



General Approach to the Clinical Care of Solid Organ Transplant Recipients with COVID-19 Infection

Management for Transplant Recipients

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Abstract

Purpose of Review Insufficient knowledge about COVID-19 and the potential risks of COVID-19 are limiting organ transplantation in wait-listed candidates and deferring essential health care in solid organ transplant recipients. In this review, we expand the understanding and present an overview of the optimized management of COVID-19 in solid organ transplant recipients.

Recent Findings Transplant recipients are at an increased risk of severe COVID-19. The unique characteristics of transplant recipients can make it more difficult to identify COVID-19. Based on the COVID-19 data to date and our experience, we present testing, management, and prevention methods for COVID-19. Comprehensive diagnostic tests should be performed to determine disease severity, phase of illness, and identify other comorbidities in transplant recipients diagnosed with COVID-19. Outpatients should receive education for preventative measures and optimal health care delivery minimizing potential infectious exposures. Multidisciplinary interventions should be provided to hospitalized transplant recipients for COVID-19 because of the complexity of caring for transplant recipients.

Summary Transplant recipients should strictly adhere to infection prevention measures. Understanding of the transplant specific pathophysiology and development of effective treatment strategies for COVID-19 should be prioritized.

Keywords COVID-19 · Transplant recipient · Prevention · Management

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has led to unique challenges in solid organ transplantation as centers balance the risk of caring for immunosuppressed patients with the best timing and urgency of transplantation. Insufficient knowledge about COVID-19 and the potential risks of COVID-19 for transplant donors and recipients are limiting organ transplantation as well as research in transplantation [1–3]. However, transplantation is essential for lifesaving

transplants of heart, lung, or liver and for deceased donor kidney transplantations (KT) in candidates with a lack of dialysis access or who are highly sensitized [4].

To assist in the timing of transplantation during the COVID-19 pandemic, Massie et al. developed a model for mortality of wait-listed patients and transplant recipients in relation to COVID-19 [5]. Kidney transplantation (KT) reliably provides survival benefit unless mortality risk for KT recipients exposed to COVID-19 is 50% or higher and community risk of COVID-19 acquisition is 50% or more per month over the first 6 months [5]. To date, the mortality of KT recipients with COVID-19 is much less than 50% (Table 2). However, this model does not account for the risk of living kidney donors, and this should be considered in transplant decision-making. Candidates and families should be educated about increased risks, and transplant teams should ensure that households are willing to adhere to the mitigation precautions that may be more stringent than local official guidance.

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Transplantation centers have rapidly adopted management practices that will continue to evolve as knowledge for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) expands [1, 2]. This review article will provide an overview of our current understanding of COVID-19 as a basis for optimizing the care of this vulnerable population.

Clinical Features of Transplant Recipients with COVID 19

COVID-19 is an infectious viral disease caused by SARS-CoV-2 [6]. SARS-CoV-2 spike proteins bind to the angiotensin-converting enzyme 2 (ACE2), which is located on the surface of many cell types including heart, lung, kidney, liver, gastrointestinal tract and triggers internalization of the virus [6]. The targeting of ACE2 by SARS-CoV-2 leads to reduced ACE2 level and increased angiotensin II levels [7]. Subsequently, this process can activate the angiotensin II pathway, cause dysregulation of complement, hypercoagulation, hypoxia, hypotension, and cytokine storm [8]. In addition to direct invasion by SARS-CoV-2, these complex processes can cause damage to multiple organs [8]. In a prospective study of 20,133 hospitalized patients with COVID-19, old age, male, obesity, and comorbidities, including chronic cardiac, pulmonary, kidney, liver disease, were risk factors of death [9]. Transplant recipients have several factors contributing to the risk of worse outcomes, including advanced age, immunosuppression, defective mucocutaneous barrier, co-infection, drug-induced leukopenia, and underlying cardiovascular comorbidities [10]. The mortality rates of transplant recipients with COVID-19 may be higher than in the general population. Chaudhry et al. compared the mortality between hospitalized transplant recipients and hospitalized non-transplant patients [11]. They showed that transplant status itself does not affect the mortality in patients hospitalized with COVID-19 (22.8% in transplant recipients vs. 25% in non-transplant patients) [11]. However, the proportion of severe COVID-19 severity scores associated with mortality was 8.6% and 19% in transplant recipients and non-transplant patients [11]. Roberts et al. reported that the mortality rate was higher in transplant recipients when compared using unpublished data from non-transplant patients (16% in transplant recipients vs. 4.3% in non-transplant patients) [12]. In another study, the mortality rate was 20.5% among 376 hospitalized transplant recipients [13]. Meanwhile, in a study by Guan et al., the mortality rate was 1.4% in 1099 hospitalized non-transplant patients [14]. However, it is not yet clear whether transplantation affects COVID-19 associated mortality. In the future, more results need to be accumulated.

The common symptoms in transplant recipients are outlined in Table 1. Atypical symptoms such as diarrhea are much more common (22–67%) compared to the general population (2–14%). Fever may be absent in up to 50% of

transplant recipients [10, 15, 16]. These atypical symptoms alongside baseline cough, dyspnea, or medication side effects may make it more difficult to identify COVID-19 specific symptoms in transplant recipients. Due to high infectivity, transplant recipients may present with COVID-19 at any time after transplant (Table 1). Thus, a very low threshold for COVID-19 testing should be considered in recipients with even minor symptoms or high-risk exposures.

Tests for Transplant Recipients with COVID-19

Transplant recipients diagnosed with COVID-19 should be considered for diagnostic tests to determine disease severity, phase of illness, and identify other comorbidities. Table 3 shows the current tests recommended for transplant recipients with COVID-19 at the Johns Hopkins Comprehensive Transplant Center (JH-CTC). Lymphopenia is a common finding that correlates with disease severity (Tables 2 and 3). COVID-19 associated lymphopenia may be caused by direct virus-induced cell death or cytokine storm [8, 26], and further augmented by drug-associated myelotoxicity in transplant recipients receiving lymphocyte-depleting agents and/or anti-metabolites. Levels of C-reactive protein (CRP) and IL-6 may be higher in transplant recipients with COVID-19 than the general population (Table 2) [17–19, 21, 24, 25]. Considering that lymphopenia, CRP, and IL-6 are independent factors related to the severity of COVID-19 [27, 28], these should be monitored closely in transplant recipients hospitalized with COVID-19.

The incidence of liver dysfunction ranges from 14 to 53% in hospitalized patients with COVID-19 [34]. Although liver dysfunction seems to be mild in most patients, liver injury, especially hepatocellular type or mixed type, was detrimental in patients with severe COVID-19 [35]. Liver dysfunction may be caused by a direct virus-induced injury and/or provoked inflammatory response [34]. Cai et al. showed that elevated liver enzymes and histopathology were also associated with hepatotoxic medications in patients with COVID-19 [35]. Thus, liver enzymes should be frequently monitored and efforts considered to reduce non-essential medications with hepatotoxic potential.

Kidney injury is common in COVID-19 patients. In a study of 701 patients with COVID-19, 14.4% exhibited an elevated serum creatinine at admission and 5.1% developed acute kidney injury (AKI) during hospitalization [36]. Further, 43.9% had proteinuria and 26.7% had hematuria at hospital admission [36]. AKI may develop in response to the inflammatory phase and cytokine storm, and be exacerbated by hypercoagulation, microangiopathy, rhabdomyolysis, acute tubular necrosis, hypoxia, and hypotension [8, 37]. Proteinuria may be caused by direct infection of SARS-CoV-2 in podocytes and proximal tubular cells [38].

Table 1 Baseline characteristics and clinical symptoms of transplant recipients and non-transplant recipients with COVID-19

	Akalin et al. [17] (n = 36)	Pereira et al. [18] (n = 90)	Yi et al. [19] (n = 21)	Chaudhry et al. [11] ^a (n = 35)	Fernandez-Ruiz et al. [20] ^a (n = 18)	Kates et al. [13] ^a (n = 482)	Mohan et al. [21] ^a (n = 15)	Tschopp et al. [22] ^a (n = 21)	Alberici et al. [23] ^b (n = 20)	Wang et al. [24] (n = 69)	Chaudhry et al. [11] ^a (n = 100)	Docherty et al. [9] ^a (n = 20,133)	Guan et al. [14] ^a (n = 1099)	Shi et al. [25] ^b (n = 81)	
Transplanted organs (n)	Kidney 36	Kidney 46 Liver 13 Lung 17 Heart 9 Dual-organs 5	Kidney 12 Liver 3 Lung 2 Dual-organs 4	Kidney 26 Liver 0 Lung 4 Heart 5 Pancreas 1	Kidney 8 Liver 6 Heart 4	Kidney or Kidney/Pancreas 318 Liver or Liver/kidney 73 Heart or Heart/Kidney 57 Lung 30 Others 4	Kidney 15	Kidney 10 Liver 5 Lung 1 Heart 1 Pancreas 1 Dual 3	Kidney 20						
Time from transplant to diagnosis (years)	6.64 (2.87–10.61)	5.58 (2.25–7.33)				4.08 (3.16–9.83)			13 (9–12)						
Within 1 month (%)	3					6.7									
Within 1 year (%)	14					6.7									
Age (years)	60	57	54.8	62	71	57.5	51	56	59	42	60	73	47	49.5	
Male (%)	72	59	62	65.7	77.7	61.2	67	71	80	46	50	60	58.1	52	
Comorbidities															
HTN (%)	94	64	84	94.3	72.2	77.4		66.7	85	13	72	28.1	15.0	15	
DM (%)	69	46	63	65.7	44.4	51		42.9	15	10	33	30.9	7.4	12	
Heart disease (%)	17		CAD 32	CHF 28.6 CAD 14.3	27.7	CHF 8.3 CAD 21.8		CHF 4.8 CAD 23.8	CAD 15	12	CHF 14 CAD 12		CAD 2.5	10	
Chronic lung disease (%)		19		17.1	5.5	10.4		19		6	13	17.7	1.1	11	
CKD (%)	63			88.6	5.5	37.3					57	16.2	0.7	4	
Clinical symptoms															
Fever (%)	58	70	86	65.7	83	54.6	87	76	100	87	69	71.6	88.7	73	
Maximal temperature (°C)	37.4												38.3		
Cough (%)	53	59	73	62.9	67	73.2	60	57.1	50	55	74	68.9	67.8	59	
Dyspnea (%)	44	43	64	68.6	61	58.5	27	30	5	29	73	71.2	18.7	42	
Diarrhea (%)	22	31	67	54.3	22		20	33.3		14	17		3.8	4	
Nausea/vomiting (%)	8	22	22				7	33.3		4			5		

^a Patients hospitalized with COVID-19 were included^b Patients hospitalized with COVID-19 pneumonia were included

Abbreviations: CHF, congestive heart failure; CAD, coronary artery disease; CKD, chronic kidney disease

Table 2 Laboratory findings and outcomes of transplant recipients and non-transplant recipients with COVID-19

	Alkaline et al. [17] (n = 36)	Pereira et al. [18] (n = 90)	Yi et al. [19] (n = 21)	Chaudhry et al. [11] ^a (n = 35)	Fernandez- Ruiz et al. [20] ^a (n = 18)	Kates et al. [13] ^a (n = 482)	Mohan et al. [21] ^a (n = 15)	Tschopp et al. [22] ^a (n = 21)	Alberici et al. [23] ^b (n = 20)	Wang et al. [24] (n = 69)	Chaudhry et al. [11] ^a (n = 100)	Docherty et al. [9] ^a (n = 20,133)	Guan et al. [14] ^a (n = 1099)	Shi et al. [25] ^b (n = 81)
Laboratory findings														
WBC (μL)	5300	5160	6400	5500			4800	4800	5470	3820	6050		4200	8110
Lymphocyte (μL)	600	700	524	500		700	800	630	1170	1150	800		1000	1100
Lymphopenia (%)	79									42				33
Platelet (×10 ³ /μL)	146	176.5		176					196	171	178		168	212.2
Albumin (g/dL)		3.6												3.3
ALT (U/L)	18								23	25				46.2
AST (U/L)	26								37	28				40.8
Creatinine (mg/dL)	1.89	1.8							1.8	0.75				0.85
LDH (U/L)	336	253		288			275		231	224	334			
CPK (U/L)	145								69					
CRP (mg/dL)	7.9	6.9	11.8	0.23			10.4	3.3	4.9	1.3				4.8
Procalcitonin (ng/mL)	0.2	0.29					0.46	0.16	0.22	0.13	0.15			
Ferritin (ng/mL)	1230	801.5		617.5			471		831		586.5			
D-dimer (μg/mL)	1.02	1.335	1.46	1.02				0.39	0.279		1.18			6.5
IL-6 (pg/mL)		20	21				24			8.5				
Outcomes														
Hospitalization (%)	78	76	67							65.7				
AKI (%)				46.8	11.1		40	42.9	30		43		0.5	
Acute cardiac injury (%)														
ARDS (%)				35.3	22.2			19	55		34		3.4	
Mechanical ventilation (%)	30.5	27		34.3			27				36		6.1	
Death (%)	28	18	5	22.8	27.8		7	9.5	25	7.5	25	26	1.4	

^a Patients hospitalized with COVID-19 were included

^b Patients hospitalized with COVID-19 pneumonia were included

Abbreviations: *INR*, international normalized ratio; *LDH*, lactate dehydrogenase; *CPK*, creatine phosphokinase; *CRP*, C-reactive protein; *IL-6*, interleukin-6; *AKI*, acute kidney injury; *ARDS*, acute respiratory distress syndrome

Table 3 Tests for hospitalized transplant recipients with COVID-19 [27–33]

Tests on hospitalization	Laboratory results related with disease severity	Considerations in interpreting test results of transplant recipients	Monitoring interval
Complete blood counts with differential	Neutrophil count > 8000/ μ L, lymphocyte < 1000/ μ L, neutrophil-lymphocyte ratio, platelet < 100×10^3 / μ L	Myelosuppression by immunosuppressants	Daily
Coagulation tests	Prothrombin time \geq 16 s		Daily
D-dimer \pm Fibrinogen	D-dimer > 1 μ g/mL		Every 48–72 hours ^a
Comprehensive metabolic panel	Albumin level < 3.4 g/dL, ALT > 40 U/L, AST, bilirubin, BUN, creatinine > 1.1 mg/dL	Side effects by immunosuppressants and antimicrobial prophylaxis, toxicity by drug-drug interactions	Daily
LDH	> 250 U/L		Every 48–72 hours ^a
CPK	> 185 U/L		
Ferritin	> 300 ng/mL		Every 48–72 hours ^a
Troponin I ^b	> 28 pg/mL		
CRP	> 4 mg/dL		Daily
Procalcitonin	\geq 0.07 ng/mL	Bacterial infection	
IL-6	> 32.1 pg/mL		
Urinalysis		New-onset proteinuria: renal involvement by SARS-COV-2	
Urine legionella and pneumococcal antigen			
Respiratory viral panel			
Culture for bacteria and fungi			
CMV antigenemia and PCR			
β -d-glucan and galactomannan			
Cryptococcal antigen			
Histoplasma antigen			
<i>Clostridium difficile</i> toxin assay			
Level of immunosuppressants			
Chest radiography			
ECG			

^a Tests should be performed daily in kidney transplant recipients with severe or rapidly progressing COVID-19

^b Troponin concentration is measured if acute myocardial infarction of new onset LV dysfunction is considered

Abbreviations: *AST*, Aspartate amino transferase; *ALT*, Alanine amino transferase; *BUN*, blood urea nitrogen; *LDH*, Lactate dehydrogenase; *CPK*, Creatinine phosphokinase; *CRP*, C-reactive protein; *IL-6*, interleukin-6; *CMV*, cytomegalovirus; *ECG*, electrocardiogram

Because renal abnormalities are associated with a high risk of in-hospital death and appear to be more prevalent in transplant recipients [36], serum creatinine and urinalysis should be monitored closely.

Thrombotic complications have been reported to occur in 31% of intensive care unit (ICU) patients with COVID-19 and pulmonary thromboembolism was the most frequent among them [39]. Typical findings include an increased D-dimer level, a relatively modest decrease in platelet count, and a prolongation of the prothrombin time in patients with COVID-19 [40]. At autopsy of COVID-19 patients, segmental fibrin thrombosis in glomeruli was observed in renal findings [41]. Considering that immobilization and vascular damage increase the risk of thrombosis [40], thrombotic complications of allografts may be more common in transplant recipients with COVID-19. The International Society of Thrombosis

and Haemostasis (ISTH) published an interim guidance statement recommending that prothrombin time, platelet count, and D-dimer concentrations should be monitored once or twice daily in patients with severe COVID-19 [29].

The prevalence of co-infection among COVID-19 patients ranges from 0% to 45% overall [42]. In a report by Zhou et al., the incidence of co-infection was 50% in non-survivors [30]. Bacterial, viral and fungal infections have all been documented and may need specialized diagnostic microbiology to identify these serious complications [42]. Most co-infections occurred within 1–4 days of onset of COVID-19 disease [31]. Generally, transplant recipients experience co-infection more commonly than immunocompetent individuals [43]. In a report by Roberts et al., co-infection was 22% and 35% in transplant recipients with COVID-19 and those admitted to ICU [12]. Thus, transplant recipients should be evaluated for

bacterial and opportunistic fungal infections when diagnosed with COVID-19. Cytomegalovirus (CMV) is common in transplant recipients and may reactivate under conditions of stress or augmented immunosuppression [43]. Table 3 shows tests that the JH-CTC examines: a respiratory viral panel, urine legionella and pneumococcal antigen, culture of blood and urine for bacteria and fungi, CMV antigenemia and PCR, β -d-glucan and galactomannan, cryptococcal antigen, histoplasma antigen in serum and urine, *Clostridium difficile* toxin assay. While bronchoscopy is not routinely available, tracheal aspirates could be considered for intubated patients to obtain microbiological samples. In instances where the risk of diagnostic procedures may be precluded sample collection, empiric antibiotics, anti-fungals, or anti-virals should be carefully considered based on the organ-specific pathogen risks.

An increase of the procalcitonin level reflects bacterial co-infection and predicts the progression toward severe disease [44]. Previously published literatures suggest that procalcitonin levels may be comparatively higher in transplant recipients with COVID-19 than in the general population with COVID-19 (Table 2) [11, 17, 18, 21, 23, 24]. The monitoring of procalcitonin may play a role in predicting bacterial infection in the absence of direct microbiology.

Chest radiography plays an important role in the diagnosis of COVID-19. Abnormal findings on chest radiography were identified in up to 76.5% of individuals, and abnormalities on chest computed tomography (CT) were 84.4% and 94.6% among patients with non-severe COVID-19 and patients with severe COVID-19, respectively [14]. Despite a higher sensitivity, the infectious precautions needed to safely transport patients with COVID-19 and decontaminate equipment necessitate thoughtful consideration of the optimal use of CT [45, 46]. Alternative modalities such as lung ultrasonography may provide results similar to chest CT to assess pneumonia and reduce staff/equipment exposure [46–48]. However, CT may still have a valuable role in the evaluation of pulmonary emboli and/or diagnosis of pneumonia when other modalities are non-diagnostic. Further studies are required to determine the optimal use of imaging in managing the care of the COVID-19 transplant recipient.

Outpatient Management for Transplant Recipients

Outpatient Prevention and Management of General Transplant Recipients

Evolving knowledge of viral transmission informs the approach to the management of transplant recipients with COVID-19. The median incubation period of COVID-19 is estimated to be 5.1 days and the majority of symptomatic patients develop symptoms within 11 days [49]. Moreover,

the infectiousness of SARS-CoV-2 starts from 2.3 days before symptom onset and up to 10 days after resolution of symptoms in the immunocompetent host, but possibly up to 4 weeks in immunocompromised hosts. Unfortunately, 44% of infection occurs at the pre-symptomatic phase [50], and due to its high transmissibility in droplets, contact and aerosols, preventive precautions are critical.

Respiratory droplets, the most common mode of transmission, are formed when an infected patient sneezes, coughs, or even talks, and viral particles are directly inhaled, or when an uninfected individual touches a contaminated surface and subsequently their mucous membranes [51]. Transmission through respiratory droplet may be reduced with the use of surgical or cloth masks, and thus transplant recipients should ensure that they and all individuals outside of their household are wearing masks during an in-person encounter [52]. Further, hand hygiene is essential to reduce transmission from contact surfaces, as SARS-CoV-2 can be detectable on the surface of the plastic and stainless steel up to 72 h [52]. Given the higher risk of serious complications from COVID-19, we recommend that patients and household contacts receive ongoing education: the importance of exposure prevention and risk reduction measures, as these behaviors may erode over time.

The complexity of routine transplant care in monitoring allograft function, toxicities, and general health has necessitated a reimagining of health care delivery during COVID-19 pandemic. In this regard, centers have instituted telemedicine, limited in-person visits, and increased remote monitoring allows uninterrupted outpatient care while limiting direct patient contact to highest priority individuals. With these tools, limited ambulatory care then ideally be provided in social distanced settings with appropriate COVID-19 screening to reduce nosocomial transmission risk [53]. Telemedicine can be performed using a combination of synchronous, asynchronous, or remote monitoring. Synchronous refers to real-time encounters via telephone or audio-video interaction. Asynchronous telemedicine is a “store-and-forward” technique that sends the collected data and images to clinicians. Remote patient monitoring refers to the direct transmission of a patient’s clinical measurements to their healthcare provider [52]. Telemedicine may also be an important component of preparation for in-person encounters to reduce the amount of time spent in direct patient contact and to conduct necessary COVID-19 symptom and behavior risk screening (Fig. 1) [54, 55]. For maximum utility, transplant centers may need to invest in resources for patient self-monitoring, including tools for vital signs monitoring, technology platforms, and resources to document objective findings.

The frequency of routine laboratory testing, routine health maintenance tests, and cancer screening should be considered to balance the infection risk of SARS-CoV-2 with the risk to health if these diagnostics are deferred. Ideally, when

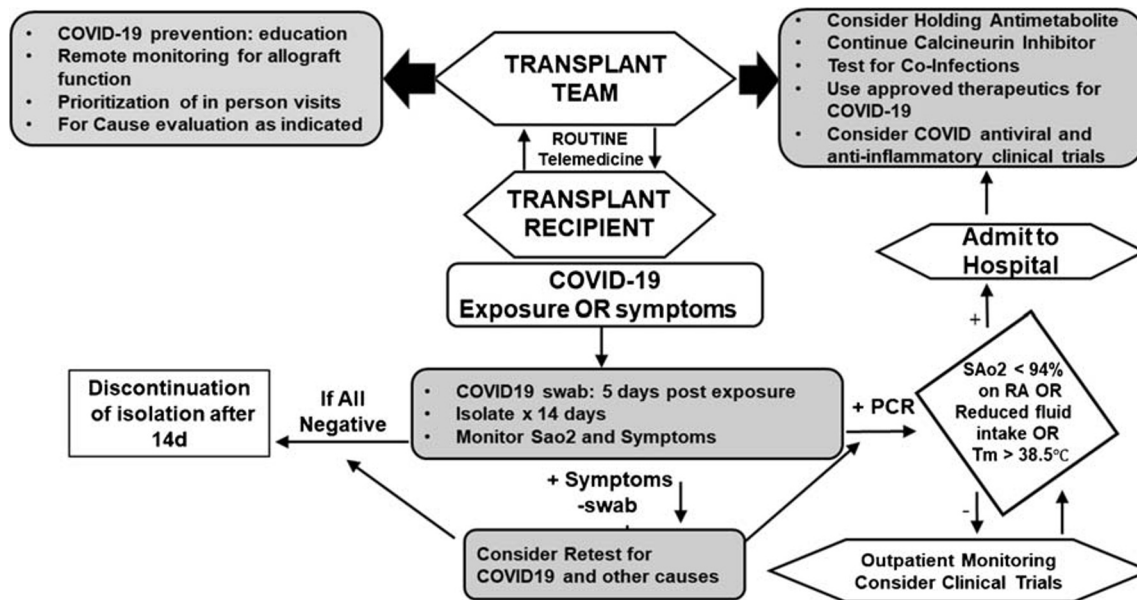


Fig. 1 Flowchart for management for solid organ recipients during COVID-19 pandemic. Abbreviations: MMF, mycophenolate mofetil; ALC, absolute lymphocyte count

required, diagnostic tests should be performed at a facility that practices mitigation behaviors such as a restricted number of persons in waiting rooms, scheduled appointments, and strict screening of patients for COVID-19. Collaboration between transplantation specialists, monitoring of local COVID infection rates, and the local health care provider may be required [54, 56]. The frequency of allograft surveillance biopsies should be determined to take into account the individual risks and benefits, especially during this epidemic period. When available, non-invasive technologies such as donor-derived cell-free DNA (dd-cfDNA), gene expression profiles, and home spirometry may allow transplant recipients to reduce invasive procedures for rejection monitoring. In KT recipients, the negative predictive value of dd-cfDNA for any active rejection at a cutoff of 1.0% was 84%, and thus may be a good non-invasive marker of allograft surveillance [57]. While its role in other solid organ transplants is still being defined, peripheral gene expression tests may also be helpful for surveillance for cardiac allograft rejection to reduce need for invasive biopsies [54].

The emotional toll of the COVID-19 pandemic should be recognized and addressed with patients. Fear of COVID-19 and health recommendations to transplant recipients to shelter in place when there is significant community spread may worsen anxiety, and/or cause patients to defer essential health care. The emotional toll of social isolation may lead transplant recipients to engage in behaviors that increase their risk of exposure to COVID-19. Thus, the transplant team should assess mental health during their patient encounters and provide referrals or interventions as appropriate during this unprecedented challenge. In transplant recipients with COVID-19, depression, anxiety, and sleep disturbances associated with

COVID-19 can worsen non-adherence to immunosuppressive therapy and increase the risk of allograft rejection [58]. Melatonin is an effective drug for anxiety and sleep disturbances, which might also be beneficial for clinical outcomes of patients with COVID-19 due to its anti-inflammatory and anti-oxidant properties [59, 60].

Outpatient Management for Transplant Recipients with Suspected or Confirmed COVID-19

Transplant recipients with COVID-19 can progress rapidly and seriously. They should be monitored and managed through frequent communication between the transplant team and patients. Figure 1 shows a model for the management of solid organ transplant recipients during COVID-19 pandemic, based on recommendations of the Centers for Disease Control and Prevention (CDC) and the American Society of Transplantation (AST) [52, 61]. Transplant recipients with direct contact (< 6 ft for ≥ 15 min) with a COVID-19 infected individual should be quarantined for 14 days and consider testing for SARS-CoV-2 after exposure or if they develop symptoms [49, 52]. Patients with confirmed COVID-19 should check their temperature and respiratory rate (RR), oxygen saturation, and symptoms. Transplant centers should consider assistance for pulse oximeters if patients experience hardship in obtaining these devices. If they have dyspnea or RR ≥ 24 per minute, oxygen saturation < 94%, persistent or high fever, difficulty eating foods with predominant gastrointestinal symptoms, low urine volume (< 400 mL per day), or worsening of general conditions, they should plan for hospitalization (Fig. 1) [52, 54].

The determination of when a transplant recipient is no longer infectious is evolving. Immunocompromised patients may have prolonged viral shedding, and further research is needed to determine the timeframe of infectivity in this population [62, 63]. The AST recommends a 28-day time-frame because the shedding of the virus can be prolonged in transplant recipients, although infectivity is unclear [61]. This is different from recommendations for immunocompetent hosts and should be communicated to health care providers and COVID-19 infected transplant recipients. Alternatively, a test-based strategy has also been used with the use of negative results of RNA PCR tests from at least two consecutive respiratory specimens ≥ 24 h apart as well as recovery of symptoms.

Management for Hospitalized Transplant Recipients for COVID-19

COVID-19 progresses through syndrome phases that include: the early infection phase, the pulmonary phase, and the hyperinflammation phase [64]. The early infection phase is triggered by the virus itself and the hyperinflammation phase is developed by the host response.

At the initial stage or infection, most patients have mild, non-specific symptoms. Because SARS-CoV-2 multiplies and establishes residence in the host during this period, the reduction of immunosuppressive agents should be considered to enhance viral clearance [64]. At the JH-CTC, it is recommended that mycophenolate be preemptively discontinued if the absolute lymphocyte count (ALC) were < 700 cells/mL and reduced if the ALC was 700–1000 cells/mL. Because calcineurin inhibitors (CNIs) block nuclear factor of activated T cells (NFAT) and thus transcription of downstream inflammatory cytokines, we do not recommend reducing the CNIs and maintain tacrolimus levels between 5 and 10 ng/mL. Clinical trials of therapies to enhance viral clearance, such as convalescent plasma may be offered at this stage.

In the second stage, viral multiplication and localized lung inflammation occur [64]. Markers of systemic inflammation may be elevated. Anti-viral therapies, as discussed in a separate article of this issue, may be indicated for patients with hypoxia, and investigational agents may be considered. A minority of COVID-19 patients progress into the hyperinflammation phase. In this stage, markers of systemic inflammation are elevated and systemic organs would be involved [64]. Immunomodulatory agents have been studied and applied to reduce systemic inflammation to try and prevent multiorgan dysfunction, but with exception of dexamethasone, remain under off-label or investigational use.

Supportive therapy includes management of hypoxia, fluid therapy, medication adjustments, and control of symptoms such as fever, cough, and diarrhea. Considering that acute respiratory distress syndrome (ARDS) is one of the most

severe complications in patients with COVID-19 and a leading cause of death (Table 2) [65], patients requiring mechanical ventilation should be managed per standard of care practices for ARDS. Proning may be required due to the distribution of parenchymal changes, and in some centers is initiated prior to intubation [66]. The optimal fluid therapy for COVID-19 patients has not been established but may need to be individualized based on the presence of AKI, Sepsis, or ARDS [37, 67]. As the risk of AKI is high in patients transplant recipients with COVID-19, avoidance of non-essential nephrotoxic agents may also be advisable [21, 30]. The use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEI/ARBs) has been controversial due to concerns that may increase susceptibility to the SARS-CoV-2 [6]. In recently published studies, use of ACEI/ARBs before or during hospitalization was not associated with mortality among hypertensive patients with COVID-19 [68, 69], and thus should be maintained as clinically indicated.

The ISTH recommends prophylactic dose low molecular weight heparin in patients with coagulopathy (D-dimer > 3 to 4 times, prolonged prothrombin time, platelet count $< 100 \times 10^3/\mu\text{L}$, or fibrinogen < 2.0 g/L) and patients hospitalized for COVID-19 in the absence of any bleeding or thrombocytopenia [29, 40]. A study demonstrated that the use of prophylactic LMWH was associated with low mortality in patients with severe COVID-19.

The optimal regulation of transplant immunosuppression in COVID-19 remains a challenging question, with a paucity of clinical data for guidance. Immunosuppressive drugs may prolong viral shedding, have beneficial anti-inflammatory effects, or even have anti-viral properties [70]. Little is known about the exact role of cyclophilin in coronavirus replication, but it has been reported that cyclosporine, which also binds cyclophilin, may inhibit the replication of coronaviruses at noncytotoxic concentrations [71, 72]. In vitro, tacrolimus inhibited the replication of SARS-CoV, suggesting the requirement of FK506-binding proteins for virus growth [73]. Further, CNIs may be capable of reducing the frequency of cytokine release syndrome through inhibition of NFAT. However, the exact role of these agents for enhancing viral clearance in COVID-19 is unknown and merits further investigation. Given these in vitro effects and the need to maintain some immunosuppression to prevent allograft rejection, many centers, including ours, have implemented reduction or holding antimetabolite and continuing the CNIs and glucocorticoids in transplant recipients with COVID-19. Others have recommended that CNIs and the antimetabolite be immediately withdrawn and the glucocorticoid dosage increased in KT recipients with severe or rapidly progressing COVID-19 [54, 74]. However, we remain hesitant to recommend complete cessation of CNIs without further clinical data to support the safety of this practice.

While there is literature in the general population to support the use of augmented dexamethasone in severely ill COVID-19 recipients, these studies have not reported the outcomes of this augmentation in immunocompromised individuals. In a preliminary report by Horby et al., dexamethasone (6 mg daily for up to 10 days) reduced mortality among COVID-19 patients receiving mechanical ventilation or oxygen [75], and this has been incorporated into routine practice. However, optimal adjustment of immunosuppression and return to maintenance dosing remains unknown. As we have previously reported, permanent discontinuation of the antimetabolite in KT patients with a severe viral infection such as CMV and BK virus is safe and effective [76, 77]. However, there are less data about the safety of the prolonged cessation of antimetabolites in other organ transplants, particularly for viruses in whom the disease severity is characterized by a hyperactive immune response, or for conditions such as in thoracic transplant where respiratory viral infections have been shown to trigger immune responses that induce chronic allograft dysfunction [78–81].

Adjunctive Supplements

There has been much interest in supplements such as vitamin D and melatonin in adjunctive therapy for patients with COVID-19 due to their anti-inflammatory and anti-oxidant properties and low risk of harm. Inadequate vitamin D levels have been found in > 70% abdominal transplant recipients [82] and may be exacerbated by glucocorticoids, CNIs, low sun exposure, and inadequate dietary intake [83]. Low vitamin D levels have been associated with a high risk of CMV infection and overall infection in transplant recipients [84, 85]. Further meta-analyses of RCT data have demonstrated that vitamin D has a protective effect against acute respiratory tract infection and with even further risk in subjects who concentrations of 25-hydroxyvitamin D (25[OH]D) below 37.5 nmol/L [86]. In these studies, once daily dosing at modest doses (400–4000 IU/day) appeared to confer benefit, particularly when Vitamin D levels were low. The prevalence of vitamin D deficiency is 40–70% in the intensive care unit and circulating 25(OH)D concentrations may drop rapidly in the early illness [87]. However, in multi-center RCTs of critically ill patients, a single dose of 540,000 IU or short term therapy (50,000 IU or 100,000 IU for 5 days) did not show mortality benefit [88, 89]. As the relationship between vitamin D supplementation and improvement in COVID-19 outcomes has not yet been established, measurement of Vitamin D levels may be a reasonable strategy to guide supplementation using modest daily dosing until further data is available. In KT recipients, we routinely give ergocalciferol 50,000 units orally daily for 5 days at the time of transplant and upon a positive COVID-19 PCR.

Melatonin lowers the levels of circulating cytokines and may reduce pro-inflammatory cytokine levels in COVID-19 patients [60]. Further, stress and sleep deprivation induce immunosuppression. These negative effects on immunity may be alleviated by restoring sleep disorder and reducing anxiety through melatonin [90]. So far, the direct evidence of melatonin application in COVID-19 is unclear. Further research is needed to determine if it has a COVID specific application outside of generalized sleep and anxiety disorders.

Cytokine release syndrome (CRS), characterized by a systemic inflammatory response resulting from the release of inflammatory cytokines including IL-6, is a hallmark of COVID-19 progression [91]. Although immunomodulatory therapy is discussed separately, we note that blocking of the catecholamine pathway with alpha-1 adrenergic receptor antagonists (α -blockers) may reduce cytokine storms [92]. In a retrospective study, Vogelstein et al. found that the use of α -blockers was associated with reduced ARDS and death from CRS [93]. As such, prospective clinical trials are underway to determine whether these agents can pre-emptively reduce COVID-19 disease progression [94].

Patients can be discharged from the hospital when clinically indicated. Isolation should be maintained if the patients are discharged to home or long-term care facility before discontinuation of isolation and may pose a challenge in a safe return to a home environment if there are uninfected individuals in the home. Long-term care facilities should follow infection prevention and control recommendations for the care of COVID-19 patients [52].

As there is a paucity of high-quality evidence to guide management of the COVID-19 infected transplant recipient, many centers have implemented practices based on biological plausibility and extrapolation from scenarios which share common features with COVID-19. At our institution, we have noted markedly low mortality of 3.7% in the 1st 27 solid organ transplant recipients cared by our providers between March 15, 2020 and May 22, 2020, compared to reports from other institutions in similar time periods (Table 2). While we cannot yet definitely determine which of our practices contributed to this excellent outcome, we have in this section, detailed our center's specific practices (Fig. 1), and look forward to further science to refine these clinical algorithms.

Conclusions

COVID-19 is an unprecedented worldwide challenge, that is, heightened in solid organ transplant recipients. While a worldwide effort is underway to identify the best therapeutics and vaccines, their risk and benefit in transplant recipients remain undetermined. Thus, it is critical to reinforce to transplant households to strictly adhere to infection prevention measures. Transplant recipients should remain in close communication

with their health team to monitor their overall health, manage comorbidities and identify any new findings that may confer risk of COVID-19. Finally, understanding of the transplant specific pathophysiology, effective treatments, and adjunctive practices for COVID-19 should be prioritized as part of a comprehensive research strategy to optimize outcomes.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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