Outpatient Management of the Kidney Transplant Recipient during the SARS-CoV-2 Virus Pandemic

Shana E. Gleeson,[1] Richard N. Formica,[2] and Ethan P. Marin[2]

Introduction

The emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the corresponding syndrome of coronavirus disease 2019 (COVID-19), has rapidly and dramatically altered the landscape of the United States' health care system. As the number of cases has increased, health care providers are forced to grapple with how to treat a disease for which there is a paucity of data regarding optimal management. Currently, there are only case reports about how this disease may manifest in solid organ transplant recipients (1) and how their management may need to be adjusted in light of immunosuppressive medications. Current management relies on early experience in patients with COVID-19 combined with experience managing other infections in kidney transplant recipients. The following guidance is for clinicians caring for ambulatory kidney transplant recipients with COVID-19. These recommendations are on the basis of our experience managing other infections in kidney transplant recipients and our center's early experience in managing our first 21 patients testing positive for COVID-19 and the 41 patients with symptoms who tested negative. Our suggestions are made with the acknowledgment that data continue to accumulate and inform disease management.

One of the challenges in this pandemic is balancing patient care needs with limited resources, such as hospital beds, ventilators, and personal protective equipment. The outpatient management of kidney transplant recipients with suspected or diagnosed COVID-19 requires consideration of public health concerns regarding exposure of uninfected individuals, both other patients and health care workers, and the benefits of social distancing. Given these concerns and the fact that many infected patients have mild disease, not all kidney transplant recipients with suspected or diagnosed COVID-19 need to be hospitalized, and selected kidney transplant recipients can be safely managed in the outpatient setting. However, experience with other infections in this population indicates that kidney transplant recipients can have subtle or delayed presentations of serious infections. Therefore, a more proactive approach in the diagnostic evaluation and monitoring of these patients and a lower threshold for hospitalization are appropriate. This will allow patients whose disease

severity is progressing to be hospitalized and started on treatment early in the course of their illness. The objective of this manuscript is to provide a strategy that clinicians may use when caring for outpatient kidney transplant recipients who test positive or are presumed to be positive for COVID-19 and more specifically, to guide decisions regarding outpatient monitoring, immunosuppressive management, and the need for hospitalization. As with other infections, these recommendations must be contextualized for an individual patient's needs, and clinical judgement should be applied when making decisions regarding medication changes and admission to the hospital.

Outpatient Management: Prevention

As with the general population, all kidney transplant recipients should be advised to practice social distancing, maintain good hand hygiene, and maintain other general safety measures during the COVID-19 pandemic. Telemedicine, including both video and telephone-only encounters, is an important mechanism for maintaining outpatient care while limiting direct patient contact. When clinically appropriate, telemedicine should be used to care for ambulatory patients with COVID-19. In an effort to reduce patient exposure and the risk of spreading the virus, routine laboratory testing should be deferred (2). If laboratory testing is required, an effort should be made to arrange for specific appointment times for blood drawing. This will minimize contact between patients.

Performance of for-cause biopsies presents another exposure risk, and during this pandemic, the risk-benefit ratio must now incorporate potential exposure to SARS-CoV-2 in the health care facility. As an alternative, practitioners may consider using non-invasive measures of transplant rejection, such as donor-derived cell-free DNA (3) (which may be used in place of for-cause biopsy) or peripheral blood gene expression tests (4) (which may substitute for protocol biopsies). Decisions to treat rejection with augmented immunosuppression also need to incorporate the risk of SARS-CoV-2 infection and must be individualized.

Outpatient Management: Diagnostics

As experience increases with this virus, it is becoming apparent that SARS-CoV-2 causes a variety of

[1]Section of Infectious Disease, Department of Medicine, Yale University, New Haven, Connecticut
[2]Section of Nephrology, Department of Medicine, Yale University, New Haven, Connecticut

Correspondence:
Dr. Ethan P. Marin, Yale University School of Medicine, Boardman 114, 330 Cedar Street, New Haven, CT 06520. Email: ethan.marin@yale.edu

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symptoms. Patients can present with upper respiratory symptoms (sore throat), lower respiratory symptoms (cough, dyspnea), constitutional symptoms (fever, malaise, myalgias), gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), or a combination thereof. Many patients have also reported anosmia and dysgeusia, which seems to be a somewhat unique feature of this syndrome. At the time of this writing, access to testing for the SARS-CoV-2 virus is still limited. If testing is available, all kidney transplant recipients with any of the above symptoms should be tested to definitively diagnose COVID-19. Additionally, kidney transplant recipients who have had an exposure to a known infected person should be considered for testing. Not all patients will have access to testing; therefore, patients who present with characteristic symptoms or at-risk exposures should be managed as presumptively positive. Finally, there is a significant rate of false negative tests results (5), and therefore, if the clinical suspicion is high and the test is negative, the test may be repeated after 48 hours. While repeat testing is pending or if repeat testing is not available, then it is reasonable to manage the patients as if they have COVID-19.

Outpatient Management: Documented Cases

In kidney transplant recipients with a definitive or presumptive diagnosis of COVID-19, it is appropriate to remain at home if the following criteria are met: lack of fever, no dyspnea, maintaining adequate oral intake, and the ability to maintain close communication with their transplant team. Patients remaining at home should be instructed to self-isolate for at least 14 days or at least 7 days after resolution of symptoms, whichever is longer. There should be frequent communication between the transplant team and the patient, at least once every 48 hours, to assess the patient's health and emotional status. Providers should assess the patient's access to medications during those conversations and identify any barriers to continued medication adherence. Patients should be instructed to check their temperature twice per day and monitor for the progression of existing symptoms and the development of new ones. Patients should be provided a pulse oximeter if possible and should monitor their oxygen saturation at least three times per day. Finally, they should be instructed to call the transplant team if they develop any of the following: shortness of breath (exertional, conversational, or at rest), persistent or high fever, oxygen saturation <94% on room air, severe vomiting or diarrhea, or general worsening of symptoms.

Kidney transplant recipients have the potential for mild symptoms even in severe disease states. Because of this, laboratory studies and imaging on kidney transplant recipients diagnosed with COVID-19 should be obtained to help identify individuals who may require hospitalization. Obtaining these studies may expose health care workers and other patients to the virus and will increased personal protective equipment usage; therefore, clinical judgment should be used. Furthermore, patients known to be SARS-CoV-2 positive require special precautions, and dedicated testing facilities should be used when available. For example, Yale New Haven Hospital has designated an off-site appointment-only laboratory draw facility exclusively for patients who are COVID-19 positive. A similar diagnostic radiology site has been dedicated to serve ambulatory patients with COVID-19. On initial diagnosis of COVID-19, the following diagnostic studies are recommended: complete blood count with differential, basic metabolic panel; liver function tests; C-reactive protein (CRP); and a chest x-ray. If the patient remains stable, then laboratory studies can be followed every 48–72 hours. After patients are clinically improving and laboratory studies remain stable, the frequency of laboratory testing can return to baseline.

If the laboratory parameters are worsening such that monitoring is required more often than every 48 hours or therapeutic intervention is required, then hospitalization should be considered. Additionally, hospitalization should be considered for patients with any one of the following: dyspnea, severe vomiting or diarrhea, inability to maintain oral hydration or take medications by mouth, confusion, persistent or worsening fevers ≥38°C, oxygen saturation below 94%, significant laboratory abnormalities (AKI, acute liver injury), or an abnormal chest radiograph. Early anecdotal experience suggests that a rise in high-sensitivity CRP may precede a drop in oxygen saturation or respiratory decompensation, and therefore, patients with high-sensitivity CRP >70 mg/L on two consecutive readings should be admitted.

As with other illnesses, individual patient circumstances and clinical judgement must be factored into the decision to admit to the hospital (Table 1). If there is concern that the patient is at high risk of decompensating, even if the patient does not meet above criteria (*e.g.*, advanced age, frailty, multiple comorbidities), then it would be reasonable to admit to the hospital. Additionally, patients may be admitted if they are not capable of maintaining close communication with the transplant team or if they are unable to provide appropriate self-care at home and do not have a caregiver.

Management of Immunosuppression

Management of the patient's immunosuppressive medication regimen remains a challenge given the lack of data specific to COVID-19. Decisions regarding immunosuppression must also be considered on a case by case basis considering factors such as time since transplantation, baseline graft function, prior history of rejection, age, and presence of donor-specific antibodies. As with other infections, there is a balance between controlling infection and maintaining graft function. Withdrawal of immunosuppression may precipitate acute rejection, and in the setting of COVID-19, it would further complicate the patient's course and pose difficult decisions about treating the rejection or losing the allograft. The exact role that immunosuppressive medications play in the disease course is unknown at this time; however, experience with other infections indicates that these medications may increase the patient's risk of infection and the risk of more severe disease.

On the basis of experience with other viral infections, such as BK virus and cytomegalovirus (6,7), a 50% dose reduction or complete cessation of a kidney transplant recipient's antimetabolite on initial diagnosis of COVID-19

Table 1. Indications to hospitalize a kidney transplant recipient with severe acute respiratory syndrome coronavirus 2 infection

Presence of the Following Signs and Symptoms	Presence of the Following Laboratory/Imaging Findings
Shortness of breath	Significant laboratory abnormalities (AKI, acute liver injury, or other concerning laboratory findings)
Severe/refractory vomiting and/or diarrhea	CRP≥70 with worsening shortness of breath
Inability to maintain adequate hydration	CRP≥70 on two consecutive laboratory checks
Inability to take medications by mouth	Abnormal CXR
Confusion	
Persistent/worsening fevers	
SpO$_2$<94%	
Clinician has concern that the patient is at high risk of decompensating at home	
Patient is unable to provide self-care at home	

CRP, C-reactive protein; CXR, chest X-ray; SpO$_2$, oxygen staturaton.

is appropriate. The decision should be on the basis of the severity of illness and an assessment of the patient's risk for rejection. However, should there be a progression of symptoms or if laboratory testing suggests worsening of disease, the antimetabolite should be discontinued entirely. The appropriate time for reduction in calcineurin inhibitor (CNI) dose is unknown; prior reports describe withholding CNI on development of severe pneumonia (8). Complicating this decision is the observation that many patients with severe COVID-19 appear to develop a hyperinflammatory state as their illness progresses, and many centers are treating such patients with immunomodulators. It is unknown if or to what extent transplant-related immunosuppression may affect this hyperinflammatory state, although withdrawal of CNI may plausibly exacerbate it. Therefore, tacrolimus dose should be adjusted to achieve a trough of 4–6 ng/ml. This recommendation is on the basis of experience in treating BK virus nephropathy (9).

Drugs given to ambulatory patients with transplants that require in-center administration require measures to minimize unintended exposure to clinic staff and other patients. For patients receiving belatacept infusions, telephone or video screening should be conducted 3–4 days in advance for indications for testing as discussed above. Patients who have a positive screen should be tested and confirmed negative for SARS-CoV-2 prior to presenting to the infusion center. If the SARS-CoV-2 test is positive or in process and home infusion is unavailable, belatacept administration should be deferred, and the patient should be converted to an alternative agent. Likewise, in an effort to minimize aerosolization and exposing staff members to infection, newly transplanted patients receiving monthly inhaled pentamidine for *Pneumocystis* jiroveci pneumonia prophylaxis should be converted to either trimethoprim-sulfamethoxazole or atovaquone.

The SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) to gain entry to cells (10,11), similar to SARS-CoV-1 (12), leading to suggestions that ACE inhibitors and/or angiotensin receptor blockers may increase risk of COVID-19, potentially *via* altered expression of ACE2. However, there are no clear clinical data supporting or refuting this hypothesis, and changing the dosing of ACE inhibitors or angiotensin receptor blockers for treating SARS-CoV-2 virus infection is not recommended (13).

Therapies for COVID-19 and Potential Drug Interactions with Immunosuppressive Medications

There is currently no known effective therapy for COVID-19, although various agents are being used in the context of clinical trials, and other agents are being used off label on the basis of *in vitro* data or biologic plausibility. Use of such therapies can be considered in kidney transplant recipients as per institutional protocols and/or clinician judgement, but attention must be paid to interactions with immunosuppressive medications. In general, any kidney transplant recipient with COVID-19 who warrants treatment should be hospitalized. Thus, a detailed review of treatments is beyond the scope of this manuscript. However, a cornerstone of managing the kidney transplant recipient is awareness of drug-drug interactions between immunosuppressive medications and other therapies. In the kidney transplant recipient being treated for COVID-19, the two interactions of primary importance are prolongation of the QT interval and alterations in the metabolism of tacrolimus.

Care must be taken when using medications that prolong the QT interval, especially because many kidney transplant recipients are taking tacrolimus, which itself may prolong the QT interval in a dose-dependent fashion (14). Congenital long QT syndrome (LQTS) is associated with potentially fatal cardiac arrhythmias and is due to mutations in one of more than a dozen genes. The prevalence of congenital LQTS is likely at least 1:2000 and possibly severalfold higher depending on the population studied (15,16). Furthermore, our center's preliminary experience is that genetic abnormalities predisposing to LQTS may be more common than appreciated. Hydroxychloroquine and azithromycin, which are under investigation in COVID-19, both can increase the corrected QT interval. Some centers are using the protease inhibitors lopinavir and ritonavir for COVID-19, although recent results did not show efficacy (17). Extreme care must be taken with kidney transplant recipients as protease inhibitors can dramatically increase tacrolimus serum levels. Belatacept and mycophenolate mofetil have no known or hypothesized interactions with the current agents being used to treat COVID-19. There is also no prohibitive drug-drug interactions between IL-6 receptor antagonists (such as tocilizumab) and immunosuppressive medications. The use of corticosteroids as treatment for COVID-19 remains controversial at this

time. Given this, we recommend that steroids be reserved for patients in the hospital setting.

As this pandemic and our understanding of this illness evolve, we expect to acquire more data and a deeper understanding of this disease and how it affects kidney transplant recipients. This information will shape the outpatient care of kidney transplant recipients with COVID-19. As this knowledge base builds, we anticipate changes in the management of this patient population. In the interim, we believe that our approach to the outpatient management of kidney transplant recipients with COVID-19 represents a good balance between caring for patients and respecting the societal context in which the pandemic is occurring. Our immunosuppressive recommendations for kidney transplant recipients use our outstanding of how other viral infections present in kidney transplant recipients and what therapies are thought to be helpful. Finally, it represents current practices in treating COVID-19 in kidney transplant recipients. However, we caution that knowledge and understanding are advancing rapidly, and additional data will likely change the recommended approach.

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