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KIDNEY TRANSPLANTATION (ML HENRY AND R PELLETIER, SECTION EDITORS)

COVID-19 and the Response of Transplant Centers: the Global Response with an Emphasis on the Kidney Recipient

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Abstract

Purpose of the Review In response to the COVID-19 pandemic, vulnerable populations, such as transplant patients, were at greater risk than the regular population. In order to protect these populations, transplant centers enacted new guidelines. We approach this review by looking at how different transplant regions responded to COVID-19 and analyze the unifying themes that have proven invaluable in the subsequent waves.

Recent Findings We noticed that most elective surgeries including living donor transplant operations were suspended in most countries. The response to deceased donor transplants varied between countries: in some deceased donor transplants continued with modified donor and recipient criteria, while in other countries this surgery was suspended. There was a general trend of decreasing or holding antimetabolites, treating the virus with hydroxychloroquine and/or azithromycin, and converting outpatient clinics to virtual clinics.

Summary We learned how to carefully select donors and recipients, tailor immunosuppressant regiments, and implement telemedicine. The kidney recipient population can be effectively managed in times of crisis with appropriate accommodations and measures. This review can be a model for the transplant community for future pandemics.

Keywords Transplant response to COVID-19 · Kidney recipients and COVID-19 · Review of transplant response to COVID-19 · COVID-19 in the transplant community

Introduction

In the winter of 2020, the first wave of SARS-CoV-2, the virus that causes coronavirus-19 (COVID-19) infection emerged from Wuhan, China. This virus spread rapidly through the world in an unprecedented way that has yet to abate. As the COVID-19 global pandemic erupted, the care of vulnerable populations was one of the primary challenges. Among them are the solid organ transplant patients, on account of their immunosuppressed status. In particular, the T cell response is significantly suppressed in this population [1••, 2•, 3, 4]. At the outset of the pandemic, when the natural history of COVID-19 infection could only be conjectured, there was bona fide concern that immunosuppressed patients would be at increased risk for infection with SARS-CoV-2 and would experience unacceptably high mortality rates [3–7]. Faced with this hypothesis, solid organ transplant programs needed to make important decisions about very practical matters [7, 8]. Is the inpatient transplant unit sufficiently physically distant from the COVID-19 unit? Should postoperative patients be seen in the outpatient clinic? How should the medical personnel be protected? Should induction immunosuppression not include lymphocyte depleting agents? Should only some transplants be performed? Should any transplants be performed?

Around the world, transplant centers made individualized decisions about the conduct of their programs, though several themes were mostly consistent: pre-operative testing of recipients and donors for COVID-19 infection, minimizing immunosuppression, rigorous limited recipient selection, and the use of telemedicine in the outpatient setting when possible [1••, 3, 5, 8, 9••]. In this paper, we explore the variations on these management strategies, to demonstrate that the

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transplant center response to the COVID-19 pandemic developed to address the individual needs of the centers, but ultimately reflected the desire to protect patients from any modifiable excessive harm.

We reviewed the published global literature for transplant centers' COVID-19 responses. The detailed findings are summarized in Table 1.

Transplant Centers' Responses by Region

North America—the USA and Canada

Our center—Montefiore Medical Center in the Bronx, New York—halted all kidney transplants starting March 22, 2020, including new evaluations of both recipients and donors. Only emergent liver, heart, and lung transplants were performed. We started doing new donor and recipient evaluations for kidney transplant via telemedicine in May 2020.With the pandemic surge winding down around June 2020 in New York City, we performed our first living donor kidney transplant in the first week of June, followed by two deceased donor kidney transplants in the same week. Currently, we are still performing both living and deceased donor kidney transplants with careful selection of recipients and donors and tailoring immunosuppression and induction to immunological risk, the psychosocial needs and living situation of the recipient, and infectious risk.

All other transplant centers in the USA discontinued living donor kidney transplants, except those on the West Coast since they were not initially as hard hit with cases as the East Coast. While some centers continued doing deceased donor transplants on a case-by-case basis, considering the level of emergency of the transplant, some centers only continued to transplant those with a lower risk of delayed graft function.

Our center initially reported a mortality rate of 28% among our kidney transplant recipients with COVID-19 [10••]. In a subsequent report, we reported an overall mortality of 20% and in-hospital mortality of 38% [11••]. Other centers in New York reported similar mortality. For immunosuppression management, the antimetabolite dose was reduced or held for most patients. Hydroxychloroquine and/or azithromycin dominated the therapeutic arsenal used. All outpatient management was switched to virtual visits via telemedicine. The handling of transplants in Canada during the pandemic mirrored that of the USA.

Asia—China

Wuhan, China, closed on January 23, 2020, due to the impending threat of COVID-19. However, the impact of COVID-19 in organ transplant recipients was minor in the Hubei Province. There were only 22 confirmed cases in organ transplant recipients (19 liver and 2 kidney) [1••]. The difference in infection rate in the transplant community compared to the rest of the community at large was credited to years of effective transplant recipient education, including practicing effective self-protection with mask compliance, hand washing, and social distancing. In response to the overwhelming healthcare demands, all organ donation stopped on January 23, 2020.

Due to the lockdown of the surrounding areas, transplant outpatient management was converted to remote follow-up. Online consultation was implemented and labs collected from home were sent to transplant centers for interpretation, including dose adjustments of calcineurin inhibitors (CNI).

COVID-19-positive transplant patients were treated by a reduction or discontinuation of immunosuppression along with supportive treatment (often with low-dose methylprednisolone) based on the severity of the lung lesions. The mortality rate was low for COVID-19-positive transplant recipients, with one death among the 22 patients. In the single-center study from Tongji Hospital, Zhu et al. describe pneumonia in COVID-19-positive renal transplant recipients and assess their center's treatment. They managed patients by discontinuing antimetabolites and CNIs and adding on antiviral medications [2•].

On May 25, 2020, organ transplantation resumed as the risk of COVID-19 dwindled and healthcare systems had sufficient resources.

Asia—Hong Kong

COVID-19 first emerged in Hong Kong in January 2020 after the Chinese New Year. Resource utilization shifted to treat the influx of COVID-19 cases, so the liver transplant department at Queen Mary Hospital reduced living donor liver transplant (LDLT) cases in half [1••]. However, LDLT for urgent conditions was permitted, and the center found itself utilizing LDLT grafts for fulminant cases, who ordinarily would have received deceased donor grafts, actually doubling the LDLT rate of the prior year. There was a vast change in deceased donor liver transplantation (DDLT), with only 2 DDLT occurring in the month of February [1••].

The center required that both potential living donors and recipients were screened for COVID-19 infection if they had symptoms or a history of recent travel. For deceased donors, screening was only performed in the presence of clinical symptoms or a recent travel history [1••].

Asia—Japan

Japan's response to organ transplantation was based on the urgency of the transplant. Heart, lung, and emergent liver transplantation continued, while kidney, pancreas, and small bowel transplantation was stopped [1••].

Table 1 Global response of transplant centers to COVID-19

Region	Asia			
Country	China			
Response	1/23/20 Suspended all organ transplantation and resumed transplantation on 5/25/20 [1••]			
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Coronavirus disease 2019 pneumonia in immunosuppressed renal transplant recipients: a summary of 10 confirmed cases in Wuhan, China Zhu et al. [2] Wuhan, China (Tongji Hospital)	10 patients	Mortality 1/10 (10%) Hospitalized 10/10 (100%) AKI 5/10 (50%) Discharged 8/10 (80%)	Discontinued MMF 9/10 (90%) Discontinued CNI 7/10 (70%) Reduced dose of CNI 8/10 (80%) IVIG 7/10 (70%) Antiviral therapy 10/10 (100%)	Online consultation
Region	Asia			
Country	Hong Kong			
Response	50% reduction in LDLT (continues in urgent conditions) Decreased DDLT Increased LDLT for liver failure [1••]			
Region	Asia			
Country	Japan			
Response	Continues life-saving transplantation for status 1 liver recipients Suspended all kidney, pancreas, and bowel transplants [1••]			
Region	Asia			
Country	South Korea			
Response	Partial suspension of LDKT (especially if desensitization for ABO or HLA incompatibility) Continued urgent LDKT and DDKT [1••]			
Region	Asia			
Country	Mongolia			
Response	3/20 suspended living donor transplantation except 1 patient [1••]			
Region	Asia			
Country	Singapore			
Response	Discontinued LDKT except 1 patient who needed who was unable to get dialysis access Discontinued DDKT except those on priority waitlist for failing dialysis access or pure red cell aplasia Liver transplantation if meet criteria for medical urgency [1••]			
Region	Asia			
Country	India			
Response	LDKT and LDLT suspended in Mumbai and outside Mumbai at the discretion of the hospital DDKT suspended in Mumbai and the region Continued DDLT [1••]			
Region	Middle East			
Country	Turkey			
Response	Postponed all transplantation except urgent cases (acute liver failure) [3]			
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
COVID-19 in kidney transplant recipients: a multicenter experience in Istanbul Demir et al. [4] Istanbul, Turkey (Istanbul University)	40 patients	Mortality 5/40 (12.5%) Hospitalized 39/40 (98%) ICU stay 7/40 (18%) AKI 14/40 (35%) Graft failure 0/40 (0%)	Discontinued antimetabolites 40/40 (100%) Discontinued mTOR-Is 4/40 (10%) Discontinued CNIs 11/40 (27.5%) Favipiravir 18/40 (45%) Tocilizumab 5/40 (12.5%) Anakinra 3/40 (7.5%) Antibiotics 24/40 (60%)	In-person if local, otherwise telehealth
Region	Middle East			

Table 1 (continued)

Country	Saudi Arabia			
Response	Continued DDRT and LDRT, but discontinued LDRT when 3 kidney recipients presented symptomatically. Continued only urgent LDLT (defined as MELD > 25, HCC beyond. Milan Criteria but within UCSF criteria, acute fulminant liver failure, and recurrent decompensations) Discontinued non-urgent LDLT [3]			
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Coronavirus disease-19: disease severity and outcomes of solid organ transplant recipients: different spectrums of disease in different populations? Ali et al. [5] Riyadh, Saudi Arabia (King Faisal Specialist Hospital & Research Center)	67 patients 44 kidney/15 liver/8 lung Mortality 2/67 (3%)	Hospitalized 47/67 (70%) ICU admission 7/47 (15%) AKI 9/47 (19%)	Discontinued antimetabolites 47/47 (100%) Hydroxychloroquine 39/47 (83%) Azithromycin 42/47 (89%) Tocilizumab 11/47 (23%) Dexamethasone 9/47 (19%)	N/A
Region	Middle East			
Country	Egypt			
Response	Discontinued majority of transplantation [3]			
Region	Middle East			
Country	Kuwait			
Response	Discontinued LDRT and LDLT transplants except to avoid dialysis [3]			
Region	Middle East			
Country	Iran			
Response	N/A			
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
A report of 85 cases of COVID-19 and abdominal transplantation from a single center: what are the associated factors with death among organ transplantation patients Malekhosseini et al. [6] Shiraz, Iran (Abu Ali Sina Hospital)	85 patients 66 liver/16 kidney/2 kidney–pancreas, and 1 liver/kidney	Mortality 17/85 (20%), Hospitalized 56/85 (66%) ICU admission 19/56 (34%)	Hydroxychloroquine 30/85 (35%) Lopinavir–ritonavir 4/85 (5%) Tavanex 4/85 (5%) Tamiflu 2/85 (2%) Azithromycin 23/85 (27%) Imipenem 4/85 (27%) Cotrimoxazole 3/85 (4%) Fluconazole 2/85 (2%) Vancomycin 2/85 (2%) Salbutamol 1/85 (1%)	N/A
Region	Europe			
Country	Denmark			

Table 1 (continued)

Response	DDKT and DDLT continued LDKT continued in some centers and suspended in others Suspended SPK [1••]			
Region	Europe			
Country	Sweden			
Response	N/A			
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Initial report from a Swedish high-volume transplant center after the first wave of the COVID-19 pandemic Felldin et al. [7] Gothenburg, Sweden (University of Gothenburg)	53 patients 31 kidney/5 lung/5 heart/8 liver /4 dual organs	Mortality rate 5/53 (9.4%) In-hospital mortality rate 5/37 (14%) Hospitalized 37/52 (70%) ICU admission 8/37 (22%) Dialysis 12/37 (32%) Severe COVID-19 disease 12/37 (32%) Mechanical ventilation 7/37 (19%)	Discontinued or reduced MMF 23/35 (66%) Reduced CNI 11/53 (21%) Hydroxychloroquine + tocilizumab 1/37 (3%) LMWH 27/37 (73%) Apixaban 1/37 (3%) Supplemental O_2 21/37 (57%)	N/A
Region	Europe			
Country	UK			
Response	Routine transplantation continued Acute liver failure listed and transplanted Cancelled routine transplant assessment Continuation of pediatric liver transplantation Suspended all LDLT Suspended all elective post-transplant surgical cases [1••]			
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Outcomes of renal transplant recipients with SARS-CoV-2 infection in the eye of the storm: a comparative study with waitlisted patients Mohamed et al. [8] London, UK (Barts Health NHS Trust)	28 patients	Mortality 9/28 (32%) Hospitalized 25/28 (89%) ICU stay 5/25 (20%) AKI 14/25 (56%)	Discontinued MMF 19/21 (90%) Halved MMF 1/21 (5%) Discontinued AZA 3/3 (100%) No change in antimetabolite 3/24 (12.5%) Steroid increased 12/27 (44%) Hydrocortisone 1/28 (4%)	Virtual clinics Medications sent via mail 24 h online support
Region	Europe			
Country	France (Paris)			
Response	Continued organ procurement including DCD donors [1••]			
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
COVID-19 infection in kidney transplant recipients: disease incidence and clinical outcomes	66 patients	Mortality 16/66 (24%) Hospitalized 60/66 (91%) ICU stay 15/66 (22%) AKI 28/66 (42%) RRT 7/28 (25%)	Discontinued only MMF/MPA/AZA 38/61 (62%) Discontinued only CNI 2/57 (4%) Belatacept infusion postponed 1/6 (17%) No change in immunosuppression 24/66 (36%) Discontinued all immunosuppression 1/66 (2%)	Cancelled all f/u appointments for liver Telehealth clinics for kidney

Table 1 (continued)

Elias M, Pievani D, Randoux C, et al. [9••] Paris, France (Saint Louis Hospital)			Hydroxychloroquine 7/66 (11%) Tocilizumab 1/66 (2%) Eculizumab 2/66 (3%)	
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
An initial report from the French SOT COVID Registry suggests high mortality due to COVID-19 in recipients of kidney transplants Caillard et al. [10••] Strasbourg, France (Strasbourg University Hospital)	279 patients	Mortality at 30 days (23%) Hospitalized 243/279 (87%) Ventilated 72/243 (30%) O_2 therapy 152/210 (72%) ICU stay 88/243 (36%) AKI 106/243 (44%) RRT 27/243 (11%) Graft loss 9/243 (4%)	CNI discontinued 58/202 (29%) Antimetabolite discontinued 136/192 (71%) mTOR-I discontinued 18/29 (62%) Belatacept discontinued 7/15 (47%) Azithromycin 71/243 (29%) Other antibiotics 153/243 (63%) Antifungal drugs 6/243 (2.5%) Remdesivir 2/243 (1%) Lopinavir/ritonavir 11/243 (4.5%) Oseltamivir 6/243 (2.5%) Hydroxychloroquine 60/243 (25%) Tocilizumab 12/243 (5%)	Cancelled all f/u appointments for liver Telehealth clinics for kidney
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Biomarkers of cytokine release syndrome predict disease severity and mortality Benotmane et al. [11••] Publication date: 11, 09, 2020 France	49 patients	Mortality 9/49 (19.5%) Hospitalized 41/49 (84%) ICU stay 14/41 (34%) AKI 31/41 (76%)	Discontinued MMF/MMPA 35/35 (100%) Discontinued mTOR-Is 6/6 (100%) Belatacept postponed ½ (50%) Discontinued CNI 15/36 (42%) Hydroxychloroquine 15/41 (37%) Azithromycin 26/41 (65%) Lopinavir–ritonavir 5/41 (12%) High dose corticosteroids 14/41 (34%) Tocilizumab 4/41 (10%)	Cancelled all f/u appointments for liver Telehealth clinics for kidney
Region Country Response	Europe France (Strasbourg) 3/9/20 discontinued DDKT and LDKT [1••]			
Region Country Response	Europe Italy N/A			
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Kidney transplant patients with SARS-CoV-2 infection: the Brescia Renal COVID Task Force experience Bossini et al. [12] Brescia, Italy (Spedali Civili Hospital)	53 patients	Mortality 15/45 (33%) Hospitalized 45/53 (85%) ICU stay 10/45 (22%) AKI 15/45 (33%) RRT 3/15 (20%) Discharged 27/45 (60%) ARDS 27/45 (60%)	Immunosuppression adjustments in hospitalized patients 34/45 (76%) F/u immunosuppression adjustments 17/20 (85%) Reduced steroids and CNI 13/17 (76%) Reduced CNI and MMF 2/17 (12%) Same dose steroids + reduced dose CNI 1/17 (6%) Same dose steroids + introduced mTOR-I 1/17 (6%) Lopinavir/ritonavir 18/53 (34%) Darunavir + ritonavir 14/53 (26%) Hydroxychloroquine 39/53 (74%)	N/A
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
A single center observational study of the clinical characteristics and short-term	20 patients	Mortality 5/20 (25%) Hospitalized 20/20 (100%)	Discontinued immunosuppression 20/20 (100%) Initiated methylprednisolone 16 mg/day 20/20 (100%)	N/A

Table 1 (continued)

outcome		ICU stay 4/20 (20%)	Antiviral therapy + hydroxychloroquine 19/20 (95%)	
of 20 kidney transplant patients		AKI 6/20 (30%)	Lopinavir/ritonavir 3/20 (15%)	
admitted for		RRT 1/6 (17%)	Darunavir + ritonavir 8/20 (4%)	
SARS-CoV2 pneumonia		Discharged 3/20 (15%)	Tocilizumab 6/12 (50%)	
Alberici et al. [13]				
Brescia, Italy (Spedali Civili Hospital)				
Region	Europe			
Country	Germany			
Response	Suspended most LDKT			
	Continued DDKT			
	High urgency pediatric liver transplantation			
	DDLT in lower urgent situations on case-by-case basis			
	Transport of organs across country borders continues with some restrictions [1••]			
Region	Europe			
Country	Netherlands			
Response	3/13/20			
	Suspended LDKT and DDKT at the largest transplant center (including patients scheduled to undergo blood group ABO-incompatible kidney transplantation already treated with alemtuzumab before the decision to stop acute kidney transplants)			
	3/23/20			
	Continued DDKT at smaller centers			
	Liver transplantation continued [1••]			
Region	Europe			
Country	Spain			
Response	Postponed all LD transplantation [1••]			
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Respiratory and GI COVID-19 phenotypes	414 patients	Hospitalized 380/414 (92%)	Hydroxychloroquine 369/414 (89%)	Cancelled all non-urgent appointments, lab tests, and procedures
in kidney transplant recipients		ICU admission 50/414 (12%)	Azithromycin 206/414 (50%)	Telehealth
Crespo et al. [14]			Glucocorticoids 203/414 (49%)	
Barcelona, Spain (Hospital del Mar)		Intubation 73/414 (18%)	Lopinavir/ritonavir 140/414 (34%)	
			Tocilizumab (anti-IL6) 77/414 (19%)	
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
COVID-19 in solid organ transplantation:	46 patients	Mortality17/46 (37%)	Discontinued tacrolimus 22/36 (61%)	N/A
a matched retrospective cohort study and	30 kidney/13 lung/3 liver	Hospitalized 46/46 (100%)	Discontinued everolimus 7/7 (100%)	
evaluation of immunosuppression management		ICU admission 10/46 (22%)	Discontinued sirolimus 4/4 (100%)	
Miarons et al. [15]		ARDS 9/46 (20%)	Hydroxychloroquine 44/46 (96%)	
Barcelona, Spain (Vall d'Hebron Hospital Universitari)			Hydroxychloroquine + azithromycin 41/46 (89%)	
			Lopinavir–ritonavir 23/46 (50%)	
			Darunavir–cobicistat 17/46 (37%)	
			Interferon beta 3/46 (7%)	
			Tocilizumab 21/46 (46%)	
			Remdesivir 1/46 (2%)	
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
COVID-19 in Elderly	16 patients	Mortality 8/16 (50%)	mTOR-I discontinued 4/5 (80%)	Cancelled all non-urgent appointments, lab tests and procedures
Kidney transplant recipients		Hospitalized 15/16 (94%)	MMF discontinued 8/8 (100%)	
Crespo et al. [16]		ICU stay 2/16 (13%)	CNI discontinued 8/14 (71%)	Telehealth
Barcelona, Spain (Hospital del Mar)		AKI 5/15 (33%)	Hydroxychloroquine 13/16 (81%)	

Table 1 (continued)

			Steroids 6/16 (37.5) Ritonavir-lopinavir/darunavir 5/16 (31%) Tocilizumab 4/16 (25%) Antibiotics (azithromycin) 14/16 (88%)	
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Clinical characteristics and risk factors for severe COVID-19 in hospitalized kidney transplant recipients: a multicentric cohort study Fava et al. [17] Barcelona, Spain (Hospital Universitari de Bellvitge)	104 patients	Mortality 28/104 (27%) Hospitalized 104/104 (100%) ICU stay 24/104 (23%) AKI 47/100 (47%) ARDS 47/104 (55%)	Discontinued at least one immunosuppressive agent 95/104 (91.3%) IV steroids 55/104 (53%) Hydroxychloroquine 101/104 (97%) Lopinavir/ritonavir 50/104 (48%) Azithromycin 67/104 (64%)	Cancelled all non-urgent appointments, lab tests, and procedures Telehealth
Region	Europe			
Country	Switzerland			
Response	3/13/20 6-stage plan: 1. Discontinued all LD transplantation 2. Discontinued all DDPT and islet transplants, discontinue all DCD donors 3. Discontinued DDKT 4. Liver, lung, and heart based on urgent status 5. Only urgent transplants 6. Discontinue all transplants 3/22/20 Discontinued all transplant and procurements except urgent cases like fulminant hepatitis [1••]			
Region	Oceania			
Country	Australia			
Response	Suspended LDKT Suspended DDKT [1]			
Region	Oceania			
Country	New Zealand			
Response	Continued DDKT at 2/3 transplant centers Discontinued LDKT [1••]			
Region	Africa			
Country	South Africa			
Response	Discontinued LDKT and DDKT in government hospitals Continued DDKT in private hospitals Discontinued LDKT in private hospitals [1••]			
Region	North America			
Country	Canada			
Response	Montreal: Suspended LDKT Suspended DDKT except recipients > 70 and highly sensitized Toronto: 3/16/20 Suspended LDKT Suspended DDKT except active patients on the waiting list medically urgent or cPRA > 99% [1••]			
Region	North America			
Country	USA			

Table 1 (continued)

Response	NY: Continued transplantation (considered emergency) [1••]			
Clinical study	**Patient number**	**clinical Outcomes**	**Inpatient treatment**	**Outpatient management**
Kidney allograft recipients, immunosuppression, and coronavirus disease-2019: a report of consecutive cases from a New York City transplant center Lubetzky M, et al. [18•] NY, USA (Weill Cornell Medicine)	54 patients	Mortality rate 7/54 (13%) Hospitalized 39/54 (72%) AKI 21/54 (39%) Graft failure 6/54 (11%) Discharged 37/39 (95%)	Tacrolimus reduction 17/54 (33%) MMF 50% reduction 15/54 (28%) MMF discontinuation 24/54 (44%) Azithromycin 12/54 (22%) Doxycycline 8/54 (17%) Hydroxychloroquine 32/54 (62%) Remdesivir 2/54 (4%) IL-6 Inhibitor 2/54 (4%) Convalescent plasma 1/54 (2%)	Virtual
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Outpatient management of kidney transplant recipients with suspected COVID-19—single-center experience during the New York City surge Mehta S, et al. [19] NY, USA (NYU Langone)	44 patients	Mortality rate 6/44 (14%) Hospitalized 34/44 (77%) AKI 18/34 (53%) Discharged 27/34 (79%)	Discontinued antimetabolites 26/33 (78.8%) Reduced dose of antimetabolites by 50-75% 6/33 (18.2%) Hydroxychloroquine 33/34 (97%) Azithromycin 27/34 (79%) Clazakizumab or tocilizumab 9/34 (26.5%)	Virtual
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
COVID-19 and kidney transplant Akalin et al. [20] NY, USA (Montefiore Medical Center)	36 patients	Mortality 10/36 (28%) Hospitalized 28/36 (78%) Viral PNA 27/28 (96%) Intubation 11/28 (39%) RRT 6/28 (21%) Discharged 10/28 (36%)	Discontinued antimetabolite 24/28 (86%) Discontinued tacrolimus 6/28 (21%) Hydroxychloroquine 24/28 (86%) Apixiban if D-dimer levels higher than 3.0 micrograms/mL Leronlimab (CCR5-I) 6/28 (21%) Tocilizumab (IL-6R antagonist) 2/28 (7%)	Virtual
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
COVID-19 in kidney transplant recipients Nair et al. [21••] NY, USA (Hofstra/Northwell Health)	10 patients	Mortality 3/10 (30%) Hospitalized 9/10 (90%) ICU stay 5/10 (50%) AKI 5/10 (50%) Discharged 7/10 (70%)	Discontinued antimetabolite (MMF/MPA) 9/10 (90%) Discontinued CNI 2/9 (22%) Discontinued Sirolimus 1/1 (100%) Hydroxychloroquine + azithromycin 9/10 (90%)	Virtual
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Early outcomes of outpatient management of kidney transplant recipients with coronavirus disease 2019 Husain et al. [22] NY, USA (Columbia University College of Physicians and Surgeons and New York Presbyterian Hospital)	41 patients	Hospitalized 13/41 (32%)	26/41 (63%) reduction in immunosuppression	Virtual
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**

Table 1 (continued)

Early description of coronavirus 2019 disease in kidney transplant recipients in New York Mohan et al. [23] NY, USA (Columbia University College of Physicians and Surgeons and New York Presbyterian Hospital)	15 patients	Mortality 2/15 (13%) Hospitalized 15/15 (100%) Intubation 4/15 (27%) AKI 6/15 (40%) RRT 2/15 (13%) Discharged 8/15 (53%)	Discontinued all immunosuppression 2/15 (14%) Discontinued only MMF/MPA/AZA/leflunomide 10/14 (71%) Reduced prednisone 1/10 (10%) Belatacept infusion postponed ½ (50%) Replaced tacrolimus and MMF with prednisone 1/15 (7%) Hydroxychloroquine w/o azithromycin 4/15 (27%) Hydroxychloroquine + azithromycin 9/15 (60%) Tocilizumab 1/15 (7%)	Virtual
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Evidence of potent humoral immune activity in COVID-19-infected kidney transplant recipients Hartzell et al. [24] NY, USA (Icahn School of Medicine at Mount Sinai)	18 patients	Mortality 7/18 (39%) Hospitalized 18/18 (100%) ICU stay 11/18 (61%) AKI 16/18 (89%) Discharged 11/18 (61%)	Discontinued MMF/MPA 5/18 (28%) Discontinued all immunosuppressive meds 1/18 (5%) Reduced dose MMF/MPA 13/18 Started on steroids (not previously on for antirejection) 2/18 (11%)	Virtual
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
COVID-19 in solid organ transplant recipients: initial report from the US epicenter Pereira et al. [25•] NY, USA (Columbia University College of Physicians and Surgeons and New York Presbyterian Hospital)	90 patients 46 kidney/17 lung/13 liver/9 heart/5 dual organs	Mortality rate 16/90 (18%) In-hospital mortality rate 16/68 (24%) Hospitalized 68/90 (76%) Mechanical ventilation 24/68 (35%) ICU admission 23/68 (34%)	Discontinued or reduced antimetabolite 42/48 (88%) Discontinued or reduced steroid 3/43 (7%) Discontinued or reduced CNI 10/56 (18%) Hydroxychloroquine 62/68 (91%) Azithromycin 45/68 (66%) Remdesivir 2/68 (3%)	N/A
Clinical study/hospital response	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
COVID-19 infection in kidney transplant recipients at the epicenter of pandemics Azzi et al. [26] NY, USA (Montefiore Medical Center)	229 patients	Mortality rate 47/229 (21%) In-hospital mortality rate 42/111 (38%) Hospitalized 111/229 (48%) Admitted to Montefiore 79/111 (71%) Intubation 28/79 (35%) AKI requiring RRT 7/79 (9%)	Discontinued antimetabolite 74/79 (94%) Discontinued CNI 11/79 (14%) Antibiotics 65/79 (82%) Hydroxychloroquine 59/79 (75%) Remdesivir 6/79 (8%) High-dose corticosteroids 35/79 (44%) Tocilizumab 11/79 (14%) Sarilumab 2/79 (3%) Leronlimab 6/79 (8%) Convalescent plasma 7/79 (9%) IVIG 1/79 (1%)	Telemedicine
Region	North America			
Country	USA (Northeast)			
Response	Northeast: Only life-saving transplantation (kidney transplants with 100% PRA 0 Ag mismatch, to avoid dialysis, vascular access failure and pediatric patients, liver transplants with high MELD, heart transplant with high HAS, lung transplant with high LAS) [1••]			
Clinical study/hospital response	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
COVID-19 in solid organ transplant recipients: dynamics of disease	52 patients	Mortality rate 8/52 (16%)	Discontinued azathioprine /MMF 12/24 (50%) azathioprine/MMF halved 7/24 (29%)	N/A

Table 1 (continued)

progression and inflammatory markers in ICU and non-ICU admitted patients Roberts et al. [27] Publication date: July 22, 2020 Boston, MA (Massachusetts General Hospital)	29 kidney/6 lung/9 liver/6 heart/2 dual organs	In-hospital mortality rate 8/40 (21%) Hospitalized 40/52 (77%) Mechanical ventilation 14/40 (35%) ICU admission 14/40 (35%)	Discontinued CNI 1/26 (4%) CNI started 1/26 (3%) Discontinued MTOR 3/3 (100%) Discontinued belatacept 2/3 (67%) Steroids increased 4 /25(16%) Antibiotics 20/32 (63%) Hydroxychloroquine 11/32 (34%) Remdesivir 1/32 (3%) Statin 22/32 (69%) Tocilizumab 1/32 (3%) Trial enrollment 9/32 (28%) Prone positioning 9/32 (28%) Vasopressor required 11/32 (34%) Supplemental O_2 required 23/32 (72%)	
Region Country Response	North America USA (Midwest) Discontinued all living donor transplants Continued deceased donor on case-by-case basis Discontinued new donor and recipient evaluations Continued organ procurements [1••]			
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
COVID-19 outcomes among solid organ transplant recipients: a case-control study Sharma et al. [28] MI, USA (University of Michigan)	41 patients 16 kidney/3 lung/9 heart/8 liver/5 dual organs	Mortality rate 6/41 (14.6%) In-hospital mortality rate 6/36 (17%) Hospitalized 36/41 (87%) Mechanical ventilation 11/36 (30.5%) Dialysis 11/36 (30.5%) Severe COVID-19 disease 18/36 (50%)	Hydroxychloroquine 12/41 (29%) IL-6 I 11/41 (27%) Vasopressors 6/41 (17%)	N/A
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Clinical characteristics and outcomes of COVID-19 in solid organ transplant recipients: a cohort study Chaudhry et al. [29] MI, USA (Henry Ford Hospital)	47 patients 38 kidney/4 lung/5 heart/1 liver /1 pancreas	Mortality rate 8/47 (17%) In-hospital mortality rate 8/35 (23%) Hospitalized 35/47 (74%) ARDS 12/35 (35.5%) AKI 16/35 (46.8%) AKI requiring dialysis 7/35 (20%) ICU admission 13/35 (37%) Mechanical ventilation 12/35 (34%)	Discontinuation or reduction of antimetabolite 27/32 (84%) Discontinuation or reduction of CNI 5/33 (15%) Discontinuation or reduction of mTOR-I 1/35 (3%) Discontinuation or reduction of belatacept 1/35 (3%) Empiric antibiotic 26/35 (74%) Hydroxychloroquine 32/35 (91%) Corticosteroid 23/35 (66%) Tocilizumab 3/35 (9%)	N/A
Region Country Response	North America USA (South) Discontinued LDKT Continued DDKT in patients w/ lower risk of DGF			

Table 1 (continued)

	Continued DDLT Discontinued kidney transplant evaluations Continued liver transplant evaluations only for those with high External procurement teams not allowed into facility, only local surgeons allowed for organ recovery [1••]			
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Early Experience with COVID-19 and Solid Organ Transplantation at a U.S. High-volume Transplant Center Yi SG, et al. [30] TX, USA (Houston Methodist Hospital)	21 patients 12 kidney/3 liver/2 heart/4 multi-organ	Hospitalization 14/21 (67%) ICU 7/14 (50%) Intubation 5/14 (36%) AKI 11/14 (69%) Discharged 8/14 (57%)	Discontinued antimetabolite 12/14 (86%) Reduced CNI 3/14 (14%) Increased baseline steroids 3/14 (5%) Antiviral therapy 12/21 (575) Hydroxychloroquine + azithromycin 7/12 (58%) Hydroxychloroquine only 2/12 (17%) Azithromycin only 2/12 (17%) Convalescent plasma 1/12 (8%) Ribavirin 6/12 (50%) Remdesivir 1/12 (8%) Immunomodulating therapy 4/21 (19%) Tocilizumab 4/4 (100%) Nebulized interferon alpha-2b 1/4 (25%) Anakinra 1/4 (25%)	Telehealth
Region	North America			
Country	USA (West Coast)			
Response	Continued LDLT, DDLT, LDKT, and DDKT Discontinued pancreas transplants [1••]			
Region	Global			
Country	Global			
Response	N/A			
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
COVID-19 and kidney transplantation: results from the Tango International Transplant Consortium Cravedi et al. [31] (USA, Italy, Spain)	144 patients	Mortality 46/144 (32%) Hospitalized 144/144 (100%) Intubation 42/144 (29%) AKI 74/144 (52%)	Discontinued tacrolimus 32/144 (22.9%) Discontinued CNI 33/144 (23%) Hydroxychloroquine 102/144 (71%) Antibiotics 107/144 (74%) Tocilizumab 19/144 (13%) Antivirals 20/144 (14%)	N/A
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
Outcomes of critically ill solid organ transplant patients with COVID-19 in the United States Molnar et al. [32] Multicenter USA	98 patients 67 kidney/13 liver/13 heart/4 lung/1 pancreas	Mortality rate 39/98 (40%) Hospitalized 98/98 (100%) ARDS 73/98 (74%) AKI requiring dialysis 36/98 (37%) New infection 24/98 (24%) ICU admission 98/98 (100%) Mechanical ventilation 55/98 (56%)	Chloroquine 2/98 (2%) Hydroxychloroquine 62/98 (63%) Azithromycin 49/98 (50%) Hydroxychloroquine + azithromycin 74/98 (76%) Remdesivir 6/98 (6%) Lopinavir–ritonavir 3/98 (3%) Anticoagulation 46/98 (47%) Corticosteroids 64/98 (65%) Statin 40/98 (41%) Tocilizumab 23/98 (23%) IL-6 inhibitor 1/98 (1%) Vitamin C 4/98 (4%) Convalescent plasma 5/98 (5%)	N/A

Table 1 (continued)

			ACE-I 2/98 (2%)	
			ARB 3/98 (3%)	
			Tissue plasminogen activator 1/98 (1%)	
			Neuromuscluar blockade 37/98 (38%)	
			Inhaled epoprostenol 5/98 (5%)	
			Inhaled nitric oxide 8/98 (8%)	
			Prone position 34/98 (35%)	
Clinical study	**Patient number**	**Clinical outcomes**	**Inpatient treatment**	**Outpatient management**
COVID-19 in solid organ transplant: a multi-center cohort study Kates et al. [33] Multicenter USA	482 patients 318 kidney or kidney–pancreas/73 liver/57 heart/30 lung	Mortality rate 90/482 (18.7%) In-hospital mortality rate 77/376 (20.5%) Hospitalized 376/482 (78%) AKI 212/482 (44%) Mechanical ventilation 117/376 (31%) ICU admission 188/482 (39%) New thromboembolic events 14/482 (3%)	Modified immunosuppression 337/482 (70%) Chloroquine or hydroxychloroquine 296 (61%) Azithromycin 149/482 (31%) Anti-IL 6 62/482 (13%) Corticosteroids 49/482 (10%) Convalescent plasma 15/482 (3.1%) Protease inhibitors 14/489 (2.9%) Remdesivir 9/482 (1.9%) IVIG 18/482 (3.7%) Other experimental treatments 18/482 (3.7%) Clinical trial 23/482 (4.8%)	N/A

Screening for COVID-19 in donors and recipients was recommended for those with significant exposure to COVID-19, travel history to high-risk countries, or for patients with fever and respiratory symptoms. It was recommended that living donors for kidney, lung, and liver transplant stay at home or isolated in the hospital for 14 days before donation to avoid unnecessary exposure. In communities with available testing, it was recommended at 14 days and at 1 day before transplantation in both donors and recipients. Chest CT scans were also recommended before transplantation in donors and recipients [1••].

Outpatient follow-up was converted to telemedicine and extended periods between visits. Additionally, to prepare patients for the lockdown, a stockpile of additional immunosuppressants was distributed to patients.

Asia—South Korea

The response to organ transplantation was mixed. Some living donor kidney transplants were postponed, especially if undergoing desensitization for ABO or human leukocyte antigen incompatibility, but urgent living donor kidney transplantation and deceased donor programs continued [1••].

Screening for COVID-19 involved testing all deceased donors, while living donors were screened based on the center's decision. On March 13, 2020, the Korean Society for Transplantation released a guideline recommending routine COVID-19 screening of both donor and recipient [1••]. There was one report of a living liver donor who tested positive for COVID-19 after liver donation to her mother, but neither the donor nor the recipient developed symptoms.

Asia—Singapore

In response to the pandemic, all living kidney transplants were cancelled except for one patient who had no other access options. For this case, a nasopharyngeal swab for COVID-19 was performed for both the recipient and the living donor on day 15 and day 2 before surgery [1••]. Additionally, chest x-ray was performed on admission and on day 2 before surgery to assess for pneumonia. Deceased donor kidney transplantation had also been cancelled except for priority waitlisted patients with failing dialysis access or pure red cell aplasia. Liver, heart, and lung transplantations were permitted if medically urgent. One combined lung–liver was performed from a single deceased donor who underwent PCR testing for COVID-19 three times in addition to a CT thorax to exclude COVID-19 infection. These recipients were reported to be doing well.

Hospital transplant teams were divided into smaller groups working separately in different areas. They set up an acute respiratory tract infection ward where renal patients, including kidney transplant recipients, with respiratory complaints were

admitted for COVID-19 screening, with bedside access to dialysis. Patients in the acute respiratory tract infection ward had to have two negative COVID-19 swabs before being transferred to the general ward. Due to case reports of transplant recipients presenting with gastroenteritis, transplant recipients with gastroenteritis were required to be screened by COVID-19 PCR.

Outpatient management included virtual clinics with remote monitoring and home delivery of medications.

Asia—India

In Mumbai, all living donor transplants stopped. Outside of Mumbai organ transplants continued at the discretion of each hospital. Deceased donor kidney transplants were suspended in Mumbai and the surrounding region. Neither the National Organ & Tissue Transplant Organization nor the Regional Organ & Tissue Transplant Organization issued edicts to stop deceased donor liver and heart transplants [1••].

Outpatient follow-up was encouraged to be performed via phone and video call. If transplant patients required in-person follow-up, then they were scheduled to come into the clinic at intervals such that there would be no wait time nor contact with other patients. It was recommended that all transplant patients had a minimum of 1 month of immunosuppressants in stock [1••].

Middle East—Turkey

All elective procedures and surgeries were postponed across Turkey. Beginning on March 20, 2020, all private hospitals were denoted as COVID-19-only hospitals. From February 1 to April 1, 2020, in Ankara and Istanbul, only 21 liver and 23 kidney transplants were performed.

In describing a multi-center experience in Istanbul, Demir et al. found that 5 out of 40 renal transplant patients infected with COVID-19 died [12]. Inpatient management of transplant patients with COVID-19 was as follows: discontinuation of antimetabolites (both mycophenolate mofetil and azathioprine) and continuation of CNIs, except if patients required ventilation with a severe pneumonia. The interleukin-6 inhibitor, tocilizumab, was considered to treat severe cytokine release symptoms [9••].

Outpatient follow-up was mostly via telemedicine.

Middle East—Saudi Arabia

The Saudi Center for Organ Transplant (SCOT) addressed the dilemmas facing the transplant community during the pandemic and issued a position statement that provided guidelines and recommendations for deceased and living donation. All deceased donors were to be screened for COVID-19 with PCR from broncheoalveolar lavage or tracheal aspirate. All positive donors were declined. COVID-19-negative donors were considered on a case-by-case basis according to the level of risk.

Only urgent liver transplants (e.g., HCC meeting UCSF criteria, acute fulminant liver failure, recurrent decompensations, MELD > 25) continued. Donor and recipients in high-risk groups were tested for COVID-19 on the day of admission. In the case of COVID-19 positivity, the transplant was cancelled. In the circumstance of a first negative COVID-19 test, a second was performed before surgery. Low-risk patients required one negative PCR test at admission. Between February 1 and April 15, 2020, 33 liver transplants including 25 from living donors were performed without COVID-19 complications.

Outpatient management involved a switch to telemedicine, blood work in the nearest laboratory with results discussed via phone, and medications delivered to the home. Only patients recently transplanted were seen in clinic. Only one post-liver transplant patient from 2016 presented positive for COVID-19; no modifications were made to his medications.

Only 40 kidney transplants were performed from February 1 to April 2020; 7 of those were from deceased donors. There were no reported COVID-19 complications. Three kidney recipients presented with fever, cough, and fatigue and tested positive for COVID-19. Inpatient management consisted of azithromycin, hydroxychloroquine, and ceftriaxone and maintenance doses of low levels of tacrolimus and steroids. The living donor kidney program suspended all transplants from March until the first week of May [9••].

Middle East—Egypt

Transplant activities in Egypt were limited to live donor liver and kidney surgeries. Most governmental and university centers suspended transplant activities based on too great a risk to the donor and an unknown impact of COVID-19 on the recipient. The proposed precautions adopted for those undergoing transplant were home isolation for both the donor and recipient for 2 weeks before the transplant, to perform COVID-19 PCR twice at 48-h intervals before transplant, and to admit the recipient 3 days and donors 1 day before transplant.

Outpatient management involved telemedicine and in-person follow-up only for patients recently transplanted and those with abnormal laboratory or radiographic findings [9••].

Middle East—Kuwait

Living donor transplants were suspended on February 19, 2020, with one exception to prevent the need for dialysis. Deceased donor transplants continued, but with a rapid decline in number. From February 1 to April 1, 2020, there were no liver transplants and only 12 kidney transplants.

Screening involved testing all donors for COVID-19.

Outpatient management focused on distributing sufficient quantity of immunosuppressants to the transplant community [9••].

Europe—Denmark

National health authorities categorized transplantation as a vital surgery that should not be suspended. As a result, deceased donor kidney, liver, lung, and heart transplantations continued at all Danish centers. However, simultaneous kidney–pancreas transplantation was stopped. Organ exchange within the Scandinavian deceased donor exchange program continued. All potential deceased donors were tested for SARS-CoV-2. Already scheduled living donor transplantation was at the discretion of the transplant center (some centers cancelled and some centers continued). However, no new living donor kidney transplantations were scheduled [1••].

Outpatient management was converted to telemedicine.

Europe—the UK

Patients with acute liver failure continued to be listed and transplanted. Pediatric liver transplantation continued. All LDLTs were cancelled. All procurement activity resumed as normal.

The UK government issued guidelines for transplant patients recommending 12 weeks of self-isolation due to the high risk of COVID-19 in a particularly vulnerable population. All transplant patients had 24-h online support.

In the single-center study in London at Barts Health NHS Trust, Mohamed et al. analyzed outcomes of COVID-19 infection in renal transplant recipients. Twenty-five of the 28 patients were hospitalized, with five patients requiring intensive care unit (ICU) admission. Nine patients died. Inpatient management involved discontinuation of mycophenolate mofetil and azathioprine and increased steroid doses [3].

Outpatient management involved cancelling all regular transplant assessments, with the implementation of virtual clinics. Medications were mailed to each patient's home.

Europe—France

Living and deceased donor kidney transplantation was halted. Any transplant patient suspected of having COVID-19 infection was seen in the infectious disease unit, tested by PCR, and then allocated to a COVID-19-positive hospital. Inpatient management involved discontinuation of mycophenolate mofetil and mammalian target of rapamycin (mTOR) inhibitors. In patients with acute respiratory distress syndrome, tacrolimus was discontinued as well. Each positive patient was called daily to monitor his/her progress [1••].

In the single-center study at Saint Louis Hospital in Paris, Elias et al. described the clinical outcomes of COVID-19-positive renal transplant recipients. Sixty of the 66 patients were hospitalized, with 15 requiring ICU care. Sixteen of the patients died. Inpatient management involved discontinuation of antimetabolites and the addition of hydroxychloroquine and monoclonal antibodies (tocilizumab and eculizumab) in a few severe cases [7].

In the multi-center study in France, Calliard et al. analyzed the outcomes of solid abdominal organ recipients with COVID-19 in a larger cohort. Of the 279 patients, 243 were hospitalized, with 88 requiring ICU care. Inpatient management was similar to the Elias et al. study cohort, with the additional use of azithromycin in 71 patients, remdesivir in 2 patients, lopinavir–ritonavir in 11 patients, antifungal drugs in 6 patients, and oseltamivir in 6 patients [13].

Outpatient care was converted to telemedicine clinics with the creation of comprehensive file of 2300 follow-up patients to reach out to about care [1••].

Europe—Italy

In the multi-center study in Brescia, Italy, Bossini et al. described kidney transplant recipients infected with COVID-19. The hospitalization rate was 45 of 53 patients, with 10 requiring ICU admission. Fifteen patients died. Inpatient management consisted of adjustments to immunosuppressive medications. A reduction in steroids and CNIs occurred in the majority of patients. Antiviral medications included lopinavir–ritonavir, darunavir–ritonavir, and hydroxychloroquine [14].

In the observational study from Spedali Civili Hospital in Brescia, Italy, Alberici et al. similarly described clinical outcomes of kidney transplant recipients who tested positive for COVID-19. Out of the 20 hospitalized patients, 4 were admitted to the ICU. Inpatient management involved a discontinuation of immunosuppression in 100% of the patients and high-dose steroid initiation. Antiviral medication included hydroxychloroquine, lopinavir–ritonavir, darunavir–ritonavir, and tocilizumab [15].

Europe—Germany

Throughout Germany, living kidney donor transplant surgeries were mostly suspended, while deceased donor transplantation continued. All deceased donors were screened for COVID-19; however, the test results did not change whether the organ was transplanted [1••].

Outpatient management consisted of prolonging the period between visits and saving in-person visits only for those recently transplanted or with an urgent need. Tele- and video-medicine were instituted [1••].

Liver transplantation followed different policies than renal transplantation. High urgency children were still eligible for

both deceased and living transplantation. Deceased donor liver transplants were performed in lower urgency situations if the COVID-19 risk was low [1••].

Transport of organs across country borders remained active with only limited restrictions.

Europe—Netherlands

The largest kidney transplant center stopped all activity on March 13, 2020. All living donor transplants were suspended, even patients scheduled to undergo ABO-incompatible kidney transplantation who had been treated with alemtuzumab [1••]. The decision to stop transplantation was based on the risk of immunosuppressed patients acquiring a more severe version of COVID-19. The other six transplant centers stopped all living donor transplantation, but continued deceased donor transplantation.

Two renal transplant patients were admitted due to severe COVID-19 infection. Inpatient management consisted of not altering the maintenance immunosuppressive regimen unless life-threatening complications occurred. The liver, lung, and heart transplant programs remained active [1••].

Outpatient management consisted of postponing appointments and a conversion to consultations via telemedicine or email [1••].

Europe—Spain

Elective and living donor transplantation was suspended with only emergency life-saving transplants allowed to proceed [1••].

In the multi-center study from Spain, Crespo et al. found that 380 of the 414 COVID-19-positive renal transplant recipients required hospitalization, with 50 requiring ICU admission. Inpatient management consisted of hydroxychloroquine, azithromycin, glucocorticoids, lopinavir–ritonavir, and a small percentage received tocilizumab [16].

In another multi-center study from Spain, Crespo et al. analyzed the effect of COVID-19 in elderly transplant recipients. Fifteen of 16 patients were hospitalized with only two patients being admitted to the ICU. The mortality rate was eight out of 16 patients, with a higher frequency in more obese and frail patients and those with underlying heart disease. Additionally, it was found that patients who died had abnormal complete blood counts and inflammatory markers that reflected more anemia, lymphopenia, higher D-dimer, C-reactive protein, and IL-6 on admission. The study concluded that COVID-19 in the elderly population of kidney transplant recipients is correlated with an early and a high mortality rate. Similar inpatient management was used with discontinuation of mTOR-Is, antimetabolites, and CNIs [17].

Telemedicine was implemented to decrease the risk of COVID-19 transmission to the transplant community. Outpatient follow-up was cancelled including all non-urgent laboratory testing and procedures [1••].

Europe—Switzerland

Together, Swisstransplant and the Federal Office of Public Health coordinated a national response to the pandemic between the six transplant centers [1••]. The plan's stages were (1) stop all live donor transplantation activities; (2) stop all deceased donor pancreas and islet cell transplants; (3) stop all deceased donor kidney transplants; (4) select and tailor approach to urgent status for liver, lung, and heart transplants; (5) only urgent transplants were to be performed; and (6) stop all transplant activities [1••].

On March 22, 2020, the last stage was reached and all transplant activities were stopped due to the limited hospital resources. The only exceptions were urgent cases, such as fulminant hepatitis [1••].

Outpatient clinics were converted to telemedicine unless there was an urgent need for inpatient visit.

Oceania—Australia and New Zealand

Throughout Australia, transplantation was greatly reduced. Living donor and deceased donor kidney transplantation was stopped due to limited intensive care unit beds and personal protective equipment, and their being too great a risk for recipients on high-dose immunosuppression in times of a worldwide pandemic. Screening for transplantation required COVID-19 testing for all deceased donors [1••].

Outpatient management transitioned to telemedicine and "apps" for consultations. Laboratory tests converted to separate labs outside of the hospital [1••].

During the first wave of COVID-19 in New Zealand, deceased donor kidney transplantation continued at two of the three transplant centers. Due to the travel restrictions, living donor renal transplantation was stopped [1••].

Outpatient follow-up was transformed by the use of telemedicine and remote monitoring. Only urgent patients were seen in the clinic [1••].

Africa—South Africa

The healthcare system within South Africa has disproportionately distributed resources, with 85% of the population reliant on the state for medical care, but the resources are mostly situated in the private sector [1••]. The transplantation resources are also limited by a lack of specialty surgeons. In response to the strain on the healthcare system of South Africa, transplantation was stopped in the state sector. However, within the private sector, deceased donor transplantation continued, but was greatly limited by very few potential deceased donors [1••]. All living donation was halted.

Ethics

The COVID-19 pandemic has highlighted many ethical issues in transplantation. The purpose of this section of the paper is not to give definitive statements. We have all learned that the transplant community is very vulnerable to outside forces and necessitates more resources than the ordinary patient population. The pandemic has heightened our awareness. It is not our role to decide for individual programs what is right or wrong. It is our duty to raise some of these questions, so that we begin to think and formulate strategies with potential answers when faced with this type of problem in the future.

These are some of the ethical questions that we have had to face during the pandemic; some of which may come back even sooner than we think:

1. How do we allocate scarce resources of hospital beds including ICU beds as well as staffing? Do we curtail activity in heavily affected regions?
2. Do we not perform living donor operations in regions which are heavily affected by COVID-19? Do we not expose living donors to risks in the hospital?
3. Do we transplant high-risk or low-risk recipients?
4. Do we not transplant kidney patients, but only do liver, heart, and lung as these patients have no alternative to staying alive?
5. Do we not transplant patients who cannot quarantine properly post-transplant?
6. Do we not utilize beds for potential deceased donors as resources are needed for COVID-19 patients?
7. Do we not send teams to regions where COVID-19 is rampant and do we not accept organs from these regions?
8. Do we tell patients that our program is unwilling to take the risk and that they should look to other programs that may not be as risk averse?

These are some of the questions that we as leaders in the transplant community have to consider now and potentially in the future [18•, 19, 20].

Vaccines

Currently, there are no proven therapeutics that work against SARS-CoV-2 virus; therefore, vaccination emerged as a crucial strategy to potentially decrease the number of infections and curtail the pandemic.

Two mRNA vaccines were given Emergency Use Authorization by the US Food and Drug Administration on December 11, 2020. Two additional ones using adenovirus as the vector for the spike protein are currently in the pipeline for approval (Table 2).

Kidney transplant recipients are known to develop low antibody response to vaccination due to the fact that they are on immunosuppression. It is unclear how they will respond to the vaccine.

mRNA vaccines have been shown to stimulate CD4 and CD8, cells which are reportedly decreased in patients infected with COVID-19, particularly those who are also kidney transplant recipients. Therefore, mRNA vaccines are an attractive option for kidney transplant recipients. Evaluating their response to the vaccine is to be determined in future studies [21••, 22–24, 25•].

Global Trends in the Kidney Transplant Response

In this review, we analyzed how different transplant centers around the world responded to the COVID-19 crisis. We noticed global trends in the varied responses to the COVID-19 pandemic. We focused on looking at transplant centers' responses to transplantation policies, the inpatient management of transplant patients infected with COVID-19, and the outpatient management of transplant recipients.

Overall, we noticed a trend of transplant centers to halt all transplantation (living and deceased donor) during peak infection times to save hospital resources and protect the vulnerable patient population. The exceptions were mostly for emergent surgery, such as kidney recipients who had exhausted all access options. It was a trend for centers to close the living donor programs first and then the deceased donor programs subsequently. However, the response to deceased donor transplants varied between countries more so than the living donor programs. In some countries, deceased donor transplants continued with modified donor and recipient criteria, while in other countries, this surgery was suspended due to the high risk of COVID-19 infection.

We noticed a few therapeutic agents dominated the inpatient management of transplant recipients infected with COVID-19. In the spring of 2020, inpatient management of kidney recipients generally consisted of hydroxychloroquine and azithromycin. The therapeutic management began to broaden in the summer and fall of 2020 to additionally include remdesivir and tocilizumab for more severe cases.

Outpatient management and follow-up was largely converted to telemedicine with remote patient monitoring. It was encouraged for transplant patients to protect themselves from COVID-19 infection and to only follow-up in person if they were a very recent transplant recipient or had an urgent or emergent indication.

The global community can learn from one another especially in times of crisis. We feel this review can share the responses of different countries and help us to understand

Table 2 COVID-19 vaccinations

Company/organization name Location	Vaccine type	Antigen and immunogenicity	Vaccine efficacy	Number of doses	Storage conditions	Side effects
Biotech/Pfizer/Forsun Germany [1••, 2•]	Modified nucleoside mRNA	Spike receptor binding domain (RBD) Seroconversion with neutralizing antibodies and ELISA binding Higher response in higher dose group Neutralizing antibody increased on booster in 10 μg and 30 μg groups Similar results seen in a second study with the same construct Comparative study with alternative construct had equivalent immunogenicity	95%	2 parental injections over a 3-week period	− 80 °C	Fatigue (3.8%) Headache (2.0%)
Moderna [3] USA	mRNA	Stabilized spike 100% seroconversion by after second dose by ELISA and neutralization Increase in response from 25 to 100 μg dose, rough equivalence between 100 and 250 μg dose Antigen-specific T cells detectable, greater in 100 μg group than 25 μg	94.1%	2 parental injections over a 4-week period	− 4 °C	Fatigue (9.7%) Arthralgia (5.2%) Injection site pain (4.1%) Myalgia (8.9%) Headache (4.5%) Injection site redness (2.0%)
University of Oxford/AstraZeneca [4, 5] UK	Adenovirus vector vaccine Adenovirus: ChAdOx1nCov-19/AZD1222	Spike Seroconversion with neutralizing antibodies, (91% after one dose, 100% after two doses).	74%	2 parenteral injection over a 4-week period	− 4 °C	Neurological (transverse myelitis)
Johnson and Johnson Janssen [6] USA	Non-replicating viral vector vaccine (Adenovirus vector vaccine) Adenovirus 26	Spike Seroconversion with neutralizing antibodies	66%	1 parenteral injection	− 4 °C	Headache Myalgias Fever Pain at injection site

and manage the transplant population in the midst of pandemics.

Conclusions

COVID-19 is an important cause of morbidity and mortality in transplant recipients worldwide. Tailoring transplant activity during a pandemic with careful selection of donors and recipients is crucial for optimal patient outcomes. Given that there are no proven therapeutics against COVID-19, vaccination of transplant recipients is key to decreasing morbidity and mortality and eventually curtailing the pandemic.

Declaration

Conflict of Interest Yorg Azzi, Abigail Brooks, Hillary Yaffe, and Stuart Greenstein declare no conflict of interest.

Human and Animals Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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