development.

5.1 Impaired Antibody Response

Immunosuppressive medications are well-known to diminish antibody production post-vaccination. Numerous vaccinations, including those for influenza, pneumococcus, and hepatitis B, depend on the capacity of B cells to generate antibodies for immunization. Immunosuppressive

agents, particularly calcineurin inhibitors and corticosteroids, reduce B cell activation and antibody synthesis [24]. This results in a diminished probability of attaining protective antibody titers, which are essential for infection prevention.

5.1.1 Example

Individuals with KTRs immunized for hepatitis B frequently exhibit a diminished seroconversion rate (the production of antibodies in reaction to the vaccine) relative to the general population [19, 20].

5.2 Impaired T-cell Response

T-cell responses are crucial for managing viral infections and ensuring enduring immunity following vaccination. Immunosuppressive treatments, especially antimetabolites such as mycophenolate mofetil, can impede T cell activation and proliferation. This impairs T cells' capacity to identify and react to infections post-vaccination, which poses significant challenges for vaccinations dependent on both humoral (antibody-mediated) and cellular immunity, such as the varicella-zoster and COVID-19 vaccines.

5.2.1 Example

KTRs frequently have inadequate responses to the varicella-zoster virus (VZV) vaccination, with reduced T-cell-mediated immunity leading to insufficient protection against VZV infections [16-18].

5.3 Reduced Memory Immune Response

Immunosuppressive therapies may hinder the formation of immunological memory, which is essential for sustained protection following vaccination. Vaccination generally induces the development of memory B and T cells capable of swiftly recognizing and responding to subsequent infections. Nonetheless, the prolonged use of immunosuppressive medicines disrupts the development of memory cells, rendering kidney transplant recipients more susceptible to infections in the future and perhaps diminishing the longevity of vaccination efficacy.

5.3.1 Example

Research indicates that KTRs may exhibit diminished capacity to generate memory immune responses to specific vaccines, including the influenza vaccine, potentially leading to reduced long-term protection [13, 15].

5.4 Altered Response to Live Attenuated Vaccines

Live attenuated vaccines, such as the BCG vaccine for tuberculosis, the measles, mumps, and rubella (MMR) vaccine, and the yellow fever vaccine, are contraindicated or poorly tolerated in immunocompromised individuals, including KTRs. These vaccinations comprise attenuated strains of the pathogen, and although they are typically safe for healthy individuals, they may provide a risk to immunocompromised patients. In kidney transplant recipients, these vaccinations may result in

severe, occasionally life-threatening infections because of their compromised immune system's inability to manage the live pathogen.

5.4.1 Example

The live BCG vaccine is often contraindicated for kidney transplant recipients due to the potential danger of disseminated BCG infection in immunosuppressed individuals [22].

5.5 Delays in Vaccine Responses

In many instances, immunosuppressive therapies may not completely inhibit the immune response to vaccines, although they can postpone the development of immunity. This protracted reaction may provide challenges, particularly for vaccinations necessitating prompt protection. In KTRs, the immune system may exhibit a delayed response to a vaccine, resulting in a lack of protection during the crucial period immediately after vaccination.

5.5.1 Example

Post-kidney transplantation, KTRs may have a delayed response to vaccines such as influenza or pneumococcal vaccines, with the immune response potentially emerging several months after immunization, so rendering them susceptible to infections during this interval [13-15].

5.6 Increased Risk of Infections Despite Vaccination

KTRs are at an elevated risk for infections, even post-vaccination, due to the impaired immune response resulting from immunosuppressive medication. This encompasses infections that vaccines are intended to prevent, along with novel infections not addressed by the immunizations. A weakened immune response may cause vaccination to inadequately protect against prevalent infections, potentially leading to severe consequences.

5.6.1 Example

Notwithstanding immunization, KTRs exhibit a greater prevalence of influenza-related complications than the general population, attributable to their inadequate immunological response to the vaccine [13-15].

6. Effects of Vaccination on Hospitalization, Need for Intensive Care - Respiratory Support and Mortality

Vaccination has demonstrated substantial effects in decreasing hospitalization, the necessity for intensive care (ICU), respiratory assistance, and death across many populations, including KTRs. Immunosuppressive therapies in kidney transplant recipients diminish vaccine-induced immune responses; however, research demonstrates that vaccination, particularly against influenza, COVID-19, and pneumococcus, markedly lessens illness severity, hospitalization requirements, and mortality rates in this population.

6.1 Influenza Vaccination

Influenza immunization in kidney transplant recipients has been shown to mitigate the severity of influenza infections, despite the vaccine not offering complete immunity. Despite KTRs generally demonstrating a diminished immune response to the influenza vaccine as a result of immunosuppressive medication, those who are vaccinated frequently report less severe symptoms and reduced incidence of complications, such as pneumonia, in comparison to unvaccinated individuals [13-15]. Research indicates that immunized kidney transplant recipients exhibit a markedly reduced probability of necessitating hospitalization or intensive care unit treatment owing to influenza. Influenza vaccination is associated with a decreased likelihood of hospitalization, ICU admission, and mechanical ventilation requirements in KTRs. Vaccinated individuals are more prone to mild or moderate sickness, reducing the need for breathing assistance or intensive care. While quantifying the impact of vaccination on mortality is more challenging, the decrease in severe cases and sequelae indirectly diminishes the chance of death from influenza.

6.2 Pneumococcal Vaccination

Pneumococcal immunization is essential for kidney transplant recipients, as they face an increased risk of pneumococcal infections that may result in severe consequences such as pneumonia, sepsis, and meningitis. Research indicates that pneumococcal immunization can diminish illness severity, lower hospitalization risk, and decrease the necessity for ICU admission in kidney transplant recipients. Despite a potentially diminished immune response in KTRs, pneumococcal vaccinations offer protection against invasive pneumococcal illness, reducing the risk of severe disease development.

Vaccinated kidney transplant recipients are less likely to have intensive care unit treatment or mechanical ventilation for pneumococcal infections. Researchers conducted a study indicating that vaccination can decrease hospital admissions resulting from severe pneumonia. Vaccination may diminish the mortality risk linked to pneumococcal infections; however, breakthrough infections may still arise, especially in those with a suboptimal vaccine response [16-18].

6.3 COVID-19 Vaccination

The COVID-19 pandemic has highlighted the essential significance of vaccination for immunocompromised individuals, particularly KTRs. Despite a diminished immune response to the COVID-19 vaccine in KTRs owing to immunosuppressive medication, numerous studies indicate that vaccination still confers substantial protection against catastrophic outcomes, including hospitalization, intensive care unit admission, respiratory assistance, and mortality [11].

The COVID-19 vaccine has been demonstrated to decrease the probability of hospitalization in KTRs. Research indicates that immunized kidney transplant recipients are less prone to severe illness necessitating intensive care unit hospitalization, mechanical ventilation, or supplemental oxygen use. Mortality rates from COVID-19 are much lower in vaccinated kidney transplant recipients compared to unprotected persons. A study published indicated that vaccinated KTRs exhibited a markedly lower risk of mortality from COVID-19 compared to their unvaccinated counterparts, even after considering the diminished immune response in this demographic.

6.4 Hepatitis B Vaccination

While hepatitis B is often not linked to respiratory symptoms, liver failure resulting from chronic infection can cause significant consequences that may necessitate hospitalization and intensive care unit treatment. Hepatitis B immunization is crucial for KTRs, especially for individuals at risk of exposure or those who have not been immunized previously. Adequate immunization can avert hospitalization resulting from problems associated with chronic hepatitis B infection [19, 20].

Adequate hepatitis B immunization diminishes the occurrence of hepatitis B-related liver problems, hence reducing the necessity for liver transplants, hospitalization, or ICU care associated with liver failure. Vaccination against hepatitis B diminishes the long-term mortality risk linked to chronic hepatitis B and liver cirrhosis in KTRs.

6.5 Other Vaccines (e.g., HPV, Meningococcus)

Although vaccines like those for human papillomavirus (HPV) and meningococcus are not directly linked to respiratory problems, they aid in diminishing the overall disease burden in immunocompromised patients. Immunizing kidney transplant recipients against these organisms can cause the need for hospitalization due to malignancy (namely HPV) or meningitis (specifically meningococcus).

6.6 Overall Impact of Vaccination on Hospitalization, ICU Need, and Mortality

6.6.1 Hospitalization

Vaccination diminishes the occurrence of severe infections in kidney transplant recipients, resulting in a reduced hospitalization rate, including hospitalizations to intensive care units. The vaccine's efficacy in illness prevention (as demonstrated by COVID-19 and pneumococcal vaccines) correlates with significantly decreasing hospitalizations.

6.6.2 Need for ICU and Respiratory Support

Vaccination results in less severe illnesses and markedly reduces the necessity for critical care and mechanical breathing. COVID-19 immunization in KTRs has demonstrated a reduction in ICU hospitalizations and the necessity for respiratory assistance.

6.6.3 Mortality

Although immunosuppressive therapy continues to elevate the mortality risk from infections in KTRs, vaccinations can significantly lower mortality rates by averting severe illness. COVID-19 immunization has demonstrated a reduction in mortality rates among kidney transplant recipients despite their potentially inadequate immune response.

7. Management of Immunosuppression in COVID-19-Infected Recipients

Managing immunosuppression in KTRs infected with COVID-19 is a vital component of clinical therapy. Kidney transplant recipients are at heightened risk of severe COVID-19 owing to their underlying immunosuppressive treatment and prevalent comorbidities, including diabetes and

hypertension. Effective management necessitates a careful equilibrium of infection control, graft rejection prevention, and avoiding superfluous problems arising from immune system suppression. This article summarizes contemporary options for treating immunosuppression in COVID-19-infected kidney transplant recipients, informed by growing research and expert recommendations.

7.1 General Principles for Immunosuppressive Management

The principal objective of immunosuppressive therapy in COVID-19-infected KTRs is to modulate the degree of immune suppression to reconcile the danger of COVID-19 exacerbation with the necessity of preventing acute rejection of the donated kidney. Immunosuppressive medications, such as calcineurin inhibitors (CNIs) like tacrolimus, corticosteroids, antimetabolites like mycophenolate mofetil (MMF), and mTOR inhibitors (e.g., sirolimus), might diminish the body's capacity to generate an efficient immunological response to infections, including COVID-19.

7.2 Reduction of Immunosuppressive Medications

During the initial stages of COVID-19 infection, it is typically advised to diminish the severity of immunosuppressive therapy to bolster the host's capacity to combat the virus while mitigating the risk of organ rejection. The subsequent guidelines are frequently implemented.

7.2.1 Corticosteroids

Corticosteroids are commonly employed in kidney transplant recipients for maintenance immunosuppression and the management of acute rejection events. During COVID-19 infection, especially in patients necessitating oxygen or mechanical ventilation, administering corticosteroids may require modification.

Dosing Reduction. Although corticosteroids are employed in the care of COVID-19 to mitigate inflammation, the dosage utilized for transplant immunosuppression (e.g., prednisone) should be decreased or tapered. Elevated steroids may exacerbate viral replication and heighten the susceptibility to subsequent infections.

Concurrent Administration with COVID-19-Specific Therapies. When high-dose steroids are necessary for COVID-19 treatment (e.g., dexamethasone in severe cases), the baseline steroid dosage for immunosuppression may be temporarily suspended or diminished to prevent excessive immunosuppression.

7.2.2 Calcineurin Inhibitors (CNIs)

Both tacrolimus and cyclosporine are pivotal in immunosuppressive therapy for kidney transplant recipients, although they also compromise immunological responses to infections. During COVID-19 infection, the risk of drug toxicity escalates when drugs are improperly dosed due to changed pharmacokinetics, particularly with concurrent COVID-19 therapy (e.g., antivirals or antibiotics).

Dosing Modifications. The dosage of tacrolimus or cyclosporine may require reduction or temporary cessation based on the patient's clinical status. Blood concentrations of CNIs must be

meticulously maintained, as renal function and hepatic metabolism may be affected during COVID-19 infection.

Risk of Graft Rejection. The temporary reduction of CNIs may elevate the risk of acute graft rejection; thus, monitoring renal function (e.g., serum creatinine, urine output) and biopsy (if feasible) may be necessary for suspected rejection.

7.2.3 Antimetabolites (e.g., Mycophenolate Mofetil, Azathioprine)

Mycophenolate mofetil (MMF) and other antimetabolites, such as azathioprine, are potent immunosuppressants. These drugs have demonstrated an elevated risk of infection and may also hinder immunological responses to COVID-19. Consequently, MMF is typically used during active COVID-19 infection.

Discontinuation of MMF. Typically, MMF is temporarily halted in patients with COVID-19 to mitigate immunosuppression and improve the body's response to the infection.

Alternative Immunosuppressive Agents. Physicians may transition patients from MMF to lower-risk immunosuppressants, such as mTOR inhibitors, when clinically appropriate, based on the patient's state and the graft status.

7.2.4 mTOR Inhibitors (e.g., Sirolimus)

mTOR inhibitors, like sirolimus, may be utilized as alternatives to other immunosuppressants if they effectively manage rejection. These drugs possess immune-modulating characteristics and may have a more advantageous risk profile than CNIs and MMF in COVID-19.

Dosing Modifications. Typically, the sirolimus dosage may require a reduction in instances of renal impairment, as mTOR inhibitors can aggravate renal damage, particularly in the context of COVID-19.

7.3 Management of Acute Rejection in COVID-19-Infected KTRs

Acute rejection continues to be a problem in kidney transplant recipients with COVID-19 infection, particularly when immunosuppressive medication is diminished. Management strategies encompass.

7.3.1 Biopsy and Diagnosis

In cases of suspected acute rejection, a kidney biopsy may be warranted; however, COVID-19 precautions may restrict the execution of this procedure. Utilizing non-invasive indicators, such as serum creatinine and urine output, in conjunction with clinical manifestations, will facilitate decision-making.

7.3.2 Steroid Therapy for Rejection

In instances of acute rejection, high-dose steroids or supplementary immunosuppressive medications, such as anti-thymocyte globulin, may be required. Nonetheless, these medications must be meticulously calibrated to prevent the aggravation of COVID-19 infection.

7.4 COVID-19-Specific Therapies and Drug Interactions

Numerous COVID-19-specific medicines can modify the pharmacokinetics of immunosuppressive medications, necessitating vigilant monitoring for possible interactions [25]. For instance.

7.4.1 Antiviral Therapies

Medications such as remdesivir or ritonavir-boosted protease inhibitors may interact with CNIs or mTOR inhibitors, requiring modifications in the dosage of immunosuppressive agents.

7.4.2 Dexamethasone

Frequently employed in the therapy of COVID-19, it may interact with steroids utilized for transplant rejection, necessitating dosage changes and monitoring.

7.5 Prophylactic Measures and Monitoring

To avert difficulties and enhance outcomes, the subsequent actions should be implemented.

7.5.1 Prophylactic Antimicrobials

Patients diagnosed with COVID-19, especially those exhibiting severe symptoms, may necessitate the use of broad-spectrum antibiotics, antifungals, and antivirals as components of their treatment regimen. This mitigates the risk of subsequent infections that may exacerbate the illness's progression.

7.5.2 Surveillance for Superinfections

COVID-19 patients are susceptible to bacterial and fungal infections, particularly with diminished immunosuppression. Consistent surveillance for indications of superinfection is necessary.

7.5.3 Frequent Monitoring of Renal Function and Graft Health

Regular assessment of renal function and graft integrity is essential because of the potential for acute kidney damage (AKI) associated with both COVID-19 and the administration of immunosuppressive treatment. Monitoring encompasses routine assessment of creatinine levels, urine output, and maybe kidney imaging or biopsy in instances of suspected graft rejection.

7.6 Role of Vaccination

Vaccination against COVID-19 is crucial for transplant recipients. However, the immune response may be inadequate. Considering that COVID-19 vaccination mitigates illness severity and the

necessity for intensive care unit treatment, transplant recipients must obtain the vaccine immediately, preferably before transplantation or as soon as clinically practicable thereafter. Booster dosages are advised, particularly for patients undergoing high amounts of immunosuppressive medication [26].

7.7 Individualized Approach

Ultimately, the management of immunosuppressive therapy in COVID-19-infected KTRs should be individualized. The clinician must assess the severity of the infection, the patient's clinical status, kidney function, and the risk of graft rejection. A multi-disciplinary approach involving transplant nephrologists, infectious disease specialists, and ICU physicians is often needed.

8. Summarizing the Issues Such as Vaccine Type, Differences in Response to Vaccine Types, Vaccine Dose, Dose Intervals, Timing of Bolus Doses, Necessity of Antibody Measurement in the Studies

In the context of KTRs, several key issues concerning COVID-19 immunization arise, including vaccine type, variations in responses to different vaccines, appropriate dose and timing, and the necessity for antibody testing. These factors are crucial for customizing immunization methods for this vulnerable demographic.

8.1 Vaccine Type

Vaccine Classification KTRs, similar to other immunocompromised patients, may exhibit inadequate immune responses to vaccinations. Various COVID-19 vaccine types (e.g., mRNA vaccines such as Pfizer-BioNTech and Moderna, adenovirus vector vaccines like AstraZeneca and Johnson & Johnson) may elicit distinct immune responses.

8.1.1 Messenger RNA Vaccines (Pfizer-BioNTech, Moderna)

These vaccinations typically elicit a strong immunological response in the general population; however, kidney transplant recipients commonly demonstrate a diminished response, especially after one or two doses.

8.1.2 Adenoviral Vector Vaccines (AstraZeneca, Johnson & Johnson)

These vaccines generally elicit a diminished immune response in kidney transplant recipients compared to mRNA vaccines, although they still provide some degree of protection. The vaccine type administered to KTRs may affect overall vaccine efficacy and immune response strength, with mRNA vaccines frequently favored when accessible due to superior performance in the general population.

8.2 Variations in Response to Vaccine Categories

Kidney transplant recipients exhibit a diminished capacity to elicit a strong immune response to COVID-19 vaccinations due to their immunosuppressive therapies. Research indicates that regardless of the vaccine type, kidney transplant recipients typically exhibit a diminished antibody

response relative to the general population. Nevertheless, specific vaccines (e.g., mRNA) generally provoke a more robust immune response than adenovirus vector vaccines in KTRs [27].

8.2.1 Antibody Response

The antibody response is generally diminished in KTRs relative to healthy individuals, and it may exhibit delays or reduced persistence.

8.2.2 Cellular Immunity

T-cell responses, crucial for sustained immunity, may be compromised in kidney transplant recipients, irrespective of the vaccination type.

8.3 Vaccine Dose

Research demonstrates that kidney transplant recipients frequently fail to achieve adequate protection using typical two-dose protocols of COVID-19 vaccinations. Consequently, supplementary doses (booster doses) are advised to augment protection in this demographic.

8.3.1 Standard Dose Versus Booster Doses

Kidney Transplant Recipients may necessitate supplementary doses, especially following the initial two-dose series, to elicit a more robust immune response. Booster doses are now advised for kidney transplant recipients to enhance vaccine efficacy, mainly due to their inadequate baseline immune response.

8.3.2 Elevated-Dose Immunization

Some studies have investigated higher vaccination dosages in kidney transplant recipients to offset their diminished immune response.

8.4 Dosage Intervals

The duration between vaccination administrations is essential for achieving effective immune responses. In KTRs, prolonged dosing intervals may allow additional time for the immune system to react and potentially enhance vaccine efficacy.

8.4.1 Optimal Interval

Research indicates that prolonging the interval between doses (e.g., from 3 weeks to 8 weeks for mRNA vaccines) may enhance the immune response in immunocompromised persons, including KTRs. The ideal interval may differ based on the vaccine type and the specific immunological condition of the patient.

8.5 Administration Timing of Bolus Doses

For KTRs, initiating the immunization schedule and subsequent booster doses should preferably align with intervals of reduced immunosuppressive medication to enhance vaccine efficacy.

Furthermore, post-transplant patients may benefit from vaccination before transplantation or promptly following the procedure when their immunosuppressive drugs may be modified.

8.5.1 Timing with Immunosuppression

Vaccination should ideally be administered while the immunosuppressive medication is at its minimal effective dosage or during intervals when immunosuppressive agents, particularly antimetabolites, are temporarily diminished or halted since this may facilitate an enhanced immune response [28].

8.5.2 Importance of Antibody Assessment

Post-vaccination antibody testing is frequently employed to evaluate vaccine efficacy in KTRs. Due to the often diminished immune response in KTRs, antibody titers may indicate vaccination effectiveness.

Antibody Monitoring. Regular assessment of antibody titers following vaccination is essential to ascertain whether a patient has attained an appropriate immune response, mainly as kidney transplant recipients may inadequately produce sufficient antibodies after routine immunization doses. In instances of inadequate response, extra booster dosages may be necessary.

Interpretation of Antibody Levels. Nonetheless, antibody levels alone may not comprehensively predict protection in kidney transplant recipients, as cellular immunity (T-cell response) also significantly contributes to preventing severe illness. Therefore, a comprehensive approach is essential, considering both antibody and T-cell responses.

9. Important Outcomes

The research on COVID-19 vaccinations and kidney transplant recipients exposes numerous significant results that underline the particular issues for this vulnerable group. First, it was discovered that compared to the general population, kidney transplant recipients have a much-reduced antibody response to COVID-19 vaccinations, therefore raising their risk of severe infection. Furthermore, the studies show that although vaccination increases the immune response, many people's levels of protective antibodies might not be enough to stop breakthrough infections. Significantly, the study also underlines the importance of tailored vaccination plans, including possible booster doses, to increase efficacy in certain patients. Finally, it emphasizes a careful approach to resuming regular activities following immunization, thereby supporting continuous preventative actions to guard kidney transplant recipients from COVID-19.

10. Highlights

A kidney transplant recipient examined in connection with COVID-19 vaccines displayed an unusual outcome: despite complete vaccination, the patient demonstrated a paradoxically strong immune response, marked by heightened specific T-cell responses, even in low antibody levels. This was especially significant considering the prevailing tendency among the broader population of kidney transplant recipients, who generally have diminished antibody responses following

immunization. Moreover, this patient's clinical trajectory following immunization was unique, exhibiting minimal impact from moderate COVID-19 symptoms and rapid recovery, suggesting the potential role of T-cell-mediated immunity in offering a degree of protection. This case illustrates the intricacy of immune responses in immunocompromised persons. It emphasizes the necessity for additional studies to investigate the role of T-cell immunity and its potential ramifications for vaccination tactics in kidney transplant recipients [29, 30].

11. Limitations

The study on COVID-19 vaccines in kidney transplant recipients presents several limitations that must be acknowledged. First, the sample size was relatively small, which may limit the generalizability of the findings to the broader population of kidney transplant recipients. Additionally, the cross-sectional design of the study means that it captures only a snapshot of the participants' immune responses at one point in time rather than longitudinal data to assess how immunity may evolve post-vaccination. Moreover, the study primarily focuses on specific demographic groups, which may introduce selection bias and overlook variability in immune responses across different ethnicities, ages, or underlying health conditions. There is also a reliance on serological tests to measure antibody levels, which may not fully correlate with protective immunity or assess the complete immune response, including T-cell activity. Finally, the lack of long-term follow-up limits our understanding of the duration of immunity and the effectiveness of various vaccination schedules or booster doses in this high-risk group. Addressing these limitations in future research will be essential in providing more precise insights into the optimal vaccination strategies for kidney transplant recipients [31-33].

12. Follow-Up of Study

Monitoring kidney transplant recipients post-COVID-19 vaccination is essential for comprehending the long-term immune response and overall vaccine effectiveness in this at-risk group. Numerous studies indicate that follow-up generally entails consistently monitoring antibody levels and evaluating T-cell responses to ascertain the temporal variations of these immunological parameters following vaccination. This longitudinal method enables researchers to assess the longevity of the immune response and the possible necessity for booster doses to augment or sustain protection against COVID-19. Furthermore, follow-up should encompass surveillance for breakthrough infections, clinical outcomes, and any adverse effects associated with immunization. By gathering data on these factors, researchers can ascertain which patients may be at elevated risk for suboptimal responses and customize immunization methods accordingly. Moreover, meticulous recording of vaccination timing in conjunction with alterations in immunosuppressive medication within the patient cohort can yield significant insights into the impact of these variables on vaccine efficacy. An organized follow-up plan is crucial for deriving substantial insights from the study and guiding clinical protocols for managing kidney transplant recipients during the ongoing COVID-19 pandemic [34].

13. Difference between Vaccinated and Non-Vaccinated Patients of COVID

This document presents a comparative analysis of COVID-19 infection outcomes, immunological response, and overall health impact between vaccinated and non-vaccinated kidney transplant recipients, organized in a tabular manner [34]. (Table 2).

Table 2 Difference between vaccinated and non-vaccinated patients of COVID.

S. No.	Aspect	Vaccinated Patients	Non-Vaccinated Patients
1	**Immune Response**	Enhanced antibody and T-cell responses, albeit often lower than the general population	Minimal or absent antibody response
2	**Risk of Breakthrough Infection**	There is a higher risk of breakthrough infections, but typically milder symptoms	Increased risk of severe infection and hospitalization
3	**Severity of Illness**	Generally milder illness, lower rates of severe complications	Higher rates of severe disease and mortality
4	**Response to Infection**	Improved recovery rates; quicker resolution of symptoms in many cases	Extended or complicated recovery
5	**Need for Hospitalization**	Lower hospitalization rates; cases that do occur tend to be less severe	Higher hospitalization rates due to severe illness
6	**Duration of Immunity**	Potential waning immunity over time, requiring booster doses	No immunity; full susceptibility to infection
7	**Long-term Outcomes**	Potential long-term protection against severe disease	Increased risk of long-term complications from COVID-19
8	**Adverse Reactions**	Common mild side effects (e.g., sore arm, fever); severe reactions are rare.	No vaccine-related side effects; higher risk from COVID-19 itself

14. Conclusion

KTRs often have attenuated immune responses to vaccines due to immunosuppressive therapies. However, vaccination remains crucial for preventing infections and improving long-term outcomes. Unique strategies, such as pre-transplant vaccination, higher doses, and booster shots, are often required to improve the immune response in KTRs. Certain vaccines, particularly live ones, are contraindicated due to the risk of serious infections in immunocompromised individuals. Vaccinated KTRs experience milder disease courses and are less likely to experience complications requiring hospitalization or intensive care. Managing immunosuppression in KTRs with COVID-19 requires careful balance, including reducing immunosuppressive medications while avoiding acute rejection. Regular monitoring, individualized adjustments to immunosuppressive regimens, and timely

interventions for acute rejection are essential for improving outcomes. Personalized vaccination strategies are necessary to optimize outcomes for this vulnerable population.

Abbreviations

KTRs	Kidney transplant recipients
MMR	Measles, mumps, and rubella
ICU	Intensive care
HPV	Human papillomavirus
CNIs	Calcineurin inhibitors
MMF	Mycophenolate mofetil
AKI	Acute kidney damage
TB	Tuberculosis
BCG	Bacille Calmette-Guérin
VZV	Varicella-zoster virus
mRNA	Messenger RNA

Author Contributions

JI and AK developed the outline of this invited article; JI, AK wrote the original draft, which was edited by AK. All authors agreed to the final version to be submitted.

Competing Interests

The authors have declared that no competing interests exist.

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