

World Journal of *Transplantation*

World J Transplant 2020 September 18; 10(9): 223-276



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ABOUT COVER

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INDEXING/ABSTRACTING

The WJT is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Li-Li Wang; Production Department Director: Yun-Xiaojian Wu; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Transplantation

ISSN

ISSN 2220-3230 (online)

LAUNCH DATE

December 24, 2011

FREQUENCY

Irregular

EDITORS-IN-CHIEF

Maurizio Salvadori, Sami Akbulut, Vassilios Papalois

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3230/editorialboard.htm>

PUBLICATION DATE

September 18, 2020

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<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Practical recommendations for kidney transplantation in the COVID-19 pandemic

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Author contributions: Imam A and Tzukert K have contributed equally to the paper and share the first authorship; Elhalel MD and Khalaileh A equal contribution; Imam A, Khalaileh A and Merhav H contributed to the research idea and study design; Imam A, Imam R, Elhalel MD, Abu-Gazala S, Merhav H and Abel R contributed to the data acquisition; Khalaileh A, Elhalel MD and Merhav H contributed to the supervision or mentorship; all the authors contributed to the manuscript writing and editing.

Conflict-of-interest statement: There are no declared conflicts of interest of any of the authors of this manuscript which could lead to bias and there were no external funding sources used for this work.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external

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Abstract

Kidney transplantation at the time of a global viral pandemic has become challenging in many aspects. Firstly, we must reassess deceased donor safety (for the recipient) especially in communities with a relatively high incidence of coronavirus disease 19 (COVID-19). With respect to elective live donors, if one decides to do them at all, similar considerations must be made that may impose undue hardship on the donor. Recipient selection is also problematic since there is clear evidence of a much higher morbidity and mortality from COVID-19 for patients older than 60 and those with comorbidities such as hypertension, diabetes, obesity and lung disease. Unfortunately, many, if not most of dialysis patients fit that mold. We may and indeed must reassess our allocation policies, but this must be done based on data rather than conjecture. Follow-up routines must be re-engineered to minimize patient travel and exposure. Reliance on technology and telemedicine is paramount. Making this technology available to patients is extremely important. Modifying or changing immunosuppression protocols is controversial and not based on clinical studies. Nevertheless, we should reassess the need for induction therapy across the board for ordinary patients and the more liberal use of mammalian target of rapamycin inhibitors in transplant patients with proven infection.

Key Words: COVID-19; Kidney transplantation; Organ donation; Coronavirus; SARS-CoV2

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Manuscript source: Unsolicited manuscript

Received: May 11, 2020

Peer-review started: May 11, 2020

First decision: May 20, 2020

Revised: May 23, 2020

Accepted: August 24, 2020

Article in press: August 24, 2020

Published online: September 18, 2020

P-Reviewer: Cantarovich F, Fukushima N, Montemurro N

S-Editor: Yan JP

L-Editor: Webster JR

P-Editor: Wang LL



Core Tip: Transplantation in areas with a high rate of the coronavirus disease 19 (COVID-19) infection may be risky for recipients, as there may be a risk of COVID-19 transmission from infected donors. All preventive measures should be taken while treating kidney transplant patients.

Citation: Imam A, Tzukert K, Merhav H, Imam R, Abu-Gazala S, Abel R, Elhalel MD, Khalaileh A. Practical recommendations for kidney transplantation in the COVID-19 pandemic. *World J Transplant* 2020; 10(9): 223-229

URL: <https://www.wjgnet.com/2220-3230/full/v10/i9/223.htm>

DOI: <https://dx.doi.org/10.5500/wjt.v10.i9.223>

INTRODUCTION

Kidney transplantation (KT) is the treatment of choice for end-stage kidney disease^[1]. The progress in immunosuppression along with the advances in surgical techniques has led to an improvement in transplantation outcomes. However, the increased risk of infection in immunocompromised patients can negatively affect the results of transplantation. The appearance of the new coronavirus disease 2019 (COVID-19), which is highly infectious and carries a high mortality risk, presents significant challenges to transplantation in general, to KT in particular and to living donor KT specifically.

COVID-19 is caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV2)^[2]. COVID-19 was confirmed following several severe cases of pneumonia in the city of Wuhan in China in December 2019^[3], and shortly thereafter, this disease spread worldwide^[4] affecting more than 1.5 million people with more than 110 thousand deaths^[5]. In Israel, the first diagnosed case of COVID-19 was announced on February 21, 2020. Since then, more than 11000 cases have been confirmed of which 110 died^[6]. As reported elsewhere, COVID-19-related mortality is far more prevalent in older patients and those with comorbidities^[7].

During the SARS epidemic in 2003 and the Middle East respiratory syndrome (MERS) in 2018, there was no increased mortality among immunocompromised patients^[8,9]. Conversely, in the current COVID-19 pandemic, several reports have demonstrated the severity of this disease among immunocompromised transplanted patients^[10,11].

Under the current circumstances, there are clear obstacles and challenges that almost all transplant centers in the world encounter due to the lack of evidence-based medicine regarding kidney transplant management in this setting. In this report, we highlight our local measures and guidelines that were adopted by the KT unit at Hadassah – Hebrew University Medical Center in Jerusalem, Israel.

DECEASED DONORS

We expected the number of organs from deceased donors to decrease during the pandemic, as a result of the extreme load on the intensive care units causing care to be diverted from brain dead potential donors. Also, at times of societal stress, the tendency to donate organs goes down and lastly due to the social distancing there are far less road accidents and brain injuries. Surprisingly, our center was only minimally affected regarding deceased donors during this period.

The risk of transmission of COVID-19 by a deceased donor is not yet known, but we believe that there is a possibility of viral transmission, since it was reported that there is a 15% chance of isolating the virus from blood^[12]. Moreover, some pathological changes were reported in organs other than the lungs in COVID-19 patients^[13].

In order to minimize the previously mentioned potential hazards, whether they are from the donor, the recipient or the team, we adopted the recommendations of the National Transplantation Steering Committee for consideration of a potential deceased kidney donor. These criteria include: (1) The donor must have a negative nasopharyngeal swab for COVID-19; (2) The donor should have no history of traveling abroad in the last 14 days and no exposure to a proven COVID-19 patient; (3) Every potential donor with diagnosed pneumonia should test negative for COVID-19, if no test can be performed the donor is rejected; (4) A donor that was treated by a medical

team that took care of proven COVID-19 patients should be rejected; and (5) In the case of a donor with cardiac death (DCD), if there is insufficient time to gather all this information, the donor should be rejected. By accumulating knowledge on COVID-19 disease, we believe the following additional factors should be considered: (1) The presence of upper respiratory symptoms or fever; (2) Lymphopenia; (3) Chest computed tomography (CT) scan with findings that can be attributed to COVID-19 infection; and (4) High suspicion of COVID-19 infection, based on epidemiologic and clinical signs, even if COVID-19 polymerase chain reaction (PCR) is negative. We also apply the same criteria for liver donors.

The importance of performing a chest CT scan and considering lymphopenia for every potential donor stems from the report published by Guan *et al*^[14] who demonstrated that in a large cohort of 1099 COVID-19 patients, 96% of the patients had specific abnormal findings in the lungs, and 82.1% had lymphopenia.

Regarding the 5th recommendation of the steering committee for a DCD donor, we recommend that the technique of machine perfusion should be utilized. This can provide a relatively safe environment for the kidneys and even enhance their performance while allowing additional time for missing data to be acquired. The application of these strict criteria on potential deceased kidney donors should decrease the risk of infection for both the transplant team and future recipients.

LIVING DONORS

Transplantation from living donors brings additional considerations. These are elective, pre-scheduled carefully planned transplantations^[15]. Thus, stringent safety criteria must be implemented in order to protect the donor, the recipient and the team.

We believe that donors must undergo a period of 14 d isolation prior to transplantation. This may prove to be an undue and indeed unbearable burden for some donors and is to be explained at length during medical and psychosocial evaluation. Of note, PCR tests still show significant percentages of false negative results, and antibody detection assays are not yet commonly available.

The recent outbreak resulted in the Ministry of Health and transplantation centers temporarily withholding all living-related transplantation activities. This will eventually lead to an increased number of patients on dialysis treatment, with its prognostic and financial implications.

KIDNEY TRANSPLANT RECIPIENTS

In Israel, there are more than 857 patients on the waiting list. All of which are treated by dialysis, nevertheless, this number does not include patients who may need preemptive kidney transplant. In 2019, a total of 411 KT were performed in Israel, 248 from living donors and 163 from deceased donors^[16].

In order to minimize the damage from the decreased number of donations, every effort should be made to stratify the patients who may be able to benefit from a kidney transplant in this pandemic era.

In Israel, we have implemented an old for old allocation policy for many years with great success. However, in these times, when it is clear that COVID-19 infection severity and mortality increase with age and comorbidities^[7,17] we may need to reconsider this policy. Our present approach is that older recipients (> 65 years) should be informed of their inherent greater risk and if they decline the offer it should be rerouted to a younger patient. Although there is presently no data to make any projection or firm recommendation, we believe that due to the pandemic a reassessment of allocation policies in order to maximize safety and reduce mortality, morbidity and graft loss may be required.

Finally, according to the recommendations that were published on March 20, 2020 by the European Dialysis Working Group of ERA-EDTA, dialysis patients should be instructed to stay away from crowds whenever possible, to use individual means of transportation, to use protective measures in order to conserve their hygiene, and even to avoid personal contact with family members^[18]. We suggest that these recommendations should be applied to kidney transplant recipients during and after hospitalization.

POST-OPERATIVE FOLLOW-UP

The clinical course following KT is fraught with complications in the best of cases. In order to minimize this, patients are advised to adhere to a strict follow-up routine. COVID-19 may expose these patients to added hazards when traveling and visiting medical clinics. As a result, we suggest tailoring an individual follow-up strategy that balances the risks with the needed intensity of visits for each patient. The plethora of technology devices and applications allowing effective telemedicine should be used as much as possible. However, patients who lack smart phones or computers with internet access may present a problem. In Israel this is almost universally due to religious prohibition and can be dealt with in an ad hoc manner. In places where economic considerations prevent patients from accessing technology, reach-out should be made to insurers, providers and charitable institutions to step into the gap. Telemedicine will assume an important future role in the care of these patients. Particular emphasis should be placed on strict adherence to the government's instructions regarding social isolation, hygiene habits and awareness of the signs and symptoms related to COVID-19. This means that patients arriving at clinics must have N95 masks and wear gloves. This personal protective equipment should be prescribed and delivered to transplant patients.

IMMUNOSUPPRESSION

Intuitively, one would tend to decrease immunosuppression in the face of a viral pandemic. We do not have any information as to whether that will benefit patients and the consequences are almost surely increased rates of rejection, increased immunosuppression, infection and graft loss. Thymoglobulin, a T cell depleting agent, is routinely used as an induction treatment. It has been linked to an increased rate of viral infections such as CMV, HSV and BK and to viral-related complications *e.g.*, post-transplant lymphoproliferative disorder^[19]. Thus, it makes sense to speculate that it will increase the rate and the severity of COVID-19 infections. Its advantage is that it decreases the rate of rejection and allows the use of lower CNI levels. If the recipient is of higher immunological risk, the importance of thymoglobulin induction rises. Therefore, should we avoid thymoglobulin and move to non-depleting regimens, *e.g.*, Basiliximab (CD25R antagonist) or avoid induction at all? This will increase the risk of acute rejection, and if rejection occurs this could result in a whole anti-rejection treatment protocol accumulating to a much larger dose of immunosuppression. The issue of induction therapy for all needs to be examined and perhaps there is logic in using induction for higher immunological risk recipients. Nevertheless, at this time, due to lack of evidence-based reports, we believe institutions should continue their induction practices as before.

Corticosteroids have a major role in all anti-rejection protocols. In our institution, high dose methylprednisolone is given with induction with rapid tapering off down to 40 mg/day on day 6. Routinely, we do not use steroid-avoidance or steroid withdrawal protocols. Should one move to steroid-avoidance protocols now? No decrease in CMV infection rate was found when steroid avoidance or withdrawal protocols were compared to steroid maintenance protocols^[20], and data regarding BK nephritis rates are conflicting. When investigating the previous, SARS-COVID experience, the Chinese reported advantageous outcomes when combining high dose steroids with hydroxychloroquine^[21] and recently, a favorable outcome was suggested when steroids were used in the context of a cytokine storm^[17,22]. However, studies in animal models indicated that long-term use of steroids facilitates viral replication^[23]. According to existing (or non-existing evidence-based data), we believe that we should continue using the current steroid protocol that we practice and are familiar with, as no clear evidence proves that avoiding steroids would be of any benefit.

Anti-metabolites, mainly mycophenolate, are used in most maintenance protocols, depleting and interfering with both B and T lymphocytes functions. MPA was shown to inhibit viral replication of 4 different coronaviruses (not including COVID-19) in cell culture^[24]. Unfortunately, animal models indicated that MPA worsened disease activity in both common marmosets (significantly higher mortality)^[25] and Balb/c mice^[26]. MPA together with interferon- β was associated with survival in one clinical report of MER-CoV patients. However, this was significant only in univariate analysis and the greater predictor of survival was disease severity at presentation^[27]. Taken together, and in agreement with our common practice during viral infections such as CMV, EBV or HSV, we tend to lower mycophenolate dose and even to hold it. In the case of the

few transplant patients we treated for COVID19 infection, who presented with leukopenia, we stopped mycophenolate. We plan to re-start mycophenolate when 2 consecutive COVID 19 PCR tests are negative.

The calcineurin inhibitors, cyclosporine and tacrolimus are the mainstay of immunosuppression regimens for solid organ transplantation, affecting T cell activation and function. Although there is no doubt regarding their efficacy, calcineurin inhibitors were linked to an increased rate of viral infections. Mammalian target of rapamycin (mTOR) inhibitors were suggested to be beneficial regarding viral infections (refs for BK, HPV viral verrucae). Should we convert the treatment protocol from CNIs to de-novo mTOR inhibitors? Should we use low dose CNI protocols together with low dose mTOR inhibitors? FK binding protein (FKBP) binds the coronavirus non-structural protein (NSP-1), thus explaining the mode of action of Tacrolimus inhibition of human coronavirus replication in cell culture^[28]. However, no data are available on CNI effectiveness in inhibiting disease progression in animal models or humans.

MTOR inhibitors were shown to inhibit MERS-CoV replication *in vitro*^[29]. Another work based on network drug repurposing suggested Sirolimus as a potential treatment for coronavirus infection^[30]. Taken together, it is still unclear if CNI should be avoided or minimized, but in low immunological risk patients, mTOR inhibitors-based protocols along with low dose CNI are a reasonable possibility.

In summary, choosing immunosuppressive protocols during the COVID-19 pandemic is challenging. This is true for induction and treatment for newly transplanted patients as well as for maintenance treatment and for infected transplanted patients. Literature is scarce and mostly inconclusive. One should probably use well practiced protocols, avoid over-immunosuppression as much as possible, and minimize it in stable patients. Infected patients should probably be evaluated for severity of symptoms and signs, and if mild, holding the anti-metabolites is acceptable. If moderate or severe, it is possible to hold CNIs, but continue, or even increase the steroids dose.

Contrary to the logic in decreasing immunosuppression during a pandemic, it is important to remember, that at these times ambulatory patients are more difficult to follow. Patients tend to refrain from arriving at the hospital for routine tests, even to outpatient clinics, and community clinics are overloaded. Downgrading the levels of immunosuppression will demand a very tight follow-up protocol that will enable detection of rejections at the earliest time.

MEDICAL STAFF SAFETY

The novel coronavirus has been threatening not only the lives of medical professionals, but also their mental health. This outbreak has caused enormous distress in many health workers who particularly deal with coronavirus patients. This is mainly explained by the various stressful situations including work overload, isolation and relentless fear of infecting patients and family and shortage of medical equipment in some cases^[31,32]. In addition to this, the transplantation team is primarily exposed to distress and anxiety due to their stressful work, and this makes the pandemic even more severe. Moreover, it was reported that a number of medical health providers had committed suicide during this pandemic. These facts have caused a serious burden on health systems worldwide.

CONCLUSION

Measurements have been adopted by some governments including creating a telephone line for psychiatric consultations and mental health support to fight depression, suicidal attempts and other psychiatric issues.

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