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COVID-19 and Abdominal Transplant: A Stepwise Approach to Practice During Pandemic Conditions

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Background. The novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) disease has transformed innumerable aspects of medical practice, particularly in the field of transplantation. **Main body.** Here we describe a single-center approach to creating a generalizable, comprehensive, and graduated set of recommendations to respond in stepwise fashion to the challenges posed by these conditions, and the underlying principles guiding such decisions. **Conclusion.** Creation of a stepwise plan will allow transplant centers to respond in a dynamic fashion to the ongoing challenges posed by the COVID-19 pandemic.

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INTRODUCTION

The novel severe acute respiratory syndrome coronavirus disease (SARS-CoV-2) has transformed innumerable aspects of medical practice, and organ transplant programs have had to adapt to a complex and continuously changing landscape of resource constraints and risks. Though it appears the most severe first wave of the pandemic may have peaked in many countries, the future disease trajectory remains unclear. Indeed, as a result of economic and social demands, many countries are relaxing social distancing, which may result in second and third waves of the disease. As we enter into the next stages of the pandemic, transplant centers continue to have to make difficult decisions about every aspect of their transplant practices.

Each program and region is unique, with distinct considerations and challenges that encompass both general and specific considerations related to candidate waitlist size and condition, deceased donor and organ availability and quality, candidate disease severity, intraoperative and postoperative resource utilization, and local, regional, and national logistical constraints driven by disease prevalence and trajectory (Figure 1). Here we describe the strategic plan developed at a single center. While our city has been fortunate to have suffered relatively low COVID-19 prevalence to date (2866 cases and 46 deaths per million[1]), we have attempted here to create a generalizable, comprehensive, and graduated set of recommendations to respond in stepwise fashion, and to outline the principles guiding these decisions – hoping this may facilitate decision-making more broadly.

Summary of the Current State

The initial focus of each program must be to understand the local disease prevalence and trajectory, and seek guidance from local and national healthcare services. Transplant centers must also regularly adjust plans to remain in alignment with the greater community goals. During the peak of disease prevalence, voluntary reduction, and even complete cessation of all transplant activity may be required to help reallocate resources to ongoing efforts to care for COVID-19 patients. However, on either side of this peak, and particularly in a recovery period characterized by unknown and unpredictable risks of recurrence, these decisions will inherently be more nuanced.

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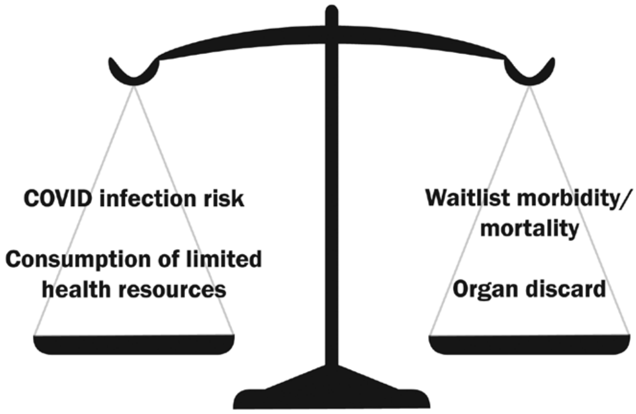

FIGURE 1. Scales of decision making during COVID-19 pandemic. Illustration of the main concepts being considered by transplant centers during the COVID-19 pandemic.

Solid-organ transplantation has been classified by many health systems as a lifesaving intervention, but comes with significant costs and risks—both to the individual who requires immunosuppression and to the health systems under strain from the pandemic. Despite this broad classification, there are clear differences in urgency among the waitlisted candidates. Moreover, the intensity of peritransplant immunosuppression, and the complexity of posttransplant recovery, varies by organ and patient, adding additional dimensions of dynamic risk. Therefore, transplant centers have a responsibility to consider the conduct of each clinical program during current and future phases of the pandemic. Transplant activity is also inherently dependent on donor organ availability. With many hospitals and intensive care units (ICUs) having been or likely to become overwhelmed, shifting priorities may deemphasize donor identification and management and result in lower numbers of deceased donors.

The strategies used at our institution for each organ are outlined below and are intended to provide scaled guidance for prioritizing and managing transplant decisions during the various phases of the COVID-19 pandemic (Figure 2). We address waitlist active status, waitlist risk-stratification workup, organ selection, transplant implications, and immunosuppression management. These critical decisions must be based on the pandemic trajectory and resource availability,[2] which may inherently be difficult to predict. Resource availability must take into account the availability of ICU beds, ventilators, blood products, and personal protective equipment (PPE). Thus, the following considerations should be stratified according to local disease prevalence and health system capacity, as might be applied in the setting of mild, moderate, severe, or critical resource deprivation (Figures 2 and 3).

Organ-specific Considerations

We first examined our current data on waitlist mortality and resource utilization to help identify specific at-risk individuals and groups in whom transplantation may still be beneficial despite the current risks. We have consolidated our best-practice considerations in an organ-specific fashion later.

Liver

Resource Utilization on Waitlist

Dependent on model for end-stage liver disease (MELD) score and local resource availability, workup of outpatients may decrease, with a shift toward more inpatient workup (Table 1).

Waitlist Data

Decisions regarding the deceased-donor liver program in a state of emergency are complex, due to the high morbidity and mortality associated with end-stage liver disease and the resource-intensive nature of liver transplantation. During this pandemic, centers may consider an approach of staged deactivation/reactivation based on local COVID-19 prevalence and resource availability. During critical periods, this may even require cessation of all transplant activity (Figures 2 and 3).

Many pathologic processes confer MELD exception points, with hepatocellular carcinoma (HCC) being the most common. During critical periods in COVID-19 disease prevalence, MELD exception patients should not be prioritized, as their overall survival is favorable compared with natural MELD counterparts. During less constrained periods, however, clinical characteristics can be used to

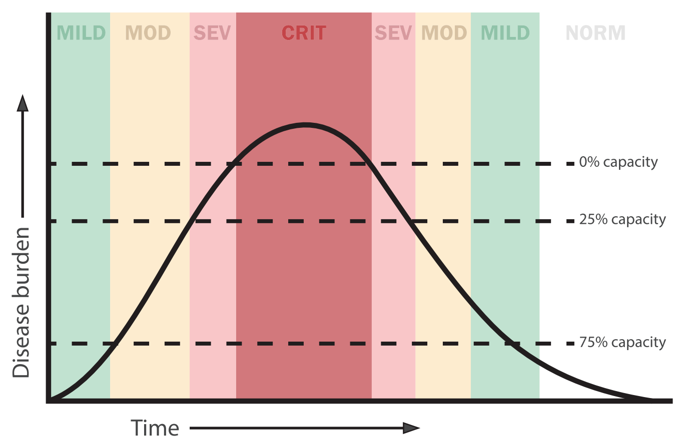

FIGURE 2. Pandemic disease burden schematic curve. Schematic of the COVID-19 disease burden curve illustrates the dynamic nature of resource availability during the pandemic. Mild, moderate, and severe resource depravity will likely guide transplant centers regarding programmatic function. During the peak disease burden and concomitant critical resource availability, most, if not all transplant activity will likely be suspended.

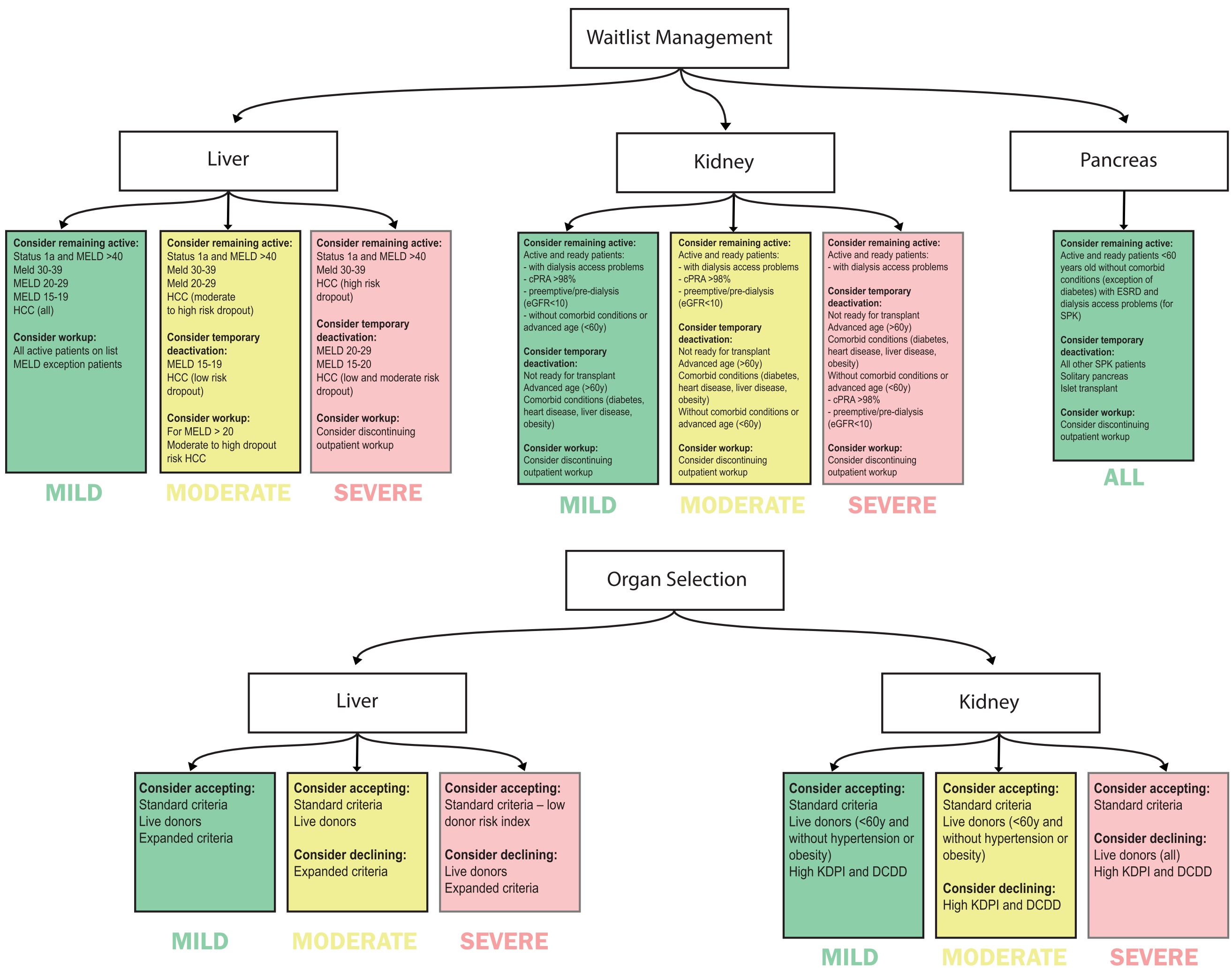

FIGURE 3. Waitlist and organ selection decision tree. This organ-specific decision tree documents considerations transplant center may make in waitlist management and organ selection depending on severity of resource availability.

identify those patients at highest risk of waitlist dropout and will aid centers identifying those candidates with greatest need. Lower-risk HCC candidates more tolerant of locoregional therapies might be managed without transplant. Consideration should be given to a staged deactivation/reactivation of HCC patients based on their waitlist dropout risk.

Organ and Donor Selection

Perioperative outcomes and the complexity of postoperative recovery are predicted by organ quality and recipient MELD score. Expanded-criteria livers include donors after circulatory determination of death, with steatosis (>30% large-droplet fat), with advanced age, or partial grafts—and each type of graft has differing risks of reperfusion syndrome and subsequent complications. These can manifest at the time of surgery with profound hemodynamic instability and coagulopathy, requiring significant blood products and prolonging OR time. In the posttransplant period, the increased incidence of early allograft dysfunction and acute kidney injury may necessitate additional interventions. These factors can result in increased postoperative ventilator and CVVHD use, longer ICU stays, reoperation, and blood product requirement. As such, acceptance of such organs should be taken with caution.

Live liver donors also need to be risk-stratified based on local disease prevalence. Indeed, with the increasing availability of real-time reverse transcription-polymerase chain reaction (RT-PCR) COVID assays, testing of all transplant patients on admission and before procedures has become the standard of care.[2] Again, local sensitivity and specificity of the assay should also be considered. Our practice is to test all live donors before donation. Additionally, we request both our donors and recipients shelter in place before testing and up until the time of surgery. Healthcare provisions such a minimizing team size, sequestration of transplant patients into designated COVID-free wards, appropriate PPE and hand hygiene practices, are essential to reduce the risk of nosocomial transmission. These factors should be reassessed at regular intervals, as more data becomes available to evaluate the safety of the live donor programs.

Organ Recovery

Our procurement team normally travels for organ recovery. However, to reduce surgeon travel and potential exposure to COVID-19, our use of local recovery teams has increased substantially.

TABLE 1.

Summary of resource utilization on the transplant waitlist, intraoperatively, and in the posttransplant settings

Organ	Liver	Kidney	Pancreas
Resource utilization on the waitlist (monitoring and risk stratification)	Clinical laboratory (all) Cardiology—echo and catheterization Radiology—MRI and CT Hepatology—endoscopy Health maintenance—PAP, mammogram	Clinical laboratory Cardiology—echo and catheterization (often) Radiology—CT Health maintenance—PAP, mammogram, endoscopy	Clinical laboratory Cardiology—echo and catheterization (all) Radiology—CT Health maintenance—PAP, mammogram, endoscopy
Resource utilization in the operating room	Organ recovery—UCSF Staffing—1 attending and 1 fellow (live donor transplant requires 2 ORs in parallel, with double the number of staff) OR time (with back table)—7.5 (6.7–8.6) h Intraoperative blood product MELD score >20 median of 5 (1–8) units of PRBCs MELD score <20 it is 2 (0–4) units of PRBCs	Organ recovery—local Staffing—1 attending, 1 fellow or resident OR time (with back table)—3–4 h Expected EBL—50–300 cc	Organ recovery—UCSF Staffing—1–2 attendings, 1 fellow, and 1 resident OR time (with back table [SPK])—6–8 h Expected EBL—200–400 cc
Resource utilization posttransplant	ICU—2.2 (1.3–3.4) d median ICU ventilator—43% of LT Average LOS—5–14 d Consultations—IR, GI/ERCP nephrology (12% postoperative dialysis frequency) 30-d readmissions—often	ICU—0 d ICU ventilator—0 d Average LOS—3–4 d Consultations—30% continue dialysis 30-d readmissions—less common	ICU—1–2 d ICU ventilator—0 d Average LOS—5–10 d Consultations—IR 30-d readmissions—often

MELD, model for end-stage liver disease; MRI, magnetic resonance imaging; SPK, simultaneous pancreas-kidney.

Kidney

Waitlist Data

Kidney transplant remains an essential, lifesaving intervention, which already distributes a very limited resource to a large number of people in need. Currently, at our center 1.2%, 2.7%, and 3.8% of our waitlisted kidney candidates die within 6, 12, and 18 months, respectively. Furthermore, dialysis centers, similar to care homes, are congregant settings, which exposes patients to significant risk of COVID-19 community transmission.

Survival on the kidney waitlist for those on dialysis is entirely dependent on the ability of these patients to maintain reliable dialysis access. Waitlisted patients with refractory dialysis access problems are a particularly high-risk population and should remain active as long as resources permit.

Preemptive kidney transplant has been associated with superior graft and patient survival. In those patients nearing dialysis (eGFR < 10), preemptive transplant will also reduce the need for additional resources and risks by avoiding dialysis. Kidney transplant may confer significant advantages in this population and facilitate social distancing, thus consideration should be given to prioritizing these patients.

Patients with higher percentage calculated panel-reactive antibody (% cPRA) have decreased overall access to organs and represent a particularly vulnerable group. For candidates with cPRA >99%, the number of potential donors needed to find an acceptable match increases exponentially[3]. With this in mind, keeping patients with a cPRA >99% listed and active may be indicated where possible. Although highly sensitized recipients will require more aggressive immunosuppression, the rare opportunity to receive a compatible transplant may outweigh the increased risks associated with more aggressive immunosuppression.

Prior literature has shown patients with advanced age and diabetes to be at the highest risk for waitlist mortality, but these patients often receive high-KDPI kidneys, which are likely more resource intensive and have a greater risk of delayed graft function (DGF). Further, advanced age[4] and comorbid conditions including diabetes[5], end-stage renal disease, and obesity have also been associated with more severe SARS-CoV-2 and higher risk of death. Hence, patients in this cohort may be considered for temporary deactivation.

Resource Utilization on Waitlist

Consideration should be given to temporarily deactivating patients not cleared for surgery, as they are unlikely to complete workup during a state of emergency (Table 1). In addition, those on the "ready" list should be reviewed carefully to identify candidates with medical or social issues which would make management during the COVID-19 pandemic difficult—being mindful to avoid biasing selection against those patients in vulnerable populations.

Organ and Donor Selection

DGF following kidney transplantation has become common at most transplant centers. Though DGF is managed regularly in the postoperative period with acceptable outcomes, during a state of emergency these additional risks need to be carefully evaluated. Resumption of dialysis postkidney transplant exposes a newly immunosuppressed patient to their dialysis centers. In addition, for those patients on peritoneal dialysis (PD), DGF may be more problematic and resource-intensive, as they require new hemodialysis access and placement in a new dialysis center. The PD catheter may also be left in place and used postoperatively if needed, though this has variable efficacy. Acceptance of kidneys with a high risk of DGF, especially in those patients on PD, should be carefully considered.

Live kidney donation also needs to be adjusted based on local disease prevalence. Live kidney transplants should be conducted in those recipients whose benefit from transplant outweighs the current infectious risk both to themselves and the donor. COVID-19 RT-PCR assays on all live donors and recipients is imperative during the pandemic. Further, advanced-age (>60 y) living kidney donors with comorbid conditions such as medication-controlled hypertension have risk factors for severe SARS-CoV-2 and should be considered for deferral. There is anecdotal data that obesity may be a risk factor for a more severe COVID-19 disease course, and until this is further been defined, consideration should be given to also deferring such donations (body mass index >30).

Immunosuppressive Risk

Highly sensitized patients and those at risk of DGF receive lymphocyte-depleting induction, and the majority of kidney transplant recipients receive calcineurin inhibitors and mycophenolate maintenance. All patients receive high-dose steroids in the peritransplant period. Overall, there is insufficient data to understand the risk of SARS-CoV-2 in immunosuppressed patients. Hence continuing standard postoperative immunosuppression protocols is our current practice.

Costimulation blockade agents such as Belatacept is used in many countries. Although the immune response to COVID-19 in patients on Belatacept and calcineurin inhibitors is unknown, the inhibition of T-cell activation may have a potentially beneficial effect by downregulating the cytokine release syndrome in coronavirus infection. For patients beyond 1-year posttransplant who encounter difficulties receiving their routine monthly infusions, extending the interval between therapies by 2 weeks may be acceptable, as the terminal half-life of Belatacept is 6–8 days, and adequate levels persist for up to 8 weeks.

The use of *de novo* Belatacept should be considered with caution. Lymphocyte-depleting agents are typically used for induction therapy in Belatacept-based regimens despite the patients' minimal sensitization, and the long-lasting and irreversible effects of these agents shortly after transplant may put these patients at unnecessarily increased risk during the pandemic.

Pancreas

Pancreas transplantation is by nature resource intensive, requiring postoperative ICU recovery, relatively common postoperative complications, and frequent readmissions and interactions with the healthcare system. Hence, pancreas transplant during pandemic conditions should be reserved for simultaneous pancreas-kidney transplant patients with end-stage renal disease and imminent risk of losing dialysis access. Due to the increased resources required for pancreas transplantation, the program was put on hold during the ascending slope of COVID-19 incidence curve.

Immunosuppressive Risk

All pancreas transplant patients receive lymphocyte-depleting induction, with calcineurin inhibitors and mycophenolate maintenance. All patients also receive high-dose steroids in the peritransplant period.

ADDITIONAL CONSIDERATIONS

COVID-19 Testing of Donors and Recipients

Currently, deceased-donor prerecovery COVID-19 RT-PCR testing is recommended and conducted by most organ procurement organizations. Bronchoalveolar lavage samples have been shown to be the most reliable, especially in those patients with clinical and radiographic features of COVID-19, but does carry a risk of aerosolization. Therefore, nasopharyngeal swab collection may be more practical. Insufficient data are available regarding the viral transmission and the use of abdominal organs from COVID-19-positive donors; hence, this practice is not currently recommended.

Recipient RT-PCR assays for COVID-19 should be done in all recipients immediately before transplant and has rapidly become the standard of care. This practice depends on a number of factors, including test availability, processing time, sensitivity and specificity, and regional COVID-19 prevalence. Testing can add additional logistical hurdles, and assay turnaround times must be factored into logistics and timing of any transplant. However, given the lack of current data of COVID-19 in the peritransplant period, transplantation in COVID-19-positive recipients is not recommended. In the absence of available real-time RT-PCR testing, robust clinical (fever, cough, anosmia, dysgeusia) and contact history is essential and should be taken before consideration of any transplant, however, due to the prevalence of asymptomatic disease with COVID-19, this approach should be used with caution. Careful clinical and contact history of anticipated caregivers should also be performed and caregivers asked to sequester when possible.

Reduction of Nosocomial Transmission

The risk of nosocomial infection remains an active concern. Early data suggest that this risk may be low, particularly when appropriate infection control measures are strictly implemented.[6,7] In an attempt to reduce nosocomial disease transmission to transplant recipients, efforts must be made to reduce contact with COVID-19-infected patients, or providers caring for them. Creation of "COVID-19-free areas" (hospital buildings, ICUs and wards, with dedicated staff) can significantly reduce transplant patients' exposure to those with COVID-19. With increasing availability of testing at our institution, all patients being admitted to the hospital are tested by RT-PCR, so their status is known before or on admission, and those with confirmed disease are preferentially cared for at a dedicated COVID site. In addition, creation of smaller teams can help reduce risk of infectious transmission between providers. Of course, continued use of PPE and hand hygiene is essential to reduce nosocomial spread in the peritransplant period.

Transplant Staff Management and Activity

Social distancing has forced transplant programs to rapidly transform many of their standard practices. The majority of the workforce has been asked to function remotely, and communication between staff and transplant center leadership is critical in this rapidly evolving state. Regular "town hall" style transplant meetings are imperative to be sure all members have a forum to voice medical, personal, and logistical concerns. Staff redeployment may also be necessary to help facilitate shifting departmental focuses, such as telemedicine. Transplant centers need to work closely with institutional information technology departments to assure appropriate hardware, software, and encryption measures are being distributed to staff members working remotely. In addition, while activities such as preparing patients for the ready list have been down-scaled, some staff might be redirected to focus on preparing systems to rapidly identify and work up patients once transplant activity increases.

Transplant centers should also be mindful of staff wellbeing and anxieties and stresses during this time. Institutional-led resources for wellbeing, stress management, childcare, and leave policies should be discussed and shared on a regular basis. Strict implementation of PPE policies and procedures are critical to safeguard those serving in clinical areas.

Regional Transplant Collaboration, and Clarity in Communication

A collaborative approach will need to be taken between centers to protect vulnerable populations of patients with end-organ disease and complex posttransplant care. Creating a collaborative group of regional centers allows for appropriate patient diversion in surge situations and for appropriate access to transplant and posttransplant care. During such uncertain times, the maintenance of public trust and patient confidence is tantamount. Each center has the responsibility not just to itself and its own patients, but also to the transplant community as a whole, to clearly communicate with and inform patients of programmatic changes being made, and the implications on their waitlist status. It behooves centers to maintain similar open lines of communication with their regional and national partner institutions. Furthermore, patient informed consent must be modified to include additional risk benefit discussion of receiving a transplant during a pandemic.

Resumption of Transplant Activity

As we consider, plan for, and implement such curtailment and resumption of activity, we must also recognize that the need for transplantation is only increasing. On an annual basis, the number of solid-organ transplants being performed continues to grow. While it is clear that transplant centers must take pause to evaluate the current situation, the demand for transplant during this time will not decrease. In addition, reductions in organ donation may occur during this time; this combination of factors risks a significant increase to the size of the waitlist and a concomitant increase in waitlist mortality. Transplant centers thus have a clear responsibility to maintain and resume transplant operations as soon and as safely possible.

CONCLUSION

The COVID-19 pandemic has already caused unprecedented global morbidity and mortality. The duration and long-lasting implications of the disease are still unknown. Transplant-related strategic healthcare planning is critical to safeguard transplant recipients and live donors during this pandemic, while remaining cognizant of the real risk of waitlist morbidity and mortality. Global distribution of COVID-19 disease is evolving and yet to be fully determined, and variations in population behaviors and public health interventions will likely result in highly variable disease kinetics and impact. As such, each of these difficult decisions will inherently be personalized to the time and location and to the existing and expected conditions.

These principles reflect our own efforts to organize and systematize our reasoning to most responsibly protect those recipients who can wait, facilitate transplant in those with acute need, protect limited healthcare resources, and continue to be both advocates for our own transplant patient populations and responsible members of the larger medical community. We hope they might provide a useful framework for similar decision-making processes across a range of contexts and facilitate responsible decisions in these difficult times.

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