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## FULL LENGTH ARTICLE

# COVID-19 and Heart Transplant: A Case Series and Review of the Literature

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### ABSTRACT

Coronavirus disease 2019 (COVID-19) has resulted in many challenges in patient care, especially among high-risk populations such as heart transplant recipients. Patients with heart transplant experience a significantly higher mortality rate with COVID-19 infection, and management is based on extrapolation from clinical trials done on nontransplant patients and from clinical experience. Here we report 4 cases of patients with heart transplant who presented with COVID-19 infection in late 2020. Patients presented with symptoms similar to those seen in the general population. All 4 patients were admitted to the hospital, and they were all treated with dexamethasone. In addition, 2 patients received remdesivir. Immunosuppressive medications were adjusted to maintain adequate levels of immunosuppression but at the same time allow for an adequate immune response against the infection. All patients were discharged alive from the hospital. We then performed a literature review on studies that included heart transplant patients who developed the infection and developed suggestions for a standardized management approach, which we share in this article.

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**T**HE coronavirus disease 2019 (COVID-19) pandemic started in December 2019 and as of August 2020 affected more than 20 million people and claimed the lives of more than 750,000 worldwide [1]. As such, it is inevitable that high-risk populations, such as heart transplant recipients, will be infected. Thus far there have been several case reports and case series on outcomes and management of heart transplant recipients with COVID-19. Here we add to the growing body of knowledge with a case series on 4 heart transplant recipients who developed COVID-19.

### CASE PRESENTATIONS

Patient demographic characteristics, presentation, and management are summarized in [Tables 1, 2, and 3](#), respectively.

#### Case 1

The first case is a 62-year-old man with a history of ischemic cardiomyopathy and end-stage renal disease who received a combined heart and kidney transplant in 2016. He is maintained

on tacrolimus and mycophenolate sodium. Other medical problems include a history of stroke, coronary artery disease, hypertension, and type II diabetes. He presented with generalized weakness, shortness of breath, productive cough, and diarrhea to an outside hospital in July 2020. He was found to have an acute kidney injury with a serum creatinine of 6.22 mg/dL from a baseline of 1.9 mg/dL. On arrival to our facility, his blood oxygen saturation was 100% on room air. A severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test was positive. Tacrolimus level was supratherapeutic, and other labs showed leukopenia with lymphopenia, as well as elevated lactate dehydrogenase (LDH), D-dimer, and ferritin. Chest x-ray showed clear lung fields. He was seen by infectious disease and nephrology and started on 8 mg of dexamethasone intravenously (IV) daily empirically

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**Table 1. Patient Baseline Demographics**

	Age (y)	Sex	Cardiomyopathy	Transplant Organ	Transplant Year	BMI (kg/m <sup>2</sup> )	Comorbidities
Patient 1	62	Male	Ischemic	Heart and kidney	2016	32	DMII, HTN, stroke, prior CAD
Patient 2	62	Male	Ischemic	Heart	2020	23	DMII, HTN, prior CAD
Patient 3	65	Male	Ischemic	Heart	2017	21	HTN, prior CAD, prior LVAD
Patient 4	62	Male	Ischemic	Heart	2020	25	DMII, HTN, prior CAD, COPD, CKDIII

BMI, body mass index; CAD, coronary artery disease; CKDIII, stage 3 chronic kidney disease; COPD, chronic obstructive pulmonary disease; DMII, type 2 diabetes mellitus; HTN, hypertension; LVAD, left ventricular assist device.

**Table 2. Clinical Presentation and Home Immunosuppressive Regimen**

	Home Immunosuppression	Presenting Symptoms	WBC Count (× 1000/ $\mu$ L)	Absolute Lymphocyte Count Address correspondence to(× 1000/ $\mu$ L)	LDH (U/L)	D-Dimer ( $\mu$ g/mL)	Ferritin (ng/mL)	CRP (mg/L)
<b>Patient 1</b>	Mycophenolate sodium 360 mg BID; tacrolimus 2 mg BID	Weakness, shortness of breath, cough, diarrhea	3.71	0.31	235	1.26	3466	28
<b>Patient 2</b>	Cyclosporine 200 mg in AM and 175 mg in PM; mycophenolate mofetil 1500 mg BID; prednisone 7.5 mg QD	Anorexia, nausea, vomiting, shortness of breath, cough	1.58	0.3	532	3.06	683	11.3
<b>Patient 3</b>	Tacrolimus 2 mg BID; mycophenolate mofetil 250 mg BID	Cough, fever, chills, shortness of breath	10	0.4	435	0.81	553	49
<b>Patient 4</b>	Tacrolimus 2 mg in AM and 1 mg in PM; mycophenolate mofetil 750 mg BID; prednisone 7.5 mg QD	Myalgias, nasal congestion, anosmia, dysgeusia, cough, shortness of breath, diarrhea	2.51	0.72	524	0.64	444	20.4

BID, 2 times per day; CRP, C-reactive protein; LDH, lactate dehydrogenase; QD, once daily; WBC, white blood cell.

**Table 3. Hospital Course and Treatment**

	Medications Received	Hospital Course	Length of Stay (d)	Status at Discharge	Discharged to
Patient 1	Dexamethasone 8 mg IV QD for 6 days	Improved	6	Alive	Home
Patient 2	Remdesivir 200 mg IV QD for 10 days; dexamethasone 6 mg IV QD for 10 days	Improved	35	Alive	Home
Patient 3	Remdesivir 200 mg IV QD for 10 days; dexamethasone 6 mg IV QD for 10 days	Improved	7	Alive	Home
Patient 4	Dexamethasone 6 mg PO QD for 10 days	Improved	5	Alive	Home

IV, intravenous; PO, per mouth; QD, once daily.

for concerns for kidney rejection and as part of treatment for COVID-19. Tacrolimus and mycophenolate were both held, and tacrolimus was restarted once the level dropped to 6.8 ng/mL. The patient's renal function recovered, and he was discharged on tacrolimus but was off mycophenolate (which was restarted 2 weeks later during heart failure clinic follow-up).

## Case 2

The second case is a 62-year-old man with a history of ischemic cardiomyopathy and coronary artery bypass who received an orthotopic heart transplant (OHT) in March 2020. Immunosuppression was maintained with cyclosporine, mycophenolate mofetil, and prednisone. His other medical problems include a

history of coronary artery disease, type II diabetes, and hypertension. In August 2020, he presented with a 3-week history of decreased oral intake, nausea, and vomiting and a few-day history of shortness of breath and nonproductive cough. SARS-CoV-2 PCR assay was positive on presentation. Labs showed leukopenia with lymphopenia and elevated LDH, D-dimer, C-reactive protein, and ferritin. His chest x-ray was clear, but he required 2 L of supplemental oxygen by nasal cannula. He was continued on cyclosporine, but mycophenolate was held. He was started on 200 mg of remdesivir IV once daily for a total of 10 days and 6 mg of dexamethasone IV once daily for a total of 10 days. His hospital course was uncomplicated, and he was weaned off supplemental oxygen. His first negative SARS-CoV-2 PCR test was 24 days from presentation. He was restarted on mycophenolate and prednisone once he completed the remdesivir and dexamethasone courses. He was subsequently discharged to a rehab facility following a 35-day hospitalization.

### Case 3

Case 3 is a 65-year-old man with a history of ischemic cardiomyopathy and history of HeartMate II left ventricular assist device who received an OHT in August 2017 and was maintained on tacrolimus and mycophenolate mofetil for immunosuppression. His other medical problems include a history of coronary artery disease and hypertension. He presented with cough, fever, chills, and shortness of breath to an outside hospital in mid-September 2020. His SARS-CoV-2 PCR test was positive, and he was started on remdesivir and dexamethasone. He was transferred to our hospital a few days later because of increasing oxygen requirements. He was initially admitted to the medical intensive care unit because he needed supplemental oxygen by high-flow nasal cannula. Remdesivir and dexamethasone were continued. Labs on presentation showed leukocytosis with lymphopenia and elevated LDH, ferritin, and D-dimer. His tacrolimus level was 27.2 ng/mL and so tacrolimus was held, as well as mycophenolate in the setting of lymphopenia. Chest x-ray showed bilateral airspace opacities. His hospital course was uncomplicated, and he was weaned off supplemental oxygen. His inflammatory markers improved, and tacrolimus was restarted once the blood tacrolimus level went back down to 8 ng/mL. He completed a 10-day course of remdesivir and a 10-day course of dexamethasone (total course of 10 days for each medicine that were started at the outside hospital prior to his transfer) and was discharged home with plans to restart mycophenolate as an outpatient.

### Case 4

Case 4 is a 62-year-old man with a history of ischemic cardiomyopathy who received OHT in March 2020 and was maintained on mycophenolate mofetil, prednisone, and tacrolimus. His other medical problems include a history of coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, hypertension, and type II diabetes. He developed myalgias, nasal congestion, anosmia, dysgeusia, cough, shortness of

breath, and diarrhea and his SARS-CoV-2 PCR test was positive. He was initially managed as an outpatient and most of his symptoms improved over 2 to 3 weeks; however, he developed worsening shortness of breath and was admitted to the hospital in mid-September 2020. On presentation he was mildly hypoxic, requiring supplemental oxygen at 2 L/min via nasal cannula. His SARS-CoV-2 PCR assay was positive, and labs showed leukopenia with lymphopenia and elevated LDH, D-dimer, C-reactive protein, and ferritin. Chest computed tomography showed bilateral ground-glass opacities. Mycophenolate and prednisone were held, tacrolimus was continued, and the patient was started on 6 mg of dexamethasone orally daily. After clinical and inflammatory marker improvement, he was weaned off supplemental oxygen. He was subsequently discharged home after a total of 5 days to complete a 10-day course of dexamethasone and with instructions to restart prednisone following completion. Tacrolimus was continued on discharge, but mycophenolate continued to be held to be readdressed during follow-up in the transplant clinic.

### DISCUSSION

Management of patients with COVID-19 is challenging and is more so in patients with OHT, for which randomized trials are lacking. Several considerations come into play when managing patients with heart transplant and COVID-19, including immunosuppressive medication management and the extrapolation of results from clinical trials for COVID-19-directed therapies.

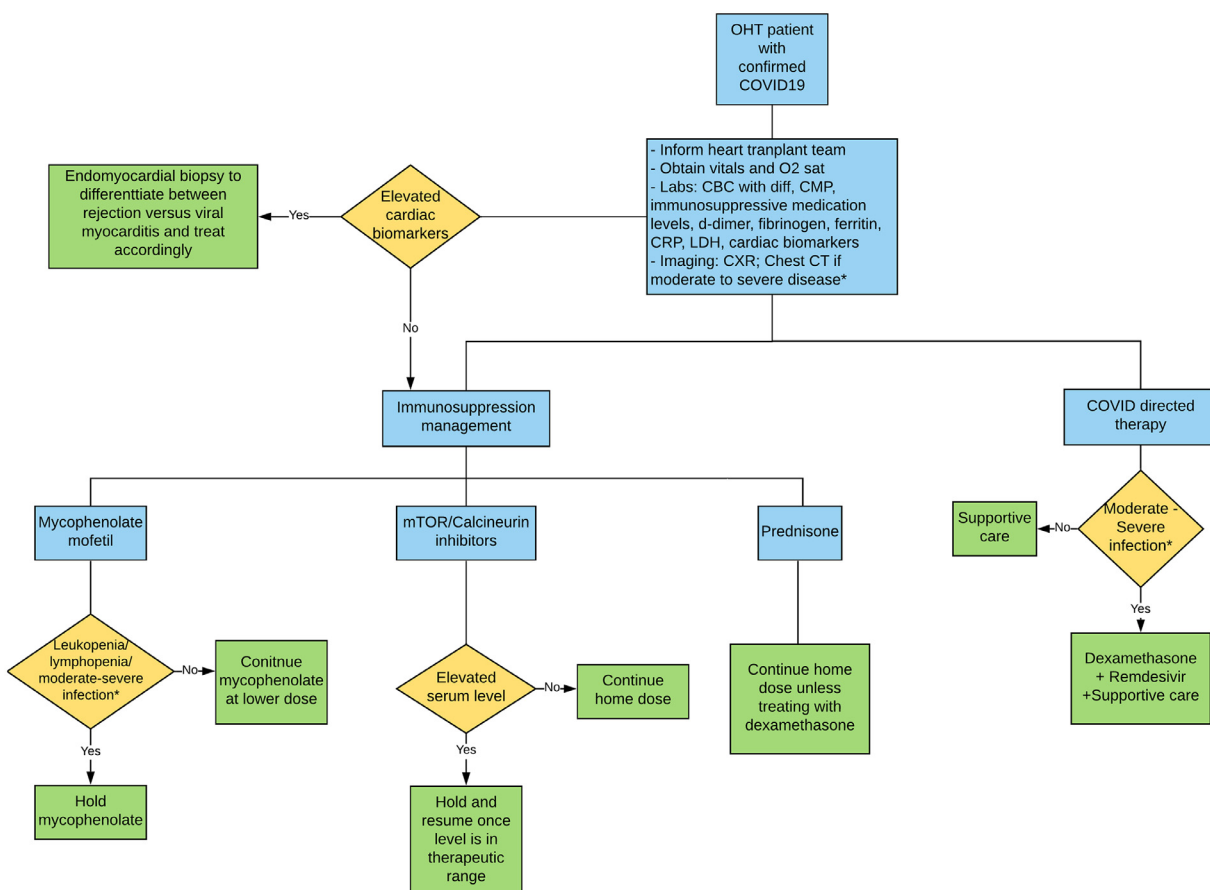
Just like the general population, the clinical presentation of post-heart transplant patients with COVID-19 is variable, ranging from asymptomatic and symptomatic to fulminant respiratory failure and death. Symptoms are also similar to those of the general population, including fever, cough, shortness of breath, and, less commonly, gastrointestinal symptoms [2-4]. However, it appears that the mortality rate in this subset of patients, in the range of 25% to 33%, far exceeds that in the general population based on some case series [2-4]. It is unclear whether this increased mortality is related to the patients' immunosuppressed state or to the fact that these patients are more likely to be older, have more comorbidities, and have more severe infection.

In our cohort, management of immunosuppressive medications was similar in all 4 patients. Given that lymphopenia is associated with worse outcomes in patients with COVID-19 [5], mycophenolate was held, especially because all patients had lymphopenia on admission labs. Similar to previously referenced studies, calcineurin inhibitors were continued in our patients, unless trough levels were supratherapeutic, at which point the medications were held until levels were back to the appropriate therapeutic range. This strategy allows for the maintenance of an appropriate level of immunosuppression while avoiding side effects and end-organ dysfunction. Finally, prednisone was continued at the same home dose unless there was an indication for treatment with dexamethasone for COVID-19, in which case prednisone was held and restarted after the dexamethasone course was completed.

Beyond management of immunosuppression, targeted therapy for COVID-19 in our patients was based on extrapolation from drug trials. In accordance with the RECOVERY trial showing reduced 28-day mortality with dexamethasone administration to hospitalized patients with COVID-19 [6], all of our patients were treated with oral/intravenous dexamethasone. In addition, 2 patients received 200 mg of remdesivir daily. This is based mostly on the ACTT-1 trial, which mostly included patients with severe COVID-19 and showed decreased time to recovery with remdesivir compared to placebo [7]. Therefore, in the setting of these results, as well as its relative safety and tolerability [8], remdesivir should be considered when treating patients with heart transplant and moderate to severe COVID-19 infection. None of our patients received hydroxychloroquine given its lack of efficacy [9], and none were treated with tocilizumab because they were not felt to be ill enough to warrant such treatment, especially in the absence of strong evidence to support treatment with tocilizumab at this

time [10,11]. Moreover, none of the patients were treated with convalescent plasma because the evidence supporting this treatment's efficacy and safety is variable based on clinical trials and systematic reviews [12-14]. Although convalescent plasma could be considered as a treatment option in patients with very severe or life-threatening disease, the available evidence does not justify its use in patients with mild to moderate disease, as with our patients.

In November 2020, the US Food and Drug Administration issued an emergency use authorization for a number of synthetic neutralizing monoclonal antibodies, including bamlanivimab, directed against viral spike proteins in order to neutralize the virus. This was administered to nonhospitalized patients with mild to moderate COVID-19 infection, based on early clinical data on these antibodies [15,16]. This emergency use authorization included immunocompromised patients or patients on immunosuppressive medications. Early trial data have shown that these antibodies reduce viral load and potentially can



**Fig 1.** Flow diagram delineating suggested treatment strategy in heart transplant recipients with COVID-19 infection. CBC, complete blood count; CMP, complete metabolic panel; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; CXR, chest X-Ray; LDH, lactate dehydrogenase; OHT, orthotopic heart transplant; mTOR, mechanistic Target of Rapamycin. \*Mild infection: O<sub>2</sub> saturation >94% on room air, without tachypnea, without pneumonia on imaging, and without end-organ dysfunction (eg. liver, kidney). Moderate infection: O<sub>2</sub> saturation <94% on room air requiring supplemental O<sub>2</sub> via nasal cannula or with tachypnea (≥24 breaths) or pneumonia on chest imaging but without evidence of end-organ dysfunction or acute respiratory distress syndrome. Severe infection: O<sub>2</sub> saturation <94% on room air requiring supplemental O<sub>2</sub> via high-flow nasal cannula/non-rebreather mask, noninvasive positive pressure ventilation/mechanical ventilation; evidence of end-organ dysfunction; and evidence of acute respiratory distress syndrome.

decrease the risk of an emergency department visit or hospitalization [17-19]. The 4 patients in our case series did not receive this regimen because they had presented prior to approval of these antibodies and thus the antibodies were not a part of our protocol, but our institution currently provides this approach as per recommendations.

Finally, OHT status adds another level of complexity; that is, patients presenting with possible myocarditis with elevated cardiac biomarkers, electrocardiograph changes, and possibly graft dysfunction. Evaluation for rejection can potentially be delayed given restrictions for endomyocardial biopsy.

Based on the above discussion, available trial data, experience with immunosuppressive regimens, and a previously developed algorithm for the management of COVID-19 in patients with OHT [20], we suggest the treatment strategy summarized in Fig 1.

## CONCLUSION

Patients with OHT and COVID-19 infection have presentations similar to those observed in the general population with COVID-19, but these patients have a higher mortality rate. Management of immunosuppression should be aimed at improving host immune defenses against the infection while also preventing acute graft rejection. There are no treatment data specific for patients with OHT and thus management is extrapolated from the general population.

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