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Coronavirus disease 2019 and renal transplantation

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Abstract

Ever since the severe acute respiratory syndrome virus causing coronavirus disease 2019 (COVID-19) struck the world, global health strategies have changed significantly. According to the Centers for Disease Control and Prevention, kidney transplant recipients are stratified as being high risk of developing fatal illness from COVID-19 infection. Kidney transplant is the gold-standard treatment for end-stage kidney disease subjects. During the pandemic, significant concerns have

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emerged regarding continuation of kidney transplant surgeries and management of kidney transplant recipients post-transplant. The added risk of immunosuppression in this cohort was and remains a theoretical concern, posing a potential risk of transplantation rather than benefit. This comprehensive review aims to cover most of the faced challenges in kidney transplantation in different stages of the pandemic. In addition, it will elucidate the epidemiology, nature, course of the disease, surgical consideration in donors and recipients as well as role of immunosuppression and management of COVID-19 infected kidney transplant recipients during these extraordinary circumstances.

Key Words: Renal transplantation; COVID-19; SARS-CoV-2; Kidney failure

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Core Tip: This comprehensive review aims to cover most of the faced challenges in kidney transplantation in different stages of the pandemic. In addition, it will elucidate the epidemiology, nature, course of the disease, surgical consideration in donors and recipients as well as role of immunosuppression and management of coronavirus disease 2019 infected kidney transplant recipients during these extraordinary circumstances.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has had a substantial international impact as the world is trying to learn how to manage this deadly disease. The virus was initially identified in Wuhan, China in 2019 and was thought to originate from a zoonotic etiology. It has now spread across borders and the United States of America alone has had over 25 million people infected, causing 400000 deaths[1]. One of the more deadly aspects of COVID-19, which has also led to many hospitalizations, is that it can cause a severe respiratory disease known as severe acute respiratory disease syndrome coronavirus 2 (SARS-CoV-2). The virus enters its host *via* the angiotensin-converting enzyme 2 receptors, which are very prominent in the lung's alveolar cells. The virus then causes pneumonia, which may lead to the often-fatal acute respiratory disease syndrome. Another possible complication of COVID-19 is a cytokine storm syndrome caused by a hypersensitive response to the virus, leading to multiorgan damage and failure, which may also be fatal[2,3].

In patients with end-organ damage, organ transplantation has become very common in treatment. Kidney failure is a prevalent complication of uncontrolled diabetes mellitus and hypertension. Many patients with chronic kidney disease progress to an end-stage renal disease characterized by a glomerular filtration rate of less than 15 mL/min. During this state, the body is unable to remove urinary substances and toxins. The only treatment in these situations is hemodialysis, which allows for extracorporeal renal replacement, or renal transplantation. Renal transplantation is more cost-effective and provides a higher quality of life to patients, but the major limitation would be obtaining a compatible kidney[4,5] and organ donation supply.

After kidney transplantation, post-transplant immunosuppressive therapy is the gold standard of treatment. The induction therapy generally starts with either lymphocyte depleting antibodies or non-depleting antibodies. This is then followed by a triple-drug regimen consisting of steroids, a calcineurin inhibitor, and an antiproliferative agent. This treatment reduces the risk of rejection and increases infection risk; hence, balance is essential between the risks and benefits. It is unclear if this level of immunosuppression would decrease the chance of a cytokine storm flair.

INCIDENCE, MORTALITY, AND MANIFESTATIONS

Kidney transplant recipients are considered to carry a higher risk for complicated COVID-19 viral infection. Other significant comorbidities including obesity, diabetes mellitus, and chronic obstructive lung disease are predisposing factors for higher risk of getting COVID-19 disease[6].

Upon literature review, many case series had shown a particularly higher mortality rate in kidney recipient patients with COVID-19 disease (*e.g.*, a case series of 36 patients reported in Montefiore Medical Center in New York[7] and another 15 kidney transplant recipients reported in Columbia University[8]. Moreover, multiple case series were reported in Europe (*e.g.*, 7 patients reported by St. George's University Hospital in London, United Kingdom)[9]. In these reports, mortality rates ranged between 20% and 28% compared to the general population's general mortality reports, which fluctuate between < 1% to 5%.

Almost all the previous studies revealed that the COVID-19 viral loads and the mortality rates were significantly higher in kidney transplant patients who had moderate to severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome as compared to immunocompetent people[10].

Fever, shortness of breath, and cough were the most common presenting symptoms, while portable chest x-ray abnormality was the main radiological finding. Other common features included elevated C-reactive protein, low lymphocyte count (lymphopenia), and increased ferritin level[11].

RENAL TRANSPLANTATION DURING COVID-19 PANDEMIC

Effect of the COVID-19 pandemic on renal transplant activities

In early 2020, shortly after the healthcare system in Europe was overwhelmed by the number of COVID-19 patients requiring hospitalizations, it was decided that elective procedures would be suspended to provide more resources to accommodate COVID-19 cases. Although kidney transplantations were postponed, kidney disease continued to progress, resulting in more patients requiring hemodialysis in the interim. Information was collected in the United Kingdom and found that the waitlist of individuals requiring renal transplants grew from about 4700 to about 6300 in the 3-6 mo since elective procedures were suspended in March 2020. This resulted in about 1300 more people requiring hemodialysis who would have otherwise been transplanted. This growing number of dialysis patients puts a greater demand on dialysis services, with associated costs more than doubling[12], and these individuals are at an increased (albeit not fully well understood) mortality risk from COVID-19.

Although healthcare systems are currently better equipped to reinstate transplant services, early case series from the United Kingdom and Italy found mortality of 7%-25% from COVID-19 infections postoperatively. This uncertainty in risks and the increased strain on resources to catch up on the backlog of transplant cases place further challenges on the workforce and decision-making when it is safe to perform transplantation. There is a need to evaluate how to optimize best kidney transplantation safety given the current COVID-19 pandemic[12]. A study examined patients in Wuhan, China early in the pandemic who were operated on unintentionally during their incubation period and were found to have acceleration and exacerbation of their disease progression. This conclusion was made based on the fact that the median time from symptom onset to dyspnea in COVID-19 patients was 8 d at the time of this study, whereas the median time from symptom onset to dyspnea postoperatively was 3.5 d. Those who were operated on who had longer surgery time (median time of 200 min *vs* 70 min) had a higher risk of more severe disease requiring management in an intensive care unit. It was also found that the mortality rate amongst these patients was higher than the reported overall case-fatality rate (2.3%) in patients without surgery. Therefore, this study emphasized the importance of investigating the stress an invasive procedure such as surgery may have on patients who may be asymptotically infected with COVID-19[13]. Viral infections are common causes of opportunistic infections after transplantation; and although there are measures in place to screen for some infections (*e.g.*, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus), there is a need for a more robust viral assay to detect coronaviruses now more urgently so given the prevalence of SARS-CoV-2 [14].

Manifestations and outcomes of COVID-19 infection in renal transplantation patients

While most studies found that patients with underlying kidney disease (or transplanted kidneys) are more vulnerable to developing COVID-19 infection and acute kidney injury, one study suggested that there may not be a significant difference in outcomes when compared to the general population[11,15].

Initially, renal transplant patients were seen to have a high risk of early mortality[7] and critical COVID illness due to chronic immunosuppression and comorbid conditions. Later, it was found that when managed by stopping immunosuppressive therapy while being maintained on intravenous stress dose steroids (to prevent adrenal insufficiency) and additional supportive measures, and then slowly re-introducing the patient's immunosuppression regimen, outcomes began to show promising results in survivability[11]. Most recently, there was a case series that followed 8 patients with renal transplants (including patients with transplants of varying ages, some patients with transplants a few months prior, and some with transplants more than a year senior) through their medical management of COVID-19 infection. Every patient's antiproliferative medication was stopped (namely mycophenolate mofetil and azathioprine). They continued to be maintained on steroids and calcineurin inhibitors (albeit with some tailoring on a case-by-case basis) as well as supportive treatment. Of the 8 individuals, only one required care in an intensive care ward (including requiring intubation), and all of them recovered well. Although its study size limits this case series, it shows promise and revealed that there might not be a significantly increased risk of severe COVID-19 illness solely based on the renal transplant or kidney function status[11].

Infection control measures in renal transplant programs

Inferior clinical outcomes have been reported for renal transplant recipients infected with COVID-19 compared to COVID-19 patients who have not received renal transplants[16,17]. Thus, patients with a renal transplant who are not infected with COVID-19 should minimize contact with non-household individuals, practice frequent hand hygiene, and use a facemask or face covering when traveling outside their homes.

Renal transplant patients who have mild COVID-19 symptoms who do not need hospitalization should practice self-confinement at home for 2 wk and reduce their interactions with their household members[18]. Given renal transplant patients' immunosuppression regimens that put them at higher risk for contracting infections, renal transplant recipients who have moderate to severe COVID-19 symptoms and need hospitalization should be admitted to a negative pressure room with droplets, contact, and eye protection isolation. Hospital staff taking care of renal transplant patients need to undergo appropriate donning and doffing of personal protective equipment, practice regular hand hygiene, and wear N95 respirator masks with protective eyewear[19].

A nationwide survey of American transplant institutes discovered that regarding deceased donor testing, 93% of respondents reported their organ procurement organization requiring a nasopharyngeal COVID-19 polymerase chain reaction (PCR) test, 3% of respondents stated needing a COVID-19 antibody test, and 19% stated needing a computed tomography scan of the chest. Transplant centers reported required testing of pre-transplant living donor candidates for COVID-19, with 97% of respondents using a PCR test, 13% using an antibody test, and 19% performing a chest computed tomography. If a possible living transplant donor was found to be positive for COVID-19, 75% of surveyed centers stated they would abort the planned donation, 44% stated they would repeat donor PCR testing until there was a negative result, and 11% of surveyed centers stated they would wait until the donor was COVID-19 antibody-positive before moving forward with a donation. Respondents did not report a consensus when it was appropriate to conduct surgery in a formerly COVID-19 positive donor. A few centers stated they would postpone surgery by at least 14 to 28 d. None of the centers reported cases of COVID-19 transmission from donor to recipient[18]. A large volume renal transplant center study performed at Cambridge University Hospital from December 30, 2019 to May 19, 2020, including 71 kidney transplantations, also did not report any cases of donor-derived COVID-19 transmission during transplantation[20].

SURGICAL CONSIDERATION FOR RENAL TRANSPLANT DURING COVID-19 PANDEMIC

The World Health Organization has recommended using personal protective equipment in addition to recommending against routine or nonemergent procedures during COVID-19 pandemic. The use of procedures causing aerosolization, such as endotracheal intubation, high flow respirators, and suction, poses an imminent risk of spreading the disease. The increasing mechanical ventilation requirement in intensive care units may limit the number of ventilators for routine procedures[21]. Despite the limitations mentioned above, some procedures, including emergency surgeries, transplant surgeries, and cancer surgeries, should be continued as lack of such services would increase morbidity and mortality. The anecdotal evidence of routine surgeries, including cholecystectomy in COVID-19 patients, have shown unfavorable outcomes [22]. Careful planning for anesthesia may help mitigate the spread during the procedure. Filtering face piece during intubation, use of disposable equipment, rapid sequence intubation avoiding manual ventilation, and the closed suction system are some of the proposed ways to prevent the spread of COVID-19[23]. The use of agents containing 62%-71% ethanol, 0.5% hydrogen peroxide, or 0.1% sodium hypochlorite effectively decreases transmission of COVID-19 in operating theatres[24]. The American Red Cross recommends a 28-d delay for donors traveling to high-risk regions or contact with COVID-19 patients[15]. The presence of a false-negative reverse transcription-PCR for COVID-19 causes the missing COVID-19 infection in both donors and recipients. Transplanted patients in the immediate postoperative period are immunocompromised and thus have a higher susceptibility of COVID-19 [25]. The requirement to monitor COVID-19 cases and restrict transplants to emergencies in case of increasing COVID-19 cases has also been proposed to decrease the spread of COVID-19[26]. Further research has to be undertaken to assess postoperative complications and risk stratification strategies in COVID-19 patients[27].

COVID-19 TREATMENT OPTIONS FOR RENAL TRANSPLANT RECIPIENTS

Kidney transplant recipients pose a particular risk because of their steady-state of immunosuppression[28]. Kidney transplant patients who contract COVID-19 are at a higher risk of developing acute kidney injury and mortality[17]. There is no global consensus on the ideal management of kidney transplant recipients with COVID-19 disease, so patients are dealt with individually from case to case. Essential aspects of the treatment are managing immunosuppression medications and considering drug-drug interactions. In kidney transplant patients, the most commonly used immunosuppressive drugs [mycophenolate mofetil (MMF), tacrolimus, and cyclosporine] have a narrow therapeutic index and fluctuating pharmacokinetics[29,30]. Mycophenolate, which inhibits T and B cell proliferation, is always withheld[31,32]. Calcineurin inhibitors (CNIs) are substrates for cytochrome P450 3Y4. Moreover, cyclosporine further inhibits cytochrome P450 (CYP) 2C9, CYP3A4, and organic anion-transporting peptides (OATP) 1B1/1B3. MMF is a substrate of OATP and uridine diphosphate-glucuronosyltransferase enzymes. Significant drug-drug interactions are tabulated in Table 1.

REMDESIVIR AND OTHER ANTIVIRALS SUCH AS FAVIPIRAVIR

Remdesivir and favipiravir are analogs of adenosine that inhibit SARS-CoV-2 RNA-dependent RNA polymerase, which is needed to replicate the virus[33]. Remdesivir is beneficial, especially in severe cases of COVID-19 infection. However, its effect is not studied in those patients with estimated glomerular filtration rate < 30 mL/min per 1.73 m², and it serves as an exclusion criterion for treatment[33,34]. As of February 2021, remdesivir is the only Food and Drug Administration-approved antiviral drug used for hospitalized adults and children with severe infection (low O₂ saturations, requiring significant supplemental oxygen, needing mechanical ventilation) for reducing time to recovery[35]. *In vitro*, remdesivir serves as a substrate of CYP3A4 and the drug carriers OATP1B and P-glycoprotein. It also acts as an inhibitor of multiple enzymes, including OATP1B1, CYP3A4, OATP1B3, and multidrug and toxin extrusion protein 1[36]. Favipiravir is more beneficial at least than lopinavir-ritonavir, and its

Table 1 Interactions between the common immunosuppressive medications and the novel therapeutic agents of coronavirus disease 2019 disease

	RMD	FAV	CL/HCL	TCZ	LPV/r
Prednisone	<->	<->	<->	<->	↑
Methylprednisone	<->	<->	<->	<->	↑
Cyclosporine	<->	<->	↑	↓	↑
Tacrolimus	<->	<->	↑	↓	↑
Sirolimus	<->	<->	↑	↓	↑↓
Mycophenolate	<->	<->	<->	<->	
Azatguoprine	<->	<->	<->	<->	<->
Anti-thymocyte globulin	<->	<->	<->	<->	<->
Basiliximab	<->	<->	<->	<->	<->

↑: Potential increase exposure of the comedication; ↓: Potential decrease exposure of the comedication; <->: No significant effect. CL/HCL: Chloroquine/hydrochloroquine; FAV: Favipiravir; LPV/r: Lopinavir/ritonavir; RMD: Remdesivir.

use is authorized in China from February 2020[37]. Although there are no clear drug-drug interactions between remdesivir and other immunosuppressive agents, careful monitoring of the drug levels is needed given the lack of sufficient data.

Ivermectin

Ivermectin is an antiparasitic drug that significantly affects SARS-CoV-2 *in vitro* with questionable efficacy in clinical trials[38]. However, it has significant interactions with immunosuppressive medications[39].

Chloroquine/hydroxychloroquine

Both the chloroquine (CL) and hydroxychloroquine (HCL) are potent inhibitors of the SARS-CoV-1 and other coronaviruses *in vitro*, but they have also been used to treat the novel coronavirus[40]. It has been shown that both CL and HCL increase the blood level of cyclosporine, tacrolimus, and mammalian target of rapamycin (mTOR) when used simultaneously. However, given the long half-life of CL/HCL, closer monitoring of the trough levels is not recommended. Generally, there is no need for dose adjustment when used in patients with reduced estimated glomerular filtration rate, *i.e.* < 30 mL/min[41].

Lopinavir–ritonavir and darunavir–cobicistat

These medications are in use more in the early phases of COVID-19 infection. Lopinavir and ritonavir are protease inhibitors that block cytochrome P4503A. CNIs and mTOR inhibitors should be withdrawn entirely if they receive ritonavir or cobicistat[42]. Tacrolimus levels were elevated when treated with lopinavir and ritonavir in a kidney transplant patient, which went down to normal levels when switched to favipiravir[43]. It must be mentioned that none of these medications have shown any clear benefit[44].

Role of corticosteroids

Steroids have a pivotal role in suppressing cytokine storm and decreasing inflammatory cell migration. The RECOVERY trial has shown a significant decrease in mortality risk using daily dexamethasone in patients requiring supplemental O₂. The World Health Organization later included that in their recommendations for treating a severe form of COVID-19 disease[45]. Dexamethasone and methylprednisolone may lower tacrolimus concentrations through induction of CYP3A4 or, more likely, CYP3A5[46]. Therefore, closer monitoring of tacrolimus/sirolimus may be needed when steroids are in use.

Role of tocilizumab and sarilumab (anti-interleukin-6/interleukin-6R monoclonal antibodies)

It is thought that COVID-19 infection induces the release of interleukin (IL)-6, a pro-

inflammatory cytokine produced by several other cell types, including bronchial epithelial cells. Tocilizumab is a recombinant monoclonal antibody against the anti-IL-6 receptor used for rheumatologic disorders and cytokine release syndrome[47]. Tocilizumab, safe in renal dysfunction, was successfully used in China and is currently in use for severe hyperinflammatory syndrome, often requiring mechanical ventilation. By that time, in transplant patients, immunosuppressive agents such as CNIs, MMF, azathioprine, and mTOR inhibitors are already withdrawn. Generally, tocilizumab is not recommended if the white blood cell is $< 1000/\text{mm}^3$ [47,48].

One-third of patients who received tocilizumab had a reactivation of cytomegalovirus, but this was not much higher than the control group. This is suggestive that the immunocompromised state from the steroids and critical illness may be more contributory to this viral activation. Thrombotic complications such as venous thrombosis or cerebrovascular events were also very similar to the control groups. Tocilizumab seems to be safe overall, similar to COVID-19 patients among solid organ transplant and non-solid organ transplant patients[49].

Intravenous immunoglobulins

Some studies reported a beneficial effect while using a high dose of intravenous immunoglobulins in managing severe COVID-19 infection to combat endothelial activation and counteract inflammation[50].

ROLE OF USING CONVALESCENT PLASMA AND HYPERIMMUNE IMMUNOGLOBULINS

Transferring a passive immunity from a healed patient through convalescent plasma has shown promising results, and more trials are underway[51,52].

COVID-19 VACCINE

The first COVID-19 vaccines were given in the United States in December of 2020. The vaccines used new technology with messenger RNA. These vaccines were initially targeted for the geriatric population and later to those of high risk, eventually making it down to the general public. Amongst this population of high-risk patients was where those with organ transplants reside.

Many studies were published regarding this population. Renal function should be closely monitored after the vaccine as there is an increased chance of rejection, especially if booster vaccines may be required[53]. Because this group is immunocompromised, there was concern that their body would not be able to elicit an appropriate response to make antibodies. A study published in kidney international showed that 85% of patients had made the appropriate antibodies 6 mo after the vaccines[54]. Another study in Germany demonstrated that 22% of the post-renal transplant patients had antibodies but were only tested 2 wk after vaccination[55]. The efficacy is not very clear in this immunocompromised population. In patients who have received the vaccine and had worsening kidney function, pulsatile steroids were given to a patient whose creatinine was increased and showed marked improvement[53]. The best solution would appear to be to get the vaccine but still abide by other appropriate precautions such as social distancing, face coverings, and hand hygiene[56].

ADVICE FOR RENAL TRANSPLANT RECIPIENTS WITH OR AT RISK OF COVID-19 INFECTION

Patients on immunosuppression are generally advised to spend as much time at home as possible unless it is essential to go outside. The patient should also play their role in spreading awareness among their community about physical distancing and personal hygiene such as frequent hand washing. If needed to go outside at all, they must wear facemasks and get vaccinated when possible. If a transplant recipient has tested positive for COVID but having mild or no symptoms, staying home and have a telephonic follow-up every 24-48 h is recommended. Patients should have frequent temperature checks and observe symptoms. If symptoms are progressing, patients must contact a healthcare worker as soon as possible for an assessment. Generally,

patients are advised to reduce prednisone to 0.2 mg/kg per day but not stop it abruptly. Similarly, consideration should be given to stopping/reducing antimetabolites[32].

MANAGEMENT OF IMMUNOSUPPRESSION IN RENAL TRANSPLANT RECIPIENTS

Immunocompromised patients are considered to be at high risk for severe disease from COVID-19 infection. Solid organ transplant recipients are of particular concern given the need to balance the potential for acute rejection and compromised immune response to a viral infection. There is currently inconclusive literature available to guide the optimal management of COVID-19 infection and baseline immunosuppression in renal transplant patients.

Ramoz *et al*[57] summarized 40 published cases detailing immunosuppression regimen management in renal transplant recipients with COVID-19 infection. Calcineurin inhibitors and antiproliferative therapy were discontinued in 75% of patients, whereas only 7.5% of patients were managed with no change in their baseline regimen. None of the patients treated without modification in their immunosuppressive therapy required mechanical ventilation[58-60].

Before the publication of the RECOVERY trial, which demonstrated lower 28-d mortality with the use of dexamethasone, a select group of patients were successfully managed with corticosteroid-sparing regimens. An example of such regimens consisted of dose-reduced antiproliferative therapy from mycophenolic acid 540 mg twice daily to 360 mg twice daily and decreased tacrolimus target trough levels from 6-8 ng/mL to 4-6 ng/mL[57,61]. The rationale for avoiding corticosteroids in these patients was based on the inconclusive evidence at the time supporting the use of corticosteroids coupled with the potential for decreased immune response, reduced pathogen clearance, promotion of secondary infections, and increased viral shedding.

An alternative strategy to manage immunosuppression is to follow a stepwise approach to reducing or holding the antimetabolite in moderate to severe COVID-19 infection[6]. Preference is generally given to the calcineurin inhibitor as they inhibit IL-6, IL-1, and tumor necrosis factor- α , inflammatory cytokines thought to contribute to the dysregulated immune response cytokine storm observed in severe COVID-19 infections[62]. According to recommendations from the American Society of Transplantation, patients receiving maintenance corticosteroids have generally been maintained during therapy[63]. In patients with unstable severe COVID-19 disease requiring mechanical ventilation, cessation of all immunosuppressive agents can be considered to initiate or continue corticosteroids[64]. For patients on dual therapy with an antimetabolite and calcineurin inhibitor, it may be reasonable to replace the antimetabolite with low-dose corticosteroids[64]. Although the optimal timing has yet to be established, immunosuppression can be cautiously resumed 5-15 d after resolving symptoms, starting with the calcineurin inhibitor[64].

POTENTIAL DRUG INTERACTIONS: IMMUNOSUPPRESSION AND AGENTS FOR COVID-19

The narrow therapeutic indexes and variable pharmacokinetic parameters of immunosuppressive medications used for renal transplant patients require careful screening and monitoring when used with specific agents[29,30]. Tacrolimus and cyclosporine are substrates of CYP3A4 and the P-glycoprotein efflux pump. Besides, cyclosporine weakly inhibits CYP2C9, CYP3A4, and OATP1B1/1B3, as well as P-glycoprotein. Mycophenolate is a substrate of specific OATP and uridine diphosphate-glucuronosyltransferase enzymes. As of January 2021, currently recommended therapies for COVID-19 include remdesivir and corticosteroids[65].

Remdesivir

Remdesivir is a novel adenosine analog that inhibits SARS-CoV-2 RNA-dependent RNA polymerase, an essential enzyme required for viral replication[33]. Remdesivir is a substrate of CYP3A4, and the drug transporters OATP1B1 and P-glycoprotein and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and multidrug and toxin extrusion protein 1 *in vitro*[66]. Despite the lack of evidence demonstrating any significant drug interactions between immunosuppression and remdesivir, careful monitoring is still

warranted due to the lack of strong evidence at this time[30].

Corticosteroids

A dysregulated immune response characterized by systemic inflammation has been shown to occur in severe COVID-19[57,61]. Corticosteroids may mitigate the systemic inflammatory response and lead to clinical improvement through the decreased production of inflammatory mediators and suppression of neutrophil migration. Although its significance is unknown, corticosteroids such as dexamethasone and methylprednisolone may decrease tacrolimus serum concentrations through induction of CYP3A4 and CYP3A5[67]. Additional monitoring of calcineurin inhibitor serum concentrations may be considered when corticosteroids are initiated, tapered, or discontinued.

CONCLUSION

This comprehensive review covered most of the faced challenges in kidney transplantation in different stages of the pandemic. In addition, it elucidated the epidemiology, nature, course of the disease, surgical consideration in donors and recipients, as well as role of immunosuppression and management of COVID-19 infected kidney transplant recipients during these extraordinary circumstances.

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