Clinical Practice Guideline for Solid Organ Donation and Transplantation During the COVID-19 Pandemic

Supplemental Material

Contents

Search Strategy and Results

A comprehensive search was designed and executed between June 18-21, 2020 with text words and controlled vocabulary terms combining concepts for COVID-19/SARS-CoV-2 and organ transplantation. An updated search in all sources, (except medRxiv and bioRxiv preprint and Chinese translations of COVID-19 journal articles from Lanzhou University's Evidence-Based Medicine Center given the maturity of the evidence at the time of the updates) was executed between August 22-28, 2020 and again between Jan 9-10, 2021. Multiple electronic databases were searched for references published since 2019 without language or publication type limits. Search results were managed, and duplicates removed in EndNote X9 (Clarivate). The complete search strategies are explicated below.

Search sources:

- MEDLINE Ovid (1946 to June 18, August 24, 2020 and then Jan 8, 2021), searched June 19, August 25, 2020 and Jan 9, 2021;
- Embase Ovid (1947 to June 18, August 24, 2020 and then Jan 8, 2021), searched June 19, August 25, 2020 and Jan 9, 2021;
- Cochrane COVID-19 Study Register (https://covid-19.cochrane.org/), searched June 19, August 25, 2020 and Jan 9, 2021;
- WHO COVID-19 Global literature on coronavirus disease
- (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/), searched June 19, August 28, 2020 and Jan 9, 2021;
- Science Citation Index (1900 to June 18, August 25, 2020 and then Jan 8, 2021) Web of Science, searched June 19, August 25, 2020 and Jan 9, 2021;
- medRxiv and bioRxiv preprint server Cold Spring Harbor Laboratory, BMJ, Yale (https://www.medrxiv.org/; https://www.biorxiv.org/; current up to August 22 2020, searched August 22, 2020;
- Chinese translations of COVID-19 journal articles from Lanzhou University's Evidence-Based Medicine Center (current up to August 22, 2020), searched August 25, 2020;
- Google Scholar (https://scholar.google.com/), searched August 25, 2020 and Jan 10, 2021;
- NHS Blood and Transplant (https://www.nhsbt.nhs.uk/news/coronavirus-update/), searched August 28, 2020 and Jan 10, 2021

Search summary:

Source	June Baseline Results (unique)	August Update Results (unique)	Jan. (2021) Update Results (unique)	June and Jan. (2021) Results (unique)
MEDLINE	261	222	422	905
Embase	81	64	239	384
Cochrane COVID-19 Study Register	52	38	79	169

WHO COVID-19 Global literature on coronavirus disease	95	47	164	306
Science Citation Index	5	11	23	39
medRxiv & bioRxiv preprints	8	3	Not searched	11
Lanzhou Translations	7	10	Not searched	17
Google Scholar	26	63	0	89
NHS Blood and Transplant	1	3	6	10
Total:	536	461	933	1930

Search results:

6784 references were retrieved by the search, 1930 once duplicates were removed. A minimum of two screeners reviewed all the citations.

Search details for initial search:

Database: Ovid MEDLINE(R) ALL 1946 to August 24, 2020
Date search conducted: August 25, 2020
Search title: COVID-19_LSR_All-Groups_Stage1
Strategy:

1 Coronavirus Infections/ (23326)
2 COVID-19.rs. (18799)
3 severe acute respiratory syndrome coronavirus 2.os. (15848)
4 2019 nCoV.tw,kf. (1072)
5 2019nCoV.tw,kf. (6)
6 2019-novel CoV.tw,kf. (6)
7 (coronavirus* or corona virus*).tw,kf. (30068)
8 COVID 19.mp. (42072)
9 COVID19.tw,kf. (520)
10 COVID 2019.tw,kf. (143)
11 nCov 2019.tw,kf. (55)
12 nCov 19.tw,kf. (22)
13 ("SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2").mp. (14080)
14 ("SARS coronavirus 2" or "SARS-like coronavirus" or "Severe Acute Respiratory Syndrome Coronavirus-2").mp. (18551)
15 or/1-14 [Set 1: COVID-19] (58492)
16 Heart Transplantation/ (34346)
17 Kidney Transplantation/ (95475)
18 Liver Transplantation/ (56553)
19 Lung Transplantation/ (15176)
20 Organ Transplantation/ (13043)
21 Pancreas Transplantation/ (7440)
22 Transplantation/ (8933)

23 ((allograft$1 or donor$1 or graft$1 or recipient$1 or transplant*) adj2 (cardiac or heart$1 or heart-lung or hepatic or intestin$ or kidney$1 or kidney-pancreas or liver$1 or lung$1 or lung-heart or multiorgan or multi-organ or organ$1 or pancreas or pancreas-kidney or renal)).tw,kf. (242421)
24 (transplant* not (cell* or faecal* or fecal*)).ti. (202419)
25 or/16-24 [Set 2: Organ Transplantation] (341369)
26 and/15,25 [Sets 1 & 2] (550)
27 limit 26 to yr="2019-Current" (510)
28 remove duplicates from 27 (507)

Database: Ovid Embase Classic+Embase 1947 to 2020 August 24
Date search conducted: August 25, 2020
Search title: COVID-19_LSR_All-Groups_Stage1_2
Strategy:
1 exp coronavirus/ (18077)
2 coronavirus infections/ (495)
3 2019 nCoV.tw,kw. (1020)
4 2019nCoV.tw,kw. (6)
5 2019-novel CoV.tw,kw. (5)
6 (coronavirus* or corona virus*).tw,kw. (30813)
7 COVID 19.af. (41549)
8 COVID19.tw,kw. (545)
9 COVID 2019.tw,kw. (142)
10 nCov 2019.tw,kw. (33)
11 nCov 19.tw,kw. (23)
12 ("SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2").af. (13514)
13 ("SARS coronavirus 2" or "SARS-like coronavirus" or "Severe Acute Respiratory Syndrome Coronavirus-2").af. (13627)
14 or/1-13 [Set 1: COVID-19] (64359)
15 exp heart transplantation/ (68336)
16 exp kidney transplantation/ (163098)
17 exp liver transplantation/ (118863)
18 exp lung transplantation/ (36877)
19 organ transplantation/ (37017)
20 exp pancreas transplantation/ (20791)
21 spleen transplantation/ (668)
22 transplantation/ (180193)
23 ((allograft$1 or donor$1 or graft$1 or recipient$1 or transplant*) adj2 (cardiac or heart$1 or heart-lung or hepatic or intestin$ or kidney$1 or kidney-pancreas or liver$1 or lung$1 or lung-heart or multiorgan or multi-organ or organ$1 or pancreas or pancreas-kidney or renal)).tw,kw. (386397)
24 (transplant* not (cell* or faecal* or fecal*)).ti. (293878)
25 or/15-24 [Set 2: Organ Transplantation] (639455)
26 and/14,25 [Sets 1 & 2] (780)
27 limit 26 to yr="2019-Current" (654)
28 remove duplicates from 27 (618)

Database: Cochrane COVID-19 Study Register
URL: https://covid-19.cochrane.org/ (searched via the Cochrane Register of Studies: https://crsweb.cochrane.org/)

Date search conducted: August 25, 2020
Strategy:
1. ((allograft* or donor* or graft* or recipient* or transplant*) AND (cardiac* or heart* or hepatic* or intestin* or kidney* or liver* or lung* or multiorgan* or organ* or pancreas* or renal*)):TI,AB (329)
2. (transplant* not (cell* or faecal* or fecal* or microbiota*)):TI (230)
3. #1 OR #2 (338)
Database: WHO COVID-19 Global literature on coronavirus disease
URL: https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/
Date search conducted: August 28, 2020
Strategy:
transplant$ (in: Title, abstract, subject) (n=752)
Filter: Database filter – references from Medline are removed
Results: 148

Note: Content: The WHO Global COVID-19 Health literature database contains primarily research articles (published AND/OR pre-publication) journal articles. Major indexing databases, PubMed, Web of Science, Global Index Medicus, Embase as well as major health publishers' websites are searched Monday to Friday (excluding WHO Headquarter Official Holidays). The database is updated at 19:00 (Geneva local time). A working document of the search strategies is available upon request (email: library@who.int). In addition, Lanzhou University submits on a daily-basis citations from CNKI as well as a number of Chinese journal publishers.

Database: Science Citation Index (1900 to 25 August 2020); Web of Science Clarivate
URL: https://webofknowledge.com
Date search conducted: August 25, 2020
Strategy:

# 6	328	#5 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2019-2020*
# 5	33,163	#4 OR #3 OR #2 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2019-2020*
# 4	2,681	TS=((cadaver* OR dead OR "heart beating" OR live OR living OR "non heart beating") NEAR/5 donor*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2019-2020*
# 3	19,893	TI=(transplant* NOT (fecal OR faecal OR cell*)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2019-2020*
# 2	29,490	TS=((allograft* or donor* or graft* or recipient* or transplant*) NEAR/5 (cardiac* or heart* or hepatic* or intestin* or kidney* or liver* or lung* or multiorgan* or organ* or pancreas* or renal*)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2019-2020*
# 1	29,946	TS=("coronavirus infection*" OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" OR "2019 ncov" OR "2019ncov" OR "2019-novel Cov" OR coronavirus* OR "corona virus*" OR "covid 19" OR covid19 OR "covid 2019" OR "ncov 2019" OR "ncov 19" OR "sars-covs-2" OR "sars-cov2" OR "sarscov-2" OR "SARS coronavirus 2" OR "Sars-like coronavirus") *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2019-2020*

Database: medRxiv and bioRxiv preprint servers Cold Spring Harbor Laboratory, BMJ, Yale (https://www.medrxiv.org/; https://www.biorxiv.org/)
Note: COVID-19/SARS-CoV-2 results from medRxiv & bioRxiv identified by the Stephen B. Thacker CDC Library, exported results current to August 22, 2020 and searched via EndNote
URL: https://www.cdc.gov/library/researchguides/2019novelcoronavirus/researcharticles.html
Date search conducted: August 22, 2020
Strategy:
Keyword used was 'transplant' (any field)
Results: 7

Database: Chinese translations of COVID-19 journal articles from Lanzhou University's Evidence-Based Medicine Center
Date search conducted: August 25, 2020
Note: COVID-19/SARS-CoV-2 Chinese translations identified by research project of Campbell UK & Ireland; translations provided by Evidence-Based Medicine Center Lanzhou University; 4046 translations current up to August 22, 2020 and searched via EndNote
Strategy: Keywords used: transplant, donation, donor, immuno*, allograft, graft, recipient (194; kept 17)

Source: Google Scholar
URL: https://scholar.google.com/
Date search conducted: August 25, 2020
Software: Publish or Perish
Strategy:
"covid-19" transplant (880)
The 880 were filtered using the keywords “transplant” and “immuno*” (798)

Source: NHS Blood and Transplant
URL:https://www.nhsbt.nhs.uk/news/coronavirus-update/ ; https://www.odt.nhs.uk/covid-19-advice-for-clinicians/
Date search conducted: August 28, 2020
Strategy: Manual search of the COVID-19 section of the NHSBT website.
Results: 4

Screening of Patients who are Potential Deceased Organ Donors

1. Transplantation from potential organ donors positive for COVID-19

PICO Question:

In adult and pediatric potential deceased organ donors, what are the outcomes of transplanting organs from COVID-19 negative donors compared to transplanting organs from COVID-19 positive donors?

Reviewers:

L. Hornby, M. Ibrahim, R. Mainra

Literature Search:

Citations Screened: 1900 Citations Included: 6

Recommendations:

1.1 We recommend against transplantation of solid organs retrieved from deceased donors with active COVID-19 infection, particularly in the case of lung transplantation (strong recommendation, very low certainty of evidence).

1.2 We suggest proceeding with transplantation of solid organs retrieved from living and deceased donors with a resolved COVID-19 infection (weak recommendation, low certainty of evidence).

Recommendation 1.1

Key Literature and Rationale:

The recommendation to avoid transplantation from donors with active COVID-19 is based on direct evidence of transmission in the case of lung transplantation[1,2] and laboratory evidence of plausible transmission from other organs[3]. In one study in addition to the recipient, the thoracic surgeon involved in the transplant procedure also tested positive for COVID-19.[1] The recipient in that study died 61 days following transplantation with active COVID-19 playing a key role in their death.

It is very clear that lung tissue is the primary target of the COVID-19 virus. However, COVID-19 viral particles have been found in other organ systems including ocular, kidney, liver, heart, bowel and pancreas[3]. While this review did not describe direct evidence that viral transmission could occur through non-pulmonary transplantation, it did not entirely rule out biologically plausible mechanisms of such transmission.

Based on the evidence and preference to preserve recipient safety, we recommend against the use of all organs from a COVID-19 positive donor for the purpose of transplantation. This recommendation is predominantly based on values and preferences along with consideration of cost utilizations. The panel strongly valued prevention of COVID-19 transmission, both to recipients and health care professionals. The panel also noted that recipients who develop COVID-19 in the post-transplant period would be at high risk to consume significant health care resources, including possible need for re-transplantation if

immunosuppression is stopped or altered. Thus, despite the lack of direct evidence, the panel agreed that there is more potential for harm as compared to benefits gained from proceeding with transplantation of an organ procured from a positive donor.

Recommendation 1.2

Key Literature and Rationale:

Another important clinical scenario is the safety of organ donation from a previously positive and currently asymptomatic COVID-19 donor. We found four published reports of previously positive COVID-19 donors (n= 6 deceased donors; 32 living donors)[4-7] who proceeded to donation following resolution of their infection and testing COVID-19 negative. Successful recovery and transplantation were reported to be between 4 weeks after symptom resolution to 14 weeks following the initial infection. Donors were COVID-19 negative at time of organ donation. There were no reports of transmission to healthcare workers and none of the recipients developed active COVID-19 infection at the last follow-up. At the last follow-up the graft and patient survival was 99%. One recipient of a liver transplant died from multi-system organ failure unrelated to COVID-19[7]. Therefore, the panel felt that the values and preferences of patients may vary considerably. Upon understanding the risks and uncertainty, some may be willing to accept such marginal donors, whereas others may not. The panel also acknowledge the uncertainty around the time at which organ donation is safe following COVID-19 infection. Published reports describe successful transplantation from living donors at least 28 days following COVID-19 infection, and 14 weeks in deceased donors.

Some transplant programs have defined criteria to determine when previously infected patients should be considered safe to become actual donors[8] The above data support our weak recommendation that patients with resolved COVID-19 can safely be considered as donors. However, it is important to note that our process did not include a search regarding the optimal laboratory methods or time frames to wait prior to determining a previously infected patient eligible and safe for organ donation. We therefore make no recommendations on how or when to consider a COVID-19 infection resolved. Considering the complexity of these decisions, it would be preferable to consult transplant focused infectious disease specialists when available prior to organ recovery from previously COVID-19 positive patients. Each case should be carefully evaluated and, considering the complexity of these decisions, it would be preferable to consult transplant focused infectious disease specialists prior to organ recovery from previously COVID-19 positive patients.

At the time of reviewing this evidence, the panel did not observe any relevant sub-group of patients for whom the recommendations may differ. Therefore, the recommendations are thus far applicable to all potential deceased donors.

This recommendation is currently broad across all donor and organ types and patient subgroups therefore there should be no issues regarding implementation.

Knowledge Gaps/Research Considerations:

More research is needed to ascertain safety guidelines regarding donation from deceased and living donors following recovery of COVID-19. Considerations include:

- How to define ‘recovery’ from COVID-19 in terms of both symptoms and screening tools
- Timing from recovery to donation

- Which recipients would be most suitable for use of these organs (e.g. recipient with previous COVID-19 or following vaccination)
- If different criteria should apply to different organ groups.

Outcomes of recipients who either accidentally or deliberately received organs from actively COVID-19 positive donors.

Further understanding of biologic mechanisms that would either support or refute the possibility of transmission of SARS-CoV-2 from non-pulmonary transplanted organs.

References:

1. Kaul DR, Valesano AL, Petrie JG, et al. Donor To Recipient Transmission Of SARS-CoV-2 By Lung Transplantation Despite Negative Donor Upper Respiratory Tract Testing. Am J Transplant 2021.
2. Kumar D, Humar A, Keshavjee S, Cypel M. A call to routinely test lower respiratory tract samples for SARS-CoV-2 in lung donors. Am J Transplant 2021.
3. Gaussen A, Hornby L, Rockl G, et al. Evidence of SARS-CoV-2 Infection in Cells, Tissues and Organs and the Risk of Transmission Through Transplantation. Transplantation 9000;Online First.
4. Ceulemans LJ, Van Slambrouck J, De Leyn P, et al. Successful double-lung transplantation from a donor previously infected with SARS-CoV-2. Lancet Respir Med 2021;9:315-8.
5. Hong HL, Kim SH, Choi DL, Kwon HH. A case of coronavirus disease 2019-infected liver transplant donor. Am J Transplant 2020;20:2938-41.
6. Kute VB, Godara S, Guleria S, et al. Is it Safe to Be Transplanted From Living Donors Who Recovered From COVID-19? Experience of 31 Kidney Transplants in a Multicenter Cohort Study From India. Transplantation 2021;105:842-50.
7. Neidlinger NA, Smith JA, D'Alessandro AM, et al. Organ recovery from deceased donors with prior COVID-19: A case series. Transpl Infect Dis 2020:e13503.
8. Dominguez-Gil B, Fernandez-Ruiz M, Hernandez D, et al. Organ Donation and Transplantation During the COVID-19 Pandemic: A Summary of the Spanish Experience. Transplantation 2021;105:29-36.

Evidence Profile:

Population: Adult and pediatric solid organ transplant recipients
Intervention: Transplanting organs from COVID-19 positive donors
Comparator: Transplanting organs from COVID-19 negative donors

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Transplanting organs from COVID-19 negative donors	Transplanting organs from COVID-19 positive donors		
COVID+ Recipient	Based on data from 41 patients in 6 studies[1] Follow up 10-162 days	All studies were in adults. Two separate case reports of a deceased donors with asymptomatic COVID-19 (both had negative NP, no lower respiratory testing done, no evidence on CT) resulted in confirmed transmission to 2 lung recipients and 1 thoracic surgeon. In addition to the lung, two kidneys and the liver from one of the donors were transplanted with no evidence of COVID transmission. Two deceased donor studies (1 case report of DCD donor and 1 case series of 6 NDD donors) and 2 living donor studies (1 case report from living liver donor, 1 observational study n=31 of living kidney donors). No control groups. Deceased donors all presumed to have had resolved COVID (time from symptom onset to donation 14 weeks- 4 months; n=5 and unknown n=2. N=1 Living donor was COVID+ test 3 days POST Tx; and n=31, all were at least 28 days after complete symptom resolution. All cases in deceased and living donors were considered mild; 22 of living donors were asymptomatic. None of the organ recipients of organs from deceased donors (n=12; 1 double lung, 5 liver, 3 double kidney and 3 heart) nor recipients of organs from living donors (n=32; 1 liver and 31 kidney) developed COVID early post Tx. Only 1 living donor appeared to have active COVID-19 at the time of transplant. We are uncertain whether transplanted organs from COVID-19 positive donors results in transmission of COVID-19 to organ recipients.		**Very Low** Due to serious risk of bias, Due to serious imprecision[2]	Transplanting lungs from donors with active (asymptomatic) COVID-19, increases the risk of recipients developing COVID-19. We are uncertain whether transplanting other organ types from COVID-19 positive donors increases the risk of COVID-19 in transplant recipients. We are also uncertain whether transplanting organs from donors with resolved COVID-19 increases or decreases the risk of recipients developing COVID-19.
Short Term Graft Outcomes	Based on data from 41 patients in 6 studies[3] Follow up 10-162 days	Same studies as those included above for transmission outcome. One recipient of lungs from donor with active COVID-19 had multi-system organ failure requiring prolonged mechanical ventilation and circulatory support and the other lung recipient remained on mechanical ventilation on day 25 with evidence of bilateral airspace disease. 2/3 other recipients are alive and well with no evidence of transmission. One kidney recipient died due to a myocardial infarction with no evidence of COVID-19. Other studies report minor post-Tx complications but none related to COVID-19. No graft failures reported. In series of n=31 recipients of living kidney donors, acute cellular rejections were observed in 2 (6.4%).		**Very Low** Due to serious risk of bias, Due to serious imprecision[4]	Transplanting lungs from donors with active (asymptomatic) COVID-19, appears to result in worse short-term graft outcomes in recipients but we are uncertain whether this impacts short term graft outcomes for other organ types. We are also uncertain whether transplanting organs from donors with resolved COVID-19 impacts short term

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Transplanting organs from COVID-19 negative donors	Transplanting organs from COVID-19 positive donors		
					graft outcomes in organ recipients.
Short Term Patient Outcomes	Based on data from 41 patients in 6 studies[5] Follow up 10-162 days	Same studies as those included above for transmission outcome. Recipient of lungs from 1 donor with active COVID-19 died PTD 61 the other lung recipient was alive on day 25. 2/3 other recipients are alive and well with no evidence of transmission. One kidney recipient died due to a myocardial infarction with no evidence of COVID-19 For other studies, 1 death was reported among all recipients. Death was not related to COVID-19 but reported as MSOF in liver transplant recipient from case series of 6 NDD donors; 100% survival of recipients of organs from living donors. Also 100% survival of living donors.		**Very Low** Due to serious risk of bias, Due to serious imprecision[6]	Transplanting lungs from donors with active (asymptomatic) COVID-19, appears to result in worse short-term patient outcomes in recipients but we are uncertain whether this impacts short term patient outcomes for other organ types. We are also uncertain whether transplanting organs from donors with resolved COVID-19 impacts short term patient outcomes in organ recipients.

1. Primary study Supporting references [36]. [52]. [37]. [35]. [38]. [51].
2. **Risk of bias: Serious.** Observational case series with poor design. No comparative study design.; **Imprecision: Serious.** 4 studies with very few patients. ;
3. Primary study Supporting references [37]. [36]. [35]. [51]. [52]. [38].
4. **Risk of bias: Serious.** Observational case series with poor design. No comparative study design.; **Imprecision: Serious.** Four studies with very few patients. ;
5. Primary study Supporting references [51]. [35]. [52]. [36]. [37]. [38].
6. **Risk of bias: Serious.** Observational case series with poor design. No comparative study design.; **Imprecision: Serious.** Four studies with very few patients;

References:

[35] Ceulemans LJ, Van Slambrouck J, De Leyn P, Decaluwé H, Van Veer H, Depypere L, Ceuterick V, Verleden SE, Vanstapel A, Desmet S, Maes P, Van Ranst M, Lormans P, Meyfroidt G, Neyrinck AP, Vanaudenaerde BM, Van Wijngaerden E, Bos S, Godinas L, Carmeliet P, Verleden GM, Van Raemdonck DE, Vos R : Successful double-lung transplantation from a donor previously infected with SARS-CoV-2. The Lancet. Respiratory medicine 2020;

[36] Neidlinger NA, Smith JA, D'Alessandro AM, Roe D, Taber TE, Pereira MR, Friedman AL : Organ recovery from deceased donors with prior COVID-19: A case series. Transplant infectious disease : an official journal of the Transplantation Society 2020; e13503

[37] Hong H-L, Kim S-H, Choi DL, Kwon HH : A case of coronavirus disease 2019-infected liver transplant donor. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2020;20(10):2938-2941

[38] Kute VB, Godara S, Guleria S, Ray DS, Aziz F, Hegde U, Sharma A, Nayak KS, Siddini V, Sarkar P, Thukral S, Mondal RRS, Goswami J, Patel HV, Abraham M A, Pathak V, Anandh U, Jha PK, Bavikar S, Bonu RS, Gulati S, B T AK, Yadav DK : Is it Safe to Be Transplanted From Living Donors Who Recovered From COVID-19? Experience of 31 Kidney Transplants in a Multicenter Cohort Study From India. Transplantation 2020;Publish Ahead of Print

[51] Kaul DR, Valesano AL, Petrie JG, Sagana R, Lyu D, Lin J, Stoneman E, Smith LM, Lephart P, Lauring AS : Donor To Recipient Transmission Of SARS-CoV-2 By Lung Transplantation Despite Negative Donor Upper Respiratory Tract Testing. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2021;

[52] Kumar D, Humar A, Keshavjee S, Cypel M : A call to routinely test lower respiratory tract samples for SARS-CoV-2 in lung donors. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2021;

2. PCR methods and repeat testing for diagnosis of COVID-19 in potential deceased organ donors

PICO Questions:

In adult and pediatric patients who are potential deceased organ donors, what is (are) the optimal method(s) of testing/screening for COVID-19?

In adult and pediatric patients who are potential deceased organ donors, does repeat PCR testing impact the sensitivity and specificity of COVID-19 detection compared to single PCR testing?

Reviewers:

S. Belga, L. Hornby, T. Shaver, I. Thomas, M. Weiss

Literature Search:

Citations Screened: 1900 Citations Included: 20

Recommendations:

2.1 We recommend PCR testing of *all patients who are potential deceased organ donors (strong recommendation, low certainty of evidence).*
2.2 We recommend both upper and lower PCR testing of all patients who are potential deceased organ donors within 24 hours of organ recovery (strong recommendation, low certainty of evidence).
2.3 We suggest against repeat PCR testing from the same collection site of patients who are potential donors (weak recommendation, low certainty of evidence).

Good Practice Statements:

Lower respiratory samples be collected by methods that produce the least risk of aerosol generation.

Screening of patients who are potential donors and recipients should include pre-recovery or pre-transplant evaluation for COVID-19 risk factors such as absence of symptoms, risk of potential exposure, and travel history.

Key Literature and Rationale:

Evidence from four systematic reviews[1-4] suggested that PCR was the preferred laboratory screening test for SARS-CoV-2. Our certainty in this evidence was reduced due to indirectness (most patients were not mechanically ventilated in an ICU setting) and risk of bias due to inconsistency of testing methods (variation in anatomic sampling sites, different assays, etc). Although these reviews do report on positive and negative predictive values, it should be noted that such measures are influenced by the prevalence of COVID-19 in the community, which needs to be considered when interpreting PCR results.

We identified 15 studies[5-19] directly assessing the accuracy of PCR testing in organ donation. Our certainty in this evidence was very low, due to serious risk of bias, serious indirectness, and serious

imprecision. The studies consisted of case series and small cohorts, where patients who were potential organ donors and tested positive for SARS-CoV-2 infection were excluded from organ donation. The majority of included patients were deceased donors, though three studies included living donors as well. These protocols included substantial heterogenicity regarding the site of sample collection, use of other screening tests (e.g. routine thoracic CT), and laboratory procedures used to process PCR samples. Of the 15 retained references, only three reported on the number of patients who were screened with PCR testing with 6/306 patients testing positive for SARS-CoV-2[7,11]. Among the 15 references that described PCR screening protocols, there were no reports of donor derived transmission of SARS-CoV-2 to recipients.

PCR remains the gold standard for SARS-CoV-2 detection in a clinical setting, and we therefore strongly recommend that all patients who are potential organ donors undergo PCR screening to evaluate the active presence of SARS-CoV-2 virus.

While PCR is recommended for all potential organ donors, emerging evidence suggests that anatomic collection site is of critical importance. A recent report described a case of donor-derived SARS-CoV-2 infection in a lung transplant recipient[20]. The infected donor tested negative from an upper respiratory tract specimen, but BAL fluid collected from the donor at the time of lung recovery was retrospectively analyzed after confirmation of SARS-CoV-2 in the recipient. This analysis confirmed SARS-CoV-2 in the lower respiratory tract specimen of the donor at the time of recovery. The recipient died following COVID-19 complications and the implanting transplant surgeon also became SARS-CoV-2 positive. In addition to this direct evidence, indirect evidence from one systematic review analyzing different donor screening sites[3] also suggests that lower respiratory tract samples had improved diagnostic accuracy compared to naso- or oropharyngeal samples.

While these data suggest that lower respiratory samples are preferable, some caveats remain. We continue to recommend collection of upper respiratory samples in the form of nasopharyngeal swabs in order to exclude the possibility of a recent infection not yet detectable in lower respiratory secretions. While there is no evidence of this possibility, this recommendation is consistent with the strong values and preference of the panel to avoid possible transmission, along with the reality that PCR testing is now readily available at low cost in most ICU settings. Also, while we recommend lower respiratory samples from all patients who are potential donors, the evidence does not suggest superiority of one sampling technique over another. Thus, we recommend that samples be collected by methods that produce the least risk of aerosol generation (e.g. endotracheal aspirate as opposed to BAL), consistent with the strong value and preferences of the panel for protecting health care workers from potential harm. Finally, the collection of upper and lower samples in the 24 hours prior to organ recovery should be done **in addition** to any other routine screening that was done for infection surveillance during the patient's ICU admission.

We recognize that local limitations to lab facilities or assays may limit the capacity of a system to perform PCR testing within 24 hours of recovery. In those settings, we encourage collection of PCR samples as closely as possible to the scheduled recovery in order to limit the potential of interim acquisition of SARS-CoV-2.

All studies included were from adult populations. While there may be clinical differences between adults and children in the donor or recipient responses to COVID-19 or screening protocols in the pediatric populations, the current data does not suggest specific recommendations for children as opposed to adults.

The assurance of internally reliable and externally validated assays is important for infection prevention strategies. Since the recommended molecular test is associated with clinical nuances, sample extraction therefore requires scrupulous technique, and subsequent testing requires careful interpretation and implementation within the context of local practices.

Knowledge Gaps/Research Considerations:

An important knowledge gap within the donation and transplantation community is the lack of reliable and accurate markers for viral infectiousness that would ideally allow us to confidently establish viral clearance from deceased donors in a timely manner. Additionally, it is important to understand when, if ever, it would be safe to utilize organs from recovered COVID-19 deceased donors that remain persistently PCR positive. Also, research addressing the potential differences in SARS-CoV-2 transmissibility between lung and non-lung solid organ transplantation is urgently needed.

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Evidence Profiles:

Population: Adult and pediatric deceased organ donors
Intervention: Screening for COVID-19 using RT-PCR
Comparator: Not Screening for COVID-19

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Not Screening for COVID-19	RT-PCR Screening for COVID-19	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
PCR Testing Accuracy - Indirect	Based on data from 11615 patients in 35 studies[1]	We found indirect evidence regarding accuracy of using RT-PCR testing for screening of donors from a Rapid SR (Jarrom, 16 studies primarily in-hospital of those with known or suspected COVID-19). Pooled Sensitivity of RT-PCR test was 87.8% (95% CI 81.5-92.2%). Estimated positive predictive values depended on the prevalence of COVID-19 in the population with a low of 43.7% at prevalence of 1% and high of 98.3% at prevalence of 39%. Estimated negative predictive values were 93.4% at prevalence of 39% and 99.9% at prevalence of 1%. For studies that were outside of China reported values ranged from PPV of 43.7%-96.4% of 96.8%-99.9%. RT-PCR testing should be used for donor screening with the following considerations: Conclusion of Jarrom SR was that the likely prevalence in the tested population should be a key consideration for decision-makers when interpreting test results and deciding on testing strategies. Despite finding of a high NPV for RT-PCR, uncertainty may remain with a negative test result, especially in the context of high clinical suspicion, and the possibility of a false-negative result also needs to be considered.		**Low** Due to serious risk of bias and serious inconsistency[2]	PCR-Testing should be used for screening for COVID-19
PCR Testing Accuracy - Direct	Based on data from patients in 15 studies[3]	No studies were found that specifically address this PICO but we found a total of 15 studies (retrospective cohorts or case series) that reported on COVID screening tests for deceased donors; 3 of these studies also included some living donors. The screening protocols described in these studies were heterogenous but most included a questionnaire along with RT-PCR testing and CT scan. The type of sample (upper vs lower respiratory) used in PCR testing also varied between studies with the most common sample type being NP but many studies used OP or BAL. The majority of studies did not report any repeat RT-PCR testing of deceased donors. Of these 15 studies, only 3 reported on the total number of potential donors that were screened (Antonio, n= 50; Dominguez-Gill, n=58; Boyarsky, n=190). Of the 306 potential donors in these 3 studies, screening identified 6 potential donors as COVID+ and these donors were not actualized. 10/15 studies (including the 3 mentioned above) reported on the total number of donors screened		**Very Low** Due to very serious risk of bias, Due to serious indirectness, Due to serious imprecision[4]	RT-PCR testing should be used to screen donors for COVID-19.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Not Screening for COVID-19	 RT-PCR Screening for COVID-19	Certainty of the Evidence (Quality of evidence)	Plain text summary
		(n=404), identifying 8 donors as COVID+, 1 indeterminate, 5 cases were screening results were not reported.The total number of recipients of organs from the deceased donors included in the 15 studies was 562; 11 of which were pediatric. The most common organs transplanted were liver and kidney but recipients of hearts, lung, pancreas and small bowel were included. Transplant recipients were screened using RT-PCR testing (usually NP) pre and post transplant. A total of 12 recipients from 15 studies were reported to be COVID+ post transplant. None of these infections were linked to donor transmission.			

1. Systematic review Supporting references [110]. [109].
2. **Risk of bias: Serious.** High or unknown or unclear ROB for majority of included studies ; **Inconsistency: Serious.** Un-explained heterogeneity as reported by Kim et al (a previous systematic review, included in the systematic review by Jerome et al.) ;
3. Primary study Supporting references [5]. [85]. [48]. [46]. [111]. [41]. [81]. [43]. [45]. [49]. [40]. [44]. [50]. [42]. [47].
4. **Risk of bias: Very Serious.** Selective outcome reporting; **Indirectness: Serious.** Direct comparisons not available; **Imprecision: Serious.** Low number of patients;

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Population: Adult and pediatric deceased organ donors
Intervention: COVID-19 screening from the lower respiratory tract
Comparator: COVID-19 screening from the upper respiratory tract

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
		COVID-19 screening from the upper respiratory tract	COVID-19 screening from the lower respiratory tract		
Accuracy of PCR Testing - Indirect	Based on data from 755 patients in 11 studies[1]	We found indirect evidence regarding sampling site for RT-PCR testing for donor screening in 1 SR that compared 3 sites: Oropharyngeal (1083 swabs), estimated percentage of positive tests were 75% (95% CI: 60–88%) between days 0–7, 35% (95% CI: 27–43%) between days 8–14 and 12% (95% CI: 2–25%) after 14 days from symptom onset; Nasopharyngeal (1299 swabs), estimated percentage positive was 80% (95% CI: 66–91%), 59% (95% CI: 53–64%) and 36% (95% CI: 18–57%) at 0–7 days, 8–14 days and > 14 days after symptom onset, respectively; Sputum (1060 samples), estimated percentage positive was 98% (95% CI: 89–100%), 69% (95% CI: 57–80%), and 46% (95% CI: 23–70%) at 0–7 days, 8–14 days, and > 14 days after symptom onset, respectively. The results support sputum sampling as a valuable method of COVID-19 diagnosis and monitoring, and highlight the importance of early testing after symptom onset to increase the rates of COVID-19 diagnosis. For every time period, sputum had the highest percentage of positive results while oropharyngeal swabs had the lowest. With respect to deceased donor screening, these findings support lower respiratory tract sampling as opposed to as opposed to upper respiratory tract (NP swabs).		**High**	Covid-19 screening from the lower respiratory tract improves accuracy of PCR testing

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		COVID-19 screening from the upper respiratory tract	COVID-19 screening from the lower respiratory tract		
Accuracy of PCR Testing -Direct	Based on data from 2 patients in 2 studies[2] Follow up 25 days and 61 days	Two case reports of deceased donors that were screened for COVID-19 and thought to be negative but was positive. The donors had no clinical history or findings suggestive of infection with SARS-CoV-2 and both tested negative by reverse transcriptase polymerase chain reaction (RT-PCR) on a nasopharyngeal (NP) swab obtained within 48 hours of procurement. Lower respiratory tract testing was not performed. CT scan was normal. Two lung recipients and a thoracic surgeon both had confirmed cases of transmission from the donors. Two kidney recipients and 1 liver recipient had no evidence of COVID transmission.		**Very Low** Due to very serious risk of bias, Due to very serious imprecision[3]	Covid-19 screening from the lower respiratory tract of deceased donors improves accuracy of PCR testing

1. Systematic review Supporting references [108].
2. Primary study Supporting references [52]. [51].
3. **Risk of bias: Very Serious. Imprecision: Very Serious.**

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Population: Adult and pediatric deceased organ donors
Intervention: Repeat PCR testing for COVID-19
Comparator: No repeat PCR testing for COVID-19

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		No repeat PCR testing for COVID-19	Repeat PCR testing for COVID-19		
PCR Repeat Testing Accuracy	Based on data from 0 patients in 0 studies	We were unable to find any studies that reported on usefulness of repeat PCR testing as part of potential donor screening			No evidence was found to support need for repeat testing.

3. CT scan accuracy for diagnosis of COVID-19 in potential deceased organ donors

PICO Question:

In pediatric and adult patients who are potential organ donors, does application of screening thoracic computed tomography (CT) scans in all patients who are potential donors impact the sensitivity and specificity of COVID-19 detection compared to routine CT scans for clinical indication?

Reviewers:

G. Hardman, L. Hornby, M. Weiss

Literature Search:

Citations Screened: 1900 Citations Included: 7

Recommendations:

3.1 We recommend against routine thoracic computed tomography (CT) scans for COVID-19 screening for potential deceased organ donors (strong recommendation, low certainty evidence).

3.2 We suggest that the results of PCR testing supersede any contradictory information from available thoracic computed tomography (CT) scan results (weak recommendation, moderate certainty evidence).

Key Literature and Rationale:

The panel considered 6 studies[1-6] from the donation and transplantation population, and 1 systematic review[7] of indirect evidence (general population). The systematic review, based on data from 8014 patients and 31 studies, suggests that the addition of thoracic CT scan, to screen for COVID-19 in any patient population, *may* improve diagnostic accuracy. In all of these settings, the specificity and negative predictive value (NPV) was significantly lower than its sensitivity and positive predictive value, raising the possibility of false positive CT scans. However, our certainty in the evidence is low, due to the very serious risk of bias and the serious indirectness of the evidence.

We included 6 studies[1-6] (case series or cohort studies) with direct evidence from the donation and transplantation population. These describe the use of thoracic CT scan within protocols of donor screening, as either routine practice or when 'clinically indicated'. All donors in each of these studies were screened using a combination of methods that also included epidemiological screening by questionnaire and PCR testing. None of the 6 studies contained evidence that directly compared the inclusion or exclusion of CT scans from a screening protocol. The number of donors screened was only reported in 4/6 studies[1,3-5] and totaled 55 patients. Four patients who were potential donors were described as positive for COVID-19 as reported in 3/6 studies[1,3,5], none of whom became actual donors. All four patients tested positive by PCR testing; none were excluded solely based on CT scan results. The specific impact of routine thoracic CT donor screening results on decision making, was not explicitly described.

Potential recipient or post-transplant data were reported from a total of 144 patients (including adult and pediatric recipients) in 6 studies[1-6]. One study reported 5/32 patients testing positive by PCR, prior

to transplant, who did not proceed[5]. One study reported 1/16 post-transplant liver recipient testing positive for COVID-19 and developing mild symptoms[3]. This infection was thought to have been acquired post-transplantation and not judged to be donor derived. Again, the impact of thoracic CT scan result on the decision to proceed with transplantation, or the diagnosis of COVID-19 in the recipient, was not explicitly reported.

As a result of the very serious risk of bias, very serious indirectness and serious imprecision, the quality of evidence was determined to be low for the indirect evidence and very low for the direct evidence.

In reviewing the evidence summarized above, the panel agreed that there is no compelling benefit in increased sensitivity or specificity for diagnosis of COVID-19 in potential deceased donors through the use of routine thoracic CT imaging. The panel also considerably valued resource conservation (e.g. cost of imaging, risk of transport of an unstable patient to CT, infection control considerations for diagnostic imaging personnel, and potential harm from contrast materials). For this reason, the panel made a strong recommendation against the routine use of routine thoracic CT scans for COVID-19 screening among potential deceased organ donors.

Furthermore, the findings from indirect evidence indicate that thoracic CT scan is sensitive but only moderately specific in the diagnosis of COVID-19 in suspected patients. Otherwise stated, thoracic CT findings have limited capability in differentiating between SARS-CoV-2 infection and other causes of respiratory illness. Thus, thoracic CT may complicate decision making by providing a false positive COVID-19 diagnosis. Excluding patients with a false positive CT scan, in whom a negative PCR result is obtained, could lead to missed donation opportunities. This is the basis for our recommendation that regardless of CT evidence, PCR status should be the primary para-clinical data used to evaluate risk of SARS-CoV-2 infection in a patient who is a potential donor.

This recommendation is across all donor and organ types and all patient subgroup populations. The authors recognize that thoracic CT scan may form part of routine donor organ assessment for transplantation of some organs, beyond of screening/diagnosis for COVID-19, and acknowledge that this will remain the practice of specific programs, beyond the remit of this guidance.

Knowledge Gaps/Research Considerations:

Further research could lead to more specific radiologic findings either through CT scan or other modalities that could be incorporated into screening protocols if they were found to be additive to the diagnostic accuracy of PCR screening. Future trials of diagnostic strategies may most directly help in determining if there is any added benefit with the use of CT imaging for the diagnosis of COVID-19.

References:

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6. Wang Y, Yang H, Liu H, Buhler LH, Deng S. Strategies to halt 2019 novel coronavirus (SARS-CoV-2) spread for organ transplantation programs at the Sichuan Academy of Medical Science and Sichuan Provincial People's Hospital, China. Am J Transplant 2020;20:1837-9.
7. Salameh JP, Leeflang MM, Hooft L, et al. Thoracic imaging tests for the diagnosis of COVID-19. Cochrane Database Syst Rev 2020;9:CD013639.

Evidence Profile:

Population: Adult and pediatric deceased organ donors
Intervention: Addition of chest CT to screen for COVID-19
Comparator: PCR testing alone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** PCR testing alone	Addition of chest CT to screen for COVID-19	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Accuracy - Indirect	Based on data from 8014 patients in 31 studies[1]	Crossectional and Case Control; Twenty-six per cent (9/34) of all studies were available only as preprints. Nineteen studies were conducted in Asia, 10 in Europe, four in North America and one in Australia. The majority of included studies had a high or unclear risk of bias with respect to participant selection, index test, reference standard, and participant flow. Twenty-four studies included inpatients, four studies included outpatients, while the remaining 6 studies were conducted in unclear settings. Sensitivity reported as 89.9% (95% CI 85.7%-92.9%); Specificity 61.1% (95 CI 42.3%-77.1%). Findings indicate that chest CT is sensitive and moderately specific for the diagnosis of COVID-19 in suspected patients, meaning that CT may have limited capability in differentiating SARS-CoV-2 infection from other causes of respiratory illness.		**Low** Due to very serious risk of bias, Due to serious indirectness, Due to serious indirectness[2]	Addition of chest CT to screen for COVID-19 may improve diagnostic accuracy
Accuracy - Direct	Based on data from patients in 6 studies[3]	None of the retrieved studies directly addressed this PICO. We included 6 studies (case series and cohorts) that described the inclusion of CT either as a routine part of donor screening or when "clinically indicated". None of the studies reported performing a repeat CT on donors. In addition to CT, all donors were screened using RT-PCR and a questionnaire. 1 Study included primarily living donors (45 living, 2 deceased) and two studies did not report the number of potential or actual donors screened. The total donors screened as reported 4 studies was 55. Only three studies reported on the number of donors (n=4) testing positive for COVID. These donors did not proceed. The total number of recipients in the 6 studies was 144; 11 of which were pediatric. 2 studies did not report on the number of recipients testing positive for COVID, 1 study reported 0/28 positive recipients, and one study reported that 5/32 recipients tested positive by PCR pre-transplant and did not proceed. One study reported 1/16 liver recipients tested positive post transplant but had mild symptoms and was eventually discharged. Importantly there were no reports of donors being excluded based on the results of screening with CT		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to serious imprecision[4]	We are uncertain of the usefulness of CT for screening of potential donors

1. Systematic review Supporting references [112].
2. **Risk of bias: Very Serious. Indirectness: Serious.** Direct comparisons not available;
3. Primary study Supporting references [47]. [85]. [44]. [45]. [42]. [46].

4. **Risk of bias: Very Serious.** Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Serious.** Low number of patients;

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4. SARS-CoV- 2 antibodies post infection with COVID-19 in potential deceased organ donors

PICO Question:

In pediatric and adult patients without detectable COVID-19 who are potential organ donors, is the presence of COVID-19 antibodies (IgG) associated with increased risk of COVID-19 infection in the recipient?

Reviewers:

L. Hornby, A. Manara, J. Singh

Literature Search:

Citations Screened: 1900 Citations Included: 1

Recommendation:

4.1 We make no recommendation regarding the use of antibody screening to evaluate the risk of COVID-19 transmission from potential deceased organ donors to organ recipients.

Key Literature and Rationale:

No studies were identified which directly evaluated antibody screening for SARS-CoV2 in potential deceased organ donors and subsequent transmission of SARS-CoV2 to organ recipients.

One systematic review evaluated the use of antibody screening for identification of current and past infection[1]. This review included 57 publications including 15,976 samples with 8526 SARS-CoV2 infections. The sensitivity of antibody tests for diagnosis of COVID-19 was low in the first week after onset of symptoms, however sensitivity for SARS-CoV2 infections increased with increasing duration from symptom onset out to three weeks. The included studies had significant limitations: many included only patients hospitalized with suspected COVID-19, and the identified studies used 25 different commercial assays and numerous in-house assays measuring antibodies directed against a variety of viral epitopes (spike and nucleocapsid proteins), limiting generalizability of findings or extrapolation to other clinical contexts.

There were no other data available from other patient populations that might be extrapolated to deceased organ donors and recipients.

There was insufficient evidence to make a recommendation regarding the proposed PICO question.

Inferences from indirect evidence or extrapolation from other patient populations were not possible due to a lack of available and applicable evidence.

Although there were data evaluating the performance of antibody testing for the diagnosis of COVID-19, the low observed sensitivity of serological testing for diagnosis in the first two weeks after onset of symptoms makes it unlikely that the addition of serological testing will be more informative than nucleic acid amplification testing alone in screening for SARS-CoV2 in deceased organ donors. These studies

were also further limited by the heterogeneous reporting of what assays were used and a lack of reporting standards for in-house antibody assays. Many studies were also conducted in patient populations where the prevalence of COVID-19 in study populations was high, and the utility of these tests (including false positives in potential organ donors) in populations where COVID-19 is less prevalent (e.g. in the context of a negative rtPCR test) is a consideration. For these many reasons the Infectious Diseases Society of America (IDSA) recommended against serological testing to diagnose COVID-19 in the first two weeks after symptom onset[2].

Serological testing could play a role in patients in whom COVID-19 might be suspected but repeat rtPCR testing was negative. The IDSA recommends that IgG detection can be used to establish infection in patients with a high clinical suspicion and repeatedly negative rtPCR testing three to four weeks after onset of symptoms. However, we did not find any data demonstrating that the presence of antibodies in such a patient mitigated SARS-CoV2 transmission, and thus did not inform decision-making regarding potential deceased organ donors and solid organ transplantation.

Serological testing may have some utility in confirming past SARS-CoV2 infection in patients in who there is a strong clinical suspicion but in whom rtPCR testing is repeatedly negative. There are no data, however, describing the rate of COVID-19 transmission (if any) from this population, or the potential for passive infection of organ recipients from organs obtained from such patients.

Knowledge Gaps/Research Considerations:

More research is needed to ascertain the true performance of testing for SARS-CoV2 antibodies in potential deceased organ donors. Considerations for this research include:

- How to define 'recovery' from COVID-19 in terms of both symptoms and diagnostic tools (i.e. potential discordance of clinical symptoms, rtPCR and serology)
- What time interval from COVID-19 recovery and organ recovery limits potential transmission of SARS-CoV2 to recipients
- Whether the presence of neutralizing antibodies (either in the donor or recipient) protects against recipient COVID-19 from passive transmission of SARS-CoV2 through organ transplantation.
- Whether the presence of neutralizing antibodies following COVID-19 vaccination (either in donor or recipient) protects against recipient COVID-19 from passive transmission of SARS-CoV2 through organ transplantation.

References:

1. Deeks JJ, Dinnes J, Takwoingi Y, et al. Antibody tests for identification of current and past infection with SARS-CoV-2. Cochrane Database Syst Rev 2020;6:Cd013652.
2. IDSA Guidelines on the Diagnosis of COVID-19: Serologic Testing. Infectious Diseases Society of America, 2020. (Accessed March 13, 2021, at https://www.idsociety.org/practice-guideline/covid-19-guideline-serology/.)

Evidence Profile:

Population: Adult and pediatric deceased organ donors
Intervention: SARS-CoV-2 antibody testing for COVID
Comparator: RT-PCR testing for COVID

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** RT-PCR testing for COVID / SARS-CoV-2 antibody testing	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
DAY 1-7 post symptom development	Based on data from 15976 patients in 54 studies[1]	38 studies that stratified by symptom onset for main results; 54 study cohorts and data from 25 commercial tests and numerous in-house assays, a small fraction of the 279 antibody assays listed by the Foundation for Innovative Diagnostics. More than half (n = 28) of the studies included were only available as preprints. Lack of clarity about participant numbers, characteristics and study exclusions (n = 47). Most studies (n = 44) only included people hospitalised due to suspected or confirmed COVID-19 infection. Sensitivity and 95% CI compared to RT-PCR reported to be: IgG 29.7%(22.1%-38.6%); IgM 23.2% (14.9%-34.2%); IgA 28.4% (0.9%-94.3%). The sensitivity of antibody tests is too low in the first week since symptom onset to have a primary role for the diagnosis of COVID-19, but they may still have a role complementing other testing in individuals presenting later, when RT-PCR tests are negative, or are not done. IgM rises soonest and typically declines after infection. IgG and IgA persist and usually reflect longer term immune response.	**Low** Due to serious risk of bias, Due to serious publication bias[2]	Sars-cov-2 antibody testing may have little or no difference on day 1-7 post symptom development
DAY 8-14 post symptom development	Based on data from 15976 patients in 54 studies[3]	Same studies as described above. For Day 8-14 post symptom development, Sensitivity and 95% CI compared to RT-PCR was reported to be: IgG 66.5%(57.9%-74.2%); IgM 58.4% (45.5%-70.3%); IgA 78.1% (9.5-99.2%). The sensitivity of antibody tests is too low in the first week since symptom onset to have a primary role for the diagnosis of COVID-19, but they may still have a role complementing other testing in individuals presenting later, when RT-PCR tests are negative, or are not done. IgM rises soonest and typically declines after infection. IgG and IgA persist and usually reflect longer term immune response.	**Low** Due to serious risk of bias, Due to serious publication bias[4]	Sars-cov-2 antibody testing may have little or no difference on day 8-14 post symptom development
DAY 15-21 post symptom development	Based on data from 15976 patients in 54 studies[5]	Same studies as described above. For Day 15-24 post symptom development, Sensitivity and 95% CI compared to RT-PCR was reported to be: IgG 88.2%(83.5%-91.8%); IgM 75.4% (64.3%-83.8%); IgA 98.7% (39.0%-100%). Antibody tests are likely to have a useful role for detecting previous SARS-CoV-2 infection if used 15 or more days after the onset of symptoms. IgM rises soonest and typically declines after infection. IgG and IgA persist and usually reflect longer term immune response.	**Low** Due to serious risk of bias, Due to serious publication bias[6]	Sars-cov-2 antibody testing may improve day 15-21 post symptom development slightly

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** RT-PCR testing for COVID / SARS-CoV-2 antibody testing	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
DAY 22-35 post symptom development	Based on data from 15976 patients in 54 studies[7]	Same studies as described above. For Day 22-35 post symptom development, Sensitivity and 95% CI compared to RT-PCR was reported to be: IgG 80.3%(72.4%-86.4%); IgM 68.1% (55.0%-78.9%); IgA 98.7% (91.9-99.8%). Antibody tests are likely to have a useful role for detecting previous SARS-CoV-2 infection if used 15 or more days after the onset of symptoms. IgM rises soonest and typically declines after infection. IgG and IgA persist and usually reflect longer term immune response.	**Low** Due to serious risk of bias, Due to serious publication bias[8]	Sars-cov-2 antibody testing may improve day 22-35 post symptom development slightly
> 35 DAYS post symptom development	Based on data from 15976 patients in 54 studies[9]	Same studies as described above. For > 35 days post symptom development, Sensitivity and 95% CI compared to RT-PCR was reported to be: IgG 86.7%(79.6%-91.7%); IgM 53.9% (34.8%-68.6%); IgA 100% (85.2%-100%). Antibody tests are likely to have a useful role for detecting previous SARS-CoV-2 infection if used 15 or more days after the onset of symptoms. However, the duration of antibody rises is currently unknown, and very little data was found beyond 35 days post-symptom onsetThere are insufficient studies to estimate sensitivity of tests beyond 35 days post-symptom onset. Summary specificities (provided in 35 studies) exceeded 98% for all target antibodies with confidence intervals no more than 2 percentage points wide.	**Low** Due to serious risk of bias, Due to serious publication bias[10]	Sars-cov-2 antibody testing may improve > 35 days post symptom development slightly
All time points post symptom development	Based on data from 15976 patients in 54 studies[11]	Same studies as described above. For all time points post symptom development, Specificity and 95% CI compared to RT-PCR was reported to be: IgG 99.1%(98.3%-99.6%); IgM 98.7% (97.4%-99.3%); IgA NR. False positive results were more common where COVID-19 had been suspected and ruled out, but numbers were small and the difference was within the range expected by chance. Assuming a prevalence of 50%, a value considered possible in healthcare workers who have suffered respiratory symptoms, we would anticipate that 43 (28 to 65) would be missed and 7 (3 to 14) would be falsely positive in 1000 people undergoing IgG/IgM testing at days 15 to 21 post-symptom onset. At a prevalence of 20%, a likely value in surveys in high-risk settings, 17 (11 to 26) would be missed per 1000 people tested and 10 (5 to 22) would be falsely positive. At a lower prevalence of 5%, a likely value in national surveys, 4 (3 to 7) would be missed per 1000 tested, and 12 (6 to 27) would be falsely positive.	**Low** Due to serious risk of bias, Due to serious publication bias[12]	Sars-cov-2 antibody testing may have little or no difference on all time points post symptom development

1. Systematic review Supporting references [39].
2. **Risk of bias: Serious.** Selective outcome reporting; **Publication bias: Serious.** due to selective publication of findings througth omission of the identity of the tests;
3. Systematic review Supporting references [39].
4. **Risk of bias: Serious.** Selective outcome reporting; **Publication bias: Serious.** due to selective publication of findings througth omission of the identity of the tests;
5. Systematic review Supporting references [39].

6. **Risk of bias: Serious.** Selective outcome reporting; **Publication bias: Serious.** due to selective publication of findings througth omission of the identity of the tests;
7. Systematic review Supporting references [39].
8. **Risk of bias: Serious.** Selective outcome reporting; **Publication bias: Serious.** due to selective publication of findings througth omission of the identity of the tests;
9. Systematic review Supporting references [39].
10. **Risk of bias: Serious.** Selective outcome reporting; **Publication bias: Serious.** due to selective publication of findings througth omission of the identity of the tests;
11. Systematic review Supporting references [39].
12. **Risk of bias: Serious.** Selective outcome reporting; **Publication bias: Serious.** due to selective publication of findings througth omission of the identity of the tests;

References

[39] Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Spijker R, Taylor-Phillips S, Adriano A, Beese S, Dretzke J, Ferrante di Ruffano L, Harris IM, Price MJ, Dittrich S, Emperador D, Hooft L, Leeflang MM, Van den Bruel A, ： Antibody tests for identification of current and past infection with SARS-CoV-2. The Cochrane database of systematic reviews 2020;6 CD013652

Recipient Treatment and Protection

5. Modifications to induction immunosuppression and rejection treatment in solid organ transplant recipients

PICO Question:

In adult and pediatric solid organ transplant recipients in settings of COVID-19 transmission, does adjustment to their induction immunosuppression regimen (e.g. alemtuzumab, anti-thymocyte globulin, rabbit ATG, basiliximab, methylprednisolone) vs routine care (no adjustment) improve patient outcomes (e.g. respiratory failure, days in ICU, mortality, acute rejection, need for renal replacement therapy, development of COVID-19).

Reviewers:

C. Luo, A. Mah

Literature Search:

Citations Screened: 1900 Citations Included: 9

Recommendation:

5.1 We suggest no modification to induction immunosuppression to prevent COVID-19 acquisition and/or severity (weak recommendation, very low-certainty of evidence).

Key Literature and Rationale:

This recommendation is based on 9 publications of individual case reports and small case series.[1-9] None of the reviewed publications reported on the risk of acquisition of COVID-19 as an outcome. All reports were of SOTr who had developed COVID-19 within the first 6 months post-transplant. Additional data on patient level outcomes was requested and obtained from authors of two of the included articles.[1,6] The most commonly reported and most pertinent outcomes for this intervention were patient survival and development of acute rejection. Although numbers were small, there was no appreciable trend in mortality based on type of induction therapy for transplant recipients who developed COVID-19. There is no available data on the risk of developing COVID-19 stratified by induction immunosuppression.

Given the potential harms of acute and chronic allograft rejection which may occur with reduction in standard induction immunosuppression this risk is felt to outweigh any theoretical benefit that this strategy may have on reduction of COVID-19 disease and severity for recipients. This position is supported by findings from one large US centre which showed that during the early phases of the pandemic, use of lymphocyte depleting induction therapy was not associated with an increase in mortality, however, not using lymphocyte depleting induction therapy was associated with an increased risk of rejection.[10]

Many factors are considered in the selection of an induction immunosuppression strategy and clinicians should choose a regimen which they believe offers the greatest chance of recipient and graft survival while minimizing risks of over immunosuppressing. These decisions take into consideration the best available evidence as well as the individual patient circumstances and values and preferences. For this reason, clinicians may choose, certain candidates for example, to reduce induction immunosuppression. However, at a programmatic level, we suggest against broad reduction in induction immunosuppression purely to mitigate against COVID-19.

Knowledge Gaps/Research Considerations:

Considerable knowledge gaps exist. As evidence and understanding of COVID-19 emerge, the impact of the immune system and immune activation on the pathophysiology of the disease is becoming apparent. Immunosuppression is traditionally considered to pose only an increased risk of infection and poor outcomes. However, several candidate therapeutics for COVID-19 aim to target and quell the immune response to the virus in order to mitigate the disease manifestations. It is thus unknown whether immunosuppression increases, decreases or plays no role in outcomes related to COVID-19.

Future studies to optimally answer this question would be to randomize transplant recipients to standard induction immunosuppression compared to a modified immunosuppression regimen to assess the impact of different strategies on rejection, COVID-19 acquisition and recipient survival. In the absence of this, larger cohorts of all transplant recipients in a program or programs are required with detailed information about immunosuppression regimens and the development of COVID-19 and allograft and recipient outcomes to attempt to assess any correlation between risk factors and outcomes.

References:

1. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and Kidney Transplantation. N Engl J Med 2020;382:2475-7.
2. Dube GK, Husain SA, McCune KR, Sandoval PR, Ratner LE, Cohen DJ. COVID-19 in pancreas transplant recipients. Transpl Infect Dis 2020;22:e13359.
3. Fung M, Chiu CY, DeVoe C, et al. Clinical outcomes and serologic response in solid organ transplant recipients with COVID-19: A case series from the United States. Am J Transplant 2020;20:3225-33.
4. Keller BC, Le A, Sobhanie M, et al. Early COVID-19 infection after lung transplantation. Am J Transplant 2020;20:2923-7.
5. Myers CN, Scott JH, Criner GJ, et al. COVID-19 in lung transplant recipients. Transpl Infect Dis 2020;22:e13364.
6. Patrono D, Lupo F, Canta F, et al. Outcome of COVID-19 in liver transplant recipients: A preliminary report from Northwestern Italy. Transpl Infect Dis 2020;22:e13353.
7. Shingare A, Bahadur MM, Raina S. COVID-19 in recent kidney transplant recipients. Am J Transplant 2020;20:3206-9.
8. Vilaro J, Al-Ani M, Manjarres DG, et al. Severe COVID-19 After Recent Heart Transplantation Complicated by Allograft Dysfunction. JACC Case Rep 2020;2:1347-50.
9. Zhong Z, Zhang Q, Xia H, et al. Clinical characteristics and immunosuppressant management of coronavirus disease 2019 in solid organ transplant recipients. Am J Transplant 2020;20:1916-21.
10. Bae S, McAdams-DeMarco MA, Massie AB, et al. Early Changes in Kidney Transplant Immunosuppression Regimens During the COVID-19 Pandemic. Transplantation 2021;105:170-6.

Evidence Profiles:

Population: Adult lung transplant recipients in settings of COVID-19 transmission
Intervention: Adjustment to induction immunosuppression
Comparator: Routine care (no adjustment to induction immunosuppression)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment to induction immunosuppression)	**Absolute effect estimates** Adjustment to induction immunosuppression	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
COVID-19 Infection	Based on data from 0 patients in 0 studies	No studies reported on the outcome of development of COVID 19 as related to adjustment of immunosuppression regime of LT patients			No studies were found that looked at covid-19 infection
Patient Survival	Based on data from 3 patients in 2 studies[1] Follow up 35 days; 57 days	One case report (Keller) of COVID + lung Tx patient who received basilixumab (20 mg) and steroid (dose NR) who survived. Another case report of 4 lung Tx patients who became Covid + within 3 months of transplant, 2 who received basilixumab (dose NR)and died, no outcomes were reported for the other 2 recipients.		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision,[2]	We are uncertain whether adjustment to induction immunosuppression improves or worsen patient survival
Graft Survival	Based on data from 3 patients in 2 studies[3] Follow up 35 days; 57 days	One case report (Keller) of COVID + lung Tx patient who received basilixumab (20 mg) and steroid (dose NR) who had no graft failure. Another case report of 4 lung Tx patients who became Covid + within 3 months of transplant, 2 who received basilixumab (dose NR)and died, no outcomes were reported for the other 2 recipients.		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision,[4]	We are uncertain whether adjustment to induction immunosuppression improves or worsen graft survival
Acute rejection	Based on data from 1 patients in 1 studies[5] Follow up 57 days	One case report (Keller) of COVID + lung Tx patient who received basilixumab (20 mg) and steroid (dose NR) who had no acute rejection		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[6]	We are uncertain whether adjustment to induction immunosuppression improves or worsen acute rejection
Renal Failure	Based on data from 1 patients in 1 studies[7] Follow up 57 days	One case report (Keller) of COVID + lung Tx patient who received basilixumab (20 mg) and steroid (dose NR) who had renal failure at 30 days		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision,[8]	We are uncertain whether adjustment to induction immunosuppression improves or worsen renal failure
Mechanical Ventilation	Based on data from 3 patients in 3 studies[9]	One case report (Keller) of COVID + lung Tx patient who received basilixumab (20 mg) and steroid (dose NR) who received mechanical ventilation. Another case report of 4 lung Tx		**Very Low** Due to very serious risk of bias, Due to very serious	We are uncertain whether adjustment to induction immunosuppression

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment to induction immunosuppression)	Adjustment to induction immunosuppression	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
	Follow up 35 days; 57 days	patients who became Covid + within 3 months of transplant, 2 who received basilixumab (dose NR)and also received mechanical ventilation, no outcomes were reported for the other 2 recipients.		inconsistency, Due to very serious indirectness, Due to very serious imprecision,[10]	improves or worsen mechanical ventilation
Hospitalization	Based on data from 3 patients in 2 studies[11] Follow up 35 days; 57 days	One case report (Keller) of COVID + lung Tx patient who received basilixumab (20 mg) and steroid (dose NR) who was hospitalized for 57days. Another case report of 4 lung Tx patients who became Covid + within 3 months of transplant, 2 who received basilixumab (dose NR)and who were hospitalized 14 days and 35 days before dying. No outcomes were reported for the other 2 recipients.		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[12]	We are uncertain whether adjustment to induction immunosuppression improves or worsen hospitalization

1. Primary study Supporting references [71]. [68].
2. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
3. Primary study Supporting references [71]. [68].
4. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
5. Primary study Supporting references [68].
6. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
7. Primary study Supporting references [68].
8. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
9. Primary study Supporting references [68]. [71].
10. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
11. Primary study Supporting references [71]. [68].
12. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;

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[68] Keller BC, Le A., Sobhanie M., Colburn N., Burcham P., Rosenheck J., Howsare M., Ganapathi AM, Atyia SA, Haden M., Whitson BA, Mokadam NA, Nunley DR : Early COVID-19 infection after lung transplantation. Am J Transplant 2020;29 29

[71] Myers CN, Scott JH, Criner GJ, Cordova FC, Mamary AJ, Marchetti N., Shenoy KV, Galli JA, Mulhall PD, Brown JC, Shigemura N., Sehgal S., Temple University C-RG : COVID-19 in Lung Transplant Recipients. Transpl Infect Dis 2020; e13364

Population: Adult lung transplant recipients in settings of COVID-19 transmission
Intervention: Adjustment to rejection treatment
Comparator: Routine care (no adjustment to rejection treatment)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
		Routine care (no adjustment to rejection treatment)	Adjustment to rejection treatment		
COVID-19 Infection	Based on data from 0 patients in 0 studies	No studies reported on this outcome as related to adjustment of immunosuppression regime of LT patients			No studies were found that looked at covid-19 infection
Patient Survival	Based on data from 2 patients in 1 studies[1] Follow up 26 days	I case report of 2 lung recipients with COVID-19, one who had no induction therapy or treatment for rejection. Both patients survived.		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[2]	We are uncertain whether adjustment to rejection treatment improves or worsen patient survival
Graft Survival	Based on data from 2 patients in 1 studies[3] Follow up 26 days	I case report of 2 lung recipients with COVID-19, one who had no induction therapy or treatment for rejection. Both patients grafts survived.		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[4]	We are uncertain whether adjustment to rejection treatment improves or worsen graft survival
Renal Failure	Based on data from 2 patients in 1 studies[5] Follow up 26 days	I case report of 2 lung recipients with COVID-19, one who had no induction therapy or treatment for rejection. Neither had renal failure		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[6]	We are uncertain whether adjustment to rejection treatment improves or worsen renal failure
Mechanical Ventilation	Based on data from 2 patients in 1 studies[7] Follow up 26 days	I case report of 2 lung recipients with COVID-19, one who had no induction therapy or treatment for rejection. Neither had mechanical ventilation		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[8]	We are uncertain whether adjustment to rejection treatment improves or worsen mechanical ventilation
Hospitalization	Based on data from 2 patients in 1 studies[9] Follow up 26 days	I case report of 2 lung recipients with COVID-19, one who had no induction therapy or treatment for rejection. Both were hospitalized. LOS NR		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious	We are uncertain whether adjustment to rejection treatment improves or worsen hospitalization

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment to rejection treatment)	Adjustment to rejection treatment		
				indirectness, Due to very serious imprecision[10]	

1. Primary study Supporting references [69].
2. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
3. Primary study Supporting references [69].
4. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
5. Primary study Supporting references [69].
6. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
7. Primary study Supporting references [69].
8. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
9. Primary study Supporting references [69].
10. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;

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[69] Koczulla RA, Sczepanski B., Koteczki A., Kuhnert S., Hecker M., Askevold I., Schneider C., Michel S., Kneidinger N. : SARS-CoV-2 infection in two patients following recent lung transplantation. Am J Transplant 2020;12 12

Population: Adult liver transplant recipients in settings of COVID-19 transmission
Intervention: Adjustment to induction immunosuppression
Comparator: Routine care (no adjustment to induction immunosuppression)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment to induction immunosuppression)	Adjustment to induction immunosuppression		
COVID-19 Infection	Based on data from 0 patients in 0 studies	No studies reported on the outcome of development of COVID 19 as related to adjustment of immunosuppression regime of LT patients			No studies were found that looked at covid-19 infection
Patient Survival	Based on data from 3 patients in 2 studies[1] Follow up 42 days - 2 months	Both studies were case reports. One study (Patrono) reported on 2 pts 1 KT-LT and 1 KT who received methylprednisone (1000mg) and then basilixumab (20 mg) for one patient and another study (Zong) reported on 1 LT pt treated with methyprednisone (300 mg). All patients survived.		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision,[2]	We are uncertain whether adjustment to induction immunosuppression improves or worsen patient survival

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment to induction immunosuppression)	Adjustment to induction immunosuppression	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Graft Survival	Based on data from 3 patients in 2 studies[3] Follow up 42 days - 2 months	Both studies were case reports. One study (Patrono) reported on 2 pts 1 KT-LT and 1 KT who received methylprednisone (1000mg) and then basilixumab (20 mg) for one patient and another study (Zong) reported on 1 LT pt treated with methyprednisone (300 mg). No graft loss.		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision,[4]	We are uncertain whether adjustment to induction immunosuppression improves or worsen graft survival
Acute rejection	Based on data from 3 patients in 2 studies[5] Follow up 42 days - 2 months	Both studies were case reports. One study (Patrono) reported on 2 pts 1 KT-LT and 1 KT who received methylprednisone (1000mg) and then basilixumab (20 mg) for one patient reported no acute rejection but and another study (Zong) reported acute rejection for 1 LT pt treated with methyprednisone (300 mg)		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[6]	We are uncertain whether adjustment to induction immunosuppression improves or worsen acute rejection
Renal Failure	Based on data from 0 patients in 0 studies	Neither study reported on renal failure			No studies were found that looked at renal failure
Mechanical Ventilation	Based on data from 3 patients in 2 studies[7] Follow up 42 days - 2 months	Both studies were case reports. One study (Patrono) reported on 2 pts 1 KT-LT and 1 KT who received methylprednisone (1000mg) and then basilixumab (20 mg) for one patient and another study (Zong) reported on 1 LT pt treated with methyprednisone (300 mg). No patients received mechanical ventilation		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision,[8]	We are uncertain whether adjustment to induction immunosuppression improves or worsen mechanical ventilation
Hospitalization	Based on data from 3 patients in 2 studies[9] Follow up 24 days - 2 months	All studies were case reports. One study (Patrono) reported on 2 pts 1 KT-LT and 1 KT who received methylprednisone (1000mg) and then basilixumab (20 mg) for one patient. 1 pt was hospitalized for 22 days. In another study (Zong) reported on 1 LT pt treated with methyprednisone (300 mg) who was hospitalized for 42 days.		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision,[10]	We are uncertain whether adjustment to induction immunosuppression improves or worsen hospitalization

1. Systematic review Supporting references [75]. [72].
2. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
3. Systematic review Supporting references [72]. [75].
4. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
5. Systematic review Supporting references [72]. [75].
6. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
7. Primary study Supporting references [72]. [75].

8. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
9. Primary study Supporting references [75]. [72].
10. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;

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Population: Adult liver transplant recipients in settings of COVID-19 transmission
Intervention: Adjustment to rejection treatment
Comparator: Routine care (no adjustment to rejection treatment)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
		Routine care (no adjustment to rejection treatment)	Adjustment to rejection treatment		
COVID-19 Infection	Based on data from 0 patients in 0 studies	No studies reported on this outcome as related to adjustment of immunosuppression regime of LT patients			No studies were found that looked at covid-19 infection
Patient Survival	Based on data from 1 patients in 1 studies[1] Follow up NR	1 Case report of a LT patient with COVID who was treated with steroids for rejection and survived		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[2]	We are uncertain whether adjustment to rejection treatment improves or worsen patient survival
Graft Survival	Based on data from 1 patients in 1 studies[3] Follow up NR	1 Case report of a LT patient with COVID who was treated with steroids for rejection and whose graft survived		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision,[4]	1 Case report of a LT patient with COVID who was treated with steroids for rejection and whose graft survived
Renal Failure	Based on data from 0 patients in 0 studies	No studies reported on this outcome as related to adjustment of immunosuppression regime of LT patients			No studies were found that looked at renal failure
Mechanical Ventilation	Based on data from 1 patients in 1 studies[5] Follow up NR	1 Case report of a LT patient with COVID who was treated with steroids for rejection and who received only non-invasive ventilation		**Very Low** Due to very serious risk of bias, Due to very serious	We are uncertain whether adjustment to rejection

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment to rejection treatment)	Adjustment to rejection treatment		
				inconsistency, Due to very serious indirectness, Due to very serious imprecision,[6]	treatment improves or worsen mechanical ventilation
Hospitalization	Based on data from 1 patients in 1 studies[7] Follow up NR	1 Case report of a LT patient with COVID who was treated with steroids for rejection and who was hospitalized. LOS NR		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[8]	We are uncertain whether adjustment to rejection treatment improves or worsen hospitalization

1. Primary study Supporting references [70].
2. **Risk of bias: Very Serious. Indirectness: Very Serious. Imprecision: Very Serious.**
3. Primary study Supporting references [70].
4. **Risk of bias: Very Serious. Indirectness: Very Serious. Imprecision: Very Serious.**
5. Primary study Supporting references [70].
6. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
7. Primary study Supporting references [70].
8. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;

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Population: Adult pancreas transplant recipients in settings of COVID-19 transmission
Intervention: Adjustment to induction immunosuppression
Comparator: Routine care (no adjustment to induction immunosuppression)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment to induction immunosuppression)	Adjustment to induction immunosuppression		
COVID-19 Infection	Based on data from 0 patients in 0 studies	No studies reported on the outcome of development of COVID 19 as related to adjustment of immunosuppression regime of PT patients			No studies were found that looked at covid-19 infection
Patient Survival	Based on data from 1 patients in 1 studies[1] Follow up 5 weeks	1 case report of SPKT treated with AGT (no dose given) survived		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency,	We are uncertain whether adjustment to induction immunosuppres

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment to induction immunosuppression)	Adjustment to induction immunosuppression	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
				Due to very serious indirectness, Due to very serious imprecision,[2]	sion improves or worsen patient survival
Graft Survival	Based on data from 1 patients in 1 studies[3] Follow up 5 weeks	1 case report of SPKT treated with AGT (no dose given) did not have graft failure		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision,[4]	We are uncertain whether adjustment to induction immunosuppression improves or worsen graft survival
Acute rejection	Based on data from 1 patients in 1 studies[5] Follow up 5 weeks	1 case report of SPKT treated with AGT (no dose given) had not acute rejection		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[6]	We are uncertain whether adjustment to induction immunosuppression improves or worsen acute rejection
Renal Failure	Based on data from 1 patients in 1 studies[7] Follow up 5 weeks	1 case report of SPKT treated with AGT (no dose given) had no renal failure		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[8]	We are uncertain whether adjustment to induction immunosuppression improves or worsen renal failure
Mechanical Ventilation	Based on data from 1 patients in 1 studies[9] Follow up 5 weeks	1 case report of SPKT treated with AGT (no dose given) had no mechanical ventilation		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[10]	We are uncertain whether adjustment to induction immunosuppression improves or worsen mechanical ventilation
Hospitalization	Based on data from 1 patients in 1 studies[11]	1 case report of SPKT treated with AGT (no dose given) was hospitalized for 7 days		**Very Low** Due to very serious risk of	We are uncertain whether

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment to induction immunosuppression)	Adjustment to induction immunosuppression		
	Follow up 5 weeks			bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[12]	adjustment to induction immunosuppression improves or worsen hospitalization

1. Primary study Supporting references [66].
2. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
3. Primary study Supporting references [66].
4. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
5. Primary study Supporting references [66].
6. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
7. Primary study Supporting references [66].
8. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
9. Primary study Supporting references [66].
10. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
11. Primary study Supporting references [66].
12. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;

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Population: Adult kidney transplant recipients in settings of COVID-19 transmission
Intervention: Adjustment to induction immunosuppression
Comparator: Routine care (no adjustment to induction immunosuppression)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment to induction immunosuppression)	Adjustment to induction immunosuppression		
COIVD-19 infection	Based on data from 0 patients in 0 studies	No studies reported on the outcome of development of COVID 19 as related to adjustment of immunosuppression regime of KT patients			No studies were found that looked at coivd-19 infection
Patient Survival	Based on data from 9 patients in 5 studies[1] Follow up 7 days - 5 weeks	All studies were case reports. Overall survival was 78%. Only 1 study (Akalin) of 1 KT who had been treated with basilixumab followed by ATG at 1.5 mg/kg and another KT in the same study treated only with ATG at 1.5 mg/kg reported that both died. 5 KT		**Very Low** Due to very serious risk of bias, Due to very serious	We are uncertain whether adjustment to induction immunosuppressio

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment to induction immunosuppression)	Adjustment to induction immunosuppression	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
		pts in 3 studies (Shingare, Dube, Fung) received AGT (dose only reported for 2 pts as 1 mg/kg) with no additional treatment or deaths. One study (Patrono) reported on 2 pts 1 KT-LT and 1 KT who received methylprednisone (1000mg) and then basilixumab (20 mg) for one patient with no deaths.		imprecision, Due to very serious indirectness[2]	n improves or worsen patient survival
Graft Survival	Based on data from 9 patients in 5 studies[3] Follow up 7 days - 5 weeks	All studies were case reports. Only 1 study (Akalin) of 1 KT who had been treated with basilixumab followed by ATG at 1.5 mg/kg and another recipient in the same study treated only with ATG at 1.5 mg/kg reported that both died. 5 KT pts in 3 studies (Shingare, Dube, Fung) received AGT (dose only reported for 2 pts as 1 mg/kg) with no additional treatment and one study (Patrono) reported on 2 pts 1 KT-LT and 1 KT who received methylprednisone (1000mg) and then basilixumab (20 mg) for one patient. No graft loss was reported for these 6 KT pts.		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[4]	We are uncertain whether adjustment to induction immunosuppressio n improves or worsen graft survival
Acute Rejection	Based on data from 9 patients in 5 studies[5] Follow up 7 days-5 weeks	All studies were case reports. Only 1 study (Akalin) reported acute rejection in 1 KT who had been treated with basilixumab followed by ATG at 1.5 mg/kg. Another KT in the same study was only treated with ATG at 1.5 mg/kg with no rejection. 5 KT pts in 3 studies (Shingare, Dube, Fung) received AGT (dose only reported for 2 pts as 1 mg/kg) with no acute rejection or additional treatment. One study (Patrono) reported on 2 pts 1 KT-LT and 1 KT who received methylprednisone (1000mg) and then basilixumab (20 mg) for one patient without acute rejection in either.		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[6]	We are uncertain whether adjustment to induction immunosuppressio n improves or worsen acute rejection
Renal Failure	Based on data from 5 patients in 3 studies[7] Follow up 5 weeks-2 months	All studies were case reports. All 5 KT pts were treated with AGT only. No renal failure was reported in any of the KT pts		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[8]	There were too few who experienced the renal failure, to determine whether adjustment to induction immunosuppressio n made a difference
Mechanical Ventilation	Based on data from 7 patients in 4 studies[9] Follow up 32 days - 2 months	All studies were case reports. 5 KT pts in 3 studies (Shingare, Dube, Fung) received AGT (dose only reported for 2 pts as 1 mg/kg) with no additional treatment. One study (Patrono) reported on 2 pts 1 KT-LT and 1 KT who received methylprednisone (1000mg) and then basilixumab (20 mg) for one patient. None of the 6 KT pts received mechanical ventilation.		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[10]	We are uncertain whether adjustment to induction immunosuppressio n improves or worsen mechanical ventilation
Length of Hospital Stay	Based on data from 9 patients in 5 studies[11]	All studies were case reports. Overall 5/ 9 KT pts were admitted to hospital. 1 study (Akalin) of 2 KTs reported no hospitalization for 1 KT who had been		**Very Low** Due to very serious risk of	We are uncertain whether adjustment to

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment to induction immunosuppression)	Adjustment to induction immunosuppression		
	Follow up 32 days-2 months	treated with basilixumab followed by ATG at 1.5 mg/kg and another pt who was only treated with ATG at 1.5 mg/kg. 5 KT pts in 3 studies (Shingare, Dube, Fung) received AGT (dose only reported for 2 pts as 1 mg/kg) with 4/5 pts hospitalized; LOS was 7-52 days. One study (Patrono) reported hospitalization in 1/2 pts with LOS of 22 days; both pts received received methylprednisone (1000mg) and then basilixumab (20 mg) for one patient who was hospitalized.		bias, Due to very serious indirectness, Due to very serious imprecision[12]	induction immunosuppression improves or worsen length of hospital stay

1. Systematic review Supporting references [58]. [65]. [73]. [72]. [66].
2. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
3. Systematic review Supporting references [66]. [58]. [73]. [65]. [72].
4. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
5. Primary study Supporting references [58]. [65]. [73]. [72]. [66].
6. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
7. Systematic review Supporting references [58]. [66]. [73].
8. **Risk of bias: Very Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
9. Systematic review Supporting references [58]. [72]. [66]. [73].
10. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
11. Systematic review Supporting references [66]. [65]. [72]. [73]. [58].
12. **Risk of bias: Very Serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;

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[73] Shingare A., Bahadur MM, Raina S. : COVID-19 in recent kidney transplant recipients. Am J Transplant 2020;08 08

Population: Adult heart transplant recipients in settings of COVID-19 transmission
Intervention: Adjustment to induction immunosuppression
Comparator: Routine care (no adjustment to induction immunosuppression)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment to induction immunosuppression)	Adjustment to induction immunosuppression	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
COVID-19 Infection	Based on data from 0 patients in 0 studies	No studies reported on the outcome of development of COVID 19 as related to adjustment of immunosuppression regime of HT patients			No studies were found that looked at covid-19 infection
Patient Survival	Based on data from 1 patients in 1 studies[1] Follow up 14 days	One case report of a HT-KT pt treated with basilixumab (dose not reported) survived		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision,[2]	We are uncertain whether adjustment to induction immunosuppression improves or worsen patient survival
Graft Survival	Based on data from 1 patients in 1 studies[3] Follow up 14 days	One case report of a HT-KT pt treated with basilixumab (dose not reported) did not have graft failure.		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision,[4]	We are uncertain whether adjustment to induction immunosuppression improves or worsen graft survival
Acute rejection	Based on data from 1 patients in 1 studies[5] Follow up 14 days	One case report of a HT-KT pt treated with basilixumab (dose not reported) did not have acute rejection		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[6]	We are uncertain whether adjustment to induction immunosuppression improves or worsen acute rejection
Renal Failure	Based on data from 0 patients in 0 studies	Did not report on renal failure			No studies were found that looked at renal failure
Mechanical Ventilation	Based on data from 1 patients in 1 studies[7] Follow up 14 days	One case report of a HT-KT pt treated with basilixumab (dose not reported) who received mechanical ventilation		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious	We are uncertain whether adjustment to induction immunosuppression improves or worsen mechanical ventilation

			indirectness, Due to very serious imprecision,[8]	
Hospitalization	Based on data from 1 patients in 1 studies[9] Follow up 14 days	One case report of a HT-KT pt treated with basilixumab (dose not reported) who was hospitalized for 14 days	**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision,[10]	We are uncertain whether adjustment to induction immunosuppression improves or worsen hospitalization

1. Primary study Supporting references [74].
2. **Risk of bias: Very Serious.** Selective outcome reporting, Incomplete data and/or large loss to follow up; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
3. Primary study Supporting references [74].
4. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
5. Primary study Supporting references [74].
6. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
7. Primary study Supporting references [74].
8. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
9. Primary study Supporting references [74].
10. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;

References

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6. Immunosuppression therapy in the setting of COVID-19

PICO Questions:

In adult and pediatric solid organ transplant recipients with known or suspected COVID-19, does adjustment of maintenance immunosuppression therapy vs routine care (no adjustment, current care for patients independent of COVID-19 Coronavirus-2 (SARS-CoV-2) pandemic) improve patient outcomes?

In adult and pediatric transplant recipients with known or suspected COVID-19, at what point is resumption of maintenance immunosuppression therapy safe and is not associated with an increased risk of complications?

In adult and pediatric transplant recipients in areas with high COVID-19 incidence, does pre-emptive adjustment of maintenance immunosuppression therapy vs routine care (no adjustment) improve patient?

Reviewers:

R. Sapir-Pichhadze, M. Bhat, M. Gagnon, S. Srinathan

Literature Search:

Citations Screened: 1900 Citations Included: 33

Recommendations:

6.1 We suggest temporary adjustment of maintenance immunosuppression may be considered for patients with COVID-19 (weak recommendation, very low-certainty of evidence).

6.2 We suggest against pre-emptive adjustment of maintenance immunosuppression to prevent acquisition of COVID-19 (weak recommendation, very low-certainty of evidence).

Key Literature and Rationale:

The recommendation for temporary adjustment of maintenance immunosuppression is based on 32 publications (case reports and case series); 18 included kidney transplant recipients,[1-18] 5 included liver transplant recipients,[10,19-22] 7 included heart transplant recipients,[10,23-28] and 2 included lung transplant recipients.[29,30] All studies reported some form of modification to the patients' immunosuppressive regimen. None of the studies relied on an experimental design and there was no control group of patients who had no changes to their immunosuppressive agents. The reports considered SOTr who developed COVID-19 at various intervals post-transplant and follow up was relatively short. Modifications to immunosuppression regimens were temporary. In addition to reducing or holding antimetabolites, several studies reported on simultaneous reduction in doses of calcineurin inhibitors and mTOR inhibitors, and administration of steroids as well as other supplementary immune modulating therapies. Thus, the observed outcomes may not be solely attributable from the temporary reduction in maintenance immunosuppression.

The weak recommendation against pre-emptive adjustment of maintenance immunosuppression is based on indirect evidence from 9 publications, limited to cohort studies.[5,6,17,18,22,25,28,31,32] Four studies reported on incidence of COVID-19 in kidney transplant recipients.[5,6,17,18] Immunosuppression therapy was not modified pre-emptively and the incidence of COVID-19 ranged from 0% to 0.67%. One study reported on a cohort of liver transplant recipients.[22] In the absence of pre-emptive modification of immunosuppression in this cohort, the incidence of COVID-19 in this population was 0.11%. Three studies reported on incidence of COVID-19 in heart transplant recipients.[6,25,28] The incidence of COVID-19 ranged between 0.79%-5% while on standard immunosuppression therapy. One study reported on the incidence of COVID-19 in a cohort of lung transplant recipients.[6] Maintenance of standard immunosuppression regimen was associated with COVID-19 incidence of 3.3% over a follow up period of 116 days (46-187). Finally, two studies reported on cohorts of all SOTr on standard immunosuppression regimens and estimated the incidence of COVID-19 to be <1%.[31,32]

Many factors are considered in the modification of maintenance immunosuppression strategy. These decisions should take into consideration the best available evidence as well as the individual patient circumstances alongside their values and preferences. Given the potential harms of acute and chronic allograft rejection which may occur with reduction in maintenance immunosuppression, adjustment of maintenance immunosuppression in patients infected with COVID-19 is suggested to be implemented as a temporary measure. Although we suggest that this may be done, and, as demonstrated by the referenced reports, it is common practice, it is unknown if reduction of maintenance immunosuppression in transplant recipients with COVID-19 results in improved outcomes from the infection. The severe manifestations of COVID-19 are believed to be due to an amplified and aberrant immune response.[33] As such, it is unknown if reduction of immunosuppression will improve response to infection or conversely if this will worsen the immune response to the infection and lead to worse outcomes. In the absence of evidence, we are prioritizing a preference for potential decreased COVID-19 related morbidity and mortality, accepting the potential increased short-term risk of rejection. Further data on the efficacy of temporary reductions to maintenance immunosuppression and the attributable impact of immunosuppression on COVID-19 morbidity and mortality may change this recommendation significantly.

We suggest against pre-emptive reduction in maintenance immunosuppression therapy in an effort to prevent COVID-19 because we weighed the increased risk of rejection to be higher than what it believed to be a small potential benefit of a reduction of immunosuppression on the risk of *acquiring* COVID-19, especially in light of the evidence demonstrating a low incidence of COVID-19 in transplant patients on standard immunosuppression regimens.

<u>Knowledge Gaps/Research Considerations:</u>

There remain significant knowledge gaps regarding management of immunosuppression with COVID-19 infection in transplant recipients, and whether pre-emptive decrease in maintenance immunosuppression is of any benefit. Based on the literature in non-transplant patients, the immunologic response to COVID-19 infection is what causes morbidity and mortality. Thus, it has been proposed that immunosuppression may have a protective effect. In accordance with early recommendations by various transplantation societies, however, most studies in solid organ transplant recipients provide data from centres who opted to hold therapy with antimetabolites like mycophenolate in the setting of COVID-19 infection. It remains unclear whether this indeed improves COVID-19 outcomes in this patient population. Moreover, in addition to holding antimetabolites, several studies report on simultaneous reduction in doses of calcineurin inhibitors and mTOR inhibitors and

increase of steroid dose and/or administration of IL-6 receptor blockers. Thus, the observed outcomes may not be solely attributable the temporary reduction in maintenance immunosuppression. There is a need for randomized controlled trials assessing the impact of reduction of immune suppression agents versus standard therapy and the timelines such reduction should be instated in relation to the diagnosis of COVID-19. In addition to COVID-19 related outcomes such as mortality, severity of COVID-19 infection (including ICU admission, need for ventilatory support), in solid organ transplant recipients, sufficient follow up should be allowed to also evaluate outcomes like allograft rejection.

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Evidence Profiles:

Population: Adult lung transplant recipients with known or suspected COVID-19
Intervention: Adjustment to maintenance immunosuppression therapy
Comparator: Routine care (no adjustment to maintenance immunosuppression therapy)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment)	Adjustment to maintenance immunosuppression therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
In-Hospital Survival	Based on data from 12 patients in 2 studies[1] Follow up 24 d; until death or discharge	Two observational studies reported outcomes from cohorts of patients with COVID-19, admitted to transplant programs. In one study (Morlacchi n=4, age 63(48-70), 50% female), the IS regimen was reduced in all patients, typically holding the antiproliferative agent (Everolimus, Aza) and augmenting steroids. In the other study (Myers n=8, age 69 (43 – 75)), 6 received pulse-dose steroids (defined as at least 3 days of >/=125mg daily of methylprednisolone) and in 2 others IS regimen was not changed, CNI was titrated to appropriate therapeutic levels. However, outcomes were reported for the cohort as a whole. As well, 3/8 pts had negative swab test despite a clinical diagnosis. In-hospital survival for both studies was 75%.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy improves or worsens in-hospital survival
30-Day Survival	Based on data from 4 patients in 1 studies[2] Follow up death or discharge	Only 1 observational study reported on 30 day graft survival from a cohort of patients with COVID-19, admitted to transplant programs. In this study (Morlacchi n=4, age 63(48-70), 50% female), the IS regimen was reduced in all patients, typically holding the antiproliferative agent (Everolimus, Aza) and augmenting steroids. 30 day patient survival was 75%.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy improves or worsens in-hospital survival.
Graft Survival	Based on data from 12 patients in 2 studies[3] Follow up 24 d; until death or discharge	Two observational studies reported outcomes from cohorts of patients with COVID-19, admitted to transplant programs. In one study (Morlacchi n=4, age 63(48-70), 50% female), the IS regimen was reduced in all patients, typically holding the antiproliferative agent (Everolimus, Aza) and augmenting steroids. In the other study (Myers n=8, age 69 (43 – 75)), 6 received pulse-dose steroids (defined as at least 3 days of >/=125mg daily of methylprednisolone) and in 2 others IS regimen was not changed, CNI was titrated to appropriate therapeutic levels. However, outcomes were reported for the cohort as a whole. As well, 3/8 pts had negative swab test despite a clinical diagnosis. In-hospital graft survival for both studies was 75%.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy improves or worsens graft survival.
Renal Failure	Based on data from 2 patients in 12 studies[4]	Two observational studies reported outcomes from cohorts of patients with COVID-19, admitted to transplant programs. In one study		**Very Low** Observational studies without control	We are uncertain whether adjustment to maintenance

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment)	Adjustment to maintenance immunosuppression therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
	Follow up 24 d; death or discharge	(Morlacchi n=4, age 63(48-70), 50% female), the IS regimen was reduced in all patients, typically holding the antiproliferative agent (Everolimus, Aza) and augmenting steroids. There were 2 (50%) patients who had renal failure. In the other study (Myers n=8, age 69 (43 – 75)), 6 received pulse-dose steroids (defined as at least 3 days of >/=125mg daily of methylprednisolone) and in 2 others IS regimen was not changed, CNI was titrated to appropriate therapeutic levels. However, outcomes were reported for the cohort as a whole. As well, 3/8 pts had negative swab test despite a clinical diagnosis. There were 3 (38%) patients who had renal failure.		group of patients who had no changes to their immunosuppressive agents.	immunosuppression therapy improves or worsens renal failure rate.
In-Hospital Thrombosis	Based on data from 12 patients in 2 studies Follow up 24 d; death or discharge	Two observational studies reported outcomes from cohorts of patients with COVID-19, admitted to transplant programs. In one study (Morlacchi n=4, age 63(48-70), 50% female), the IS regimen was reduced in all patients, typically holding the antiproliferative agent (Everolimus, Aza) and augmenting steroids. There were 2 (50%) patients who had thrombosis. In the other study (Myers n=8, age 69 (43 – 75)), 6 received pulse-dose steroids (defined as at least 3 days of >/=125mg daily of methylprednisolone) and in 2 others IS regimen was not changed, CNI was titrated to appropriate therapeutic levels. However, outcomes were reported for the cohort as a whole. As well, 3/8 pts had negative swab test despite a clinical diagnosis. There were 3 (38%) patients who had thrombosis		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy improves or worsens in-hospital thrombosis rate.
Mechanical Ventilation	Based on data from 12 patients in 2 studies[5] Follow up 24 d; death or discharge	Two observational studies reported outcomes from cohorts of patients with COVID-19, admitted to transplant programs. In one study (Morlacchi n=4, age 63(48-70), 50% female), the IS regimen was reduced in all patients, typically holding the antiproliferative agent (Everolimus, Aza) and augmenting steroids. There were no patients who had mechanical ventilation. In the other study (Myers n=8, age 69 (43 – 75)), 6 received pulse-dose steroids (defined as at least 3 days of >/=125mg daily of methylprednisolone) and in 2 others IS regimen was not changed, CNI was titrated to appropriate therapeutic levels. However, outcomes were reported for the cohort as a whole. As well, 3/8 pts had negative swab test despite a clinical diagnosis. There were 2 (25%) patients who had mechanical ventilation.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents	We are uncertain whether adjustment to maintenance immunosuppression therapy impacts risk for mechanical ventilation.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment)	Adjustment to maintenance immunosuppression therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
In-Hospital ARDS	Based on data from 12 patients in 2 studies[6] Follow up 24 d; death or discharge	Only 1 observational study reported on ARDS from a cohort of patients with COVID-19, admitted to transplant programs. In this study (Morlacchi n=4, age 63(48-70), 50% female), the IS regimen was reduced in all patients, typically holding the antiproliferative agent (Everolimus, Aza) and augmenting steroids. 1 (25%) patient had ARDS in hospital that resolved by 30 days.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy impacts risk for ARDS.
ECMO	Based on data from 12 patients in 2 studies[7] Follow up 24 d; death or discharge	Two observational studies reported outcomes from cohorts of patients with COVID-19, admitted to transplant programs. In one study (Morlacchi n=4, age 63(48-70), 50% female), the IS regimen was reduced in all patients, typically holding the antiproliferative agent (Everolimus, Aza) and augmenting steroids. There were no patients who required ECMO. In the other study (Myers n=8, age 69 (43 – 75)), 6 received pulse-dose steroids (defined as at least 3 days of >/=125mg daily of methylprednisolone) and in 2 others IS regimen was not changed, CNI was titrated to appropriate therapeutic levels. However, outcomes were reported for the cohort as a whole. As well, 3/8 pts had negative swab test despite a clinical diagnosis. There were 3 (38%) patients who required ECMO.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy impacts risk for ECMO.
ICU Admission	Based on data from 12 patients in 2 studies[8] Follow up 24 d; death or discharge	Two observational studies reported outcomes from cohorts of patients with COVID-19, admitted to transplant programs. In one study (Morlacchi n=4, age 63(48-70), 50% female), the IS regimen was reduced in all patients, typically holding the antiproliferative agent (Everolimus, Aza) and augmenting steroids. In the other study (Myers n=8, age 69 (43 – 75)), 6 received pulse-dose steroids (defined as at least 3 days of >/=125mg daily of methylprednisolone) and in 2 others IS regimen was not changed, CNI was titrated to appropriate therapeutic levels. However, outcomes were reported for the cohort as a whole. As well, 3/8 pts had negative swab test despite a clinical diagnosis. 100% patients in both studies were admitted to the ICU.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy impacts risk for ICU admission.
Hospital Admission	Based on data from 12 patients in 2 studies[9] Follow up 24 d; until death or discharge	Two observational studies reported outcomes from cohorts of patients with COVID-19, admitted to transplant programs. In one study (Morlacchi n=4, age 63(48-70), 50% female), the IS regimen was reduced in all patients, typically holding the antiproliferative agent (Everolimus, Aza) and augmenting steroids. All patients were hospitalized and LOS was mean of 25 d with		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy impacts risk for hospital admission and length of stay.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment)	Adjustment to maintenance immunosuppression therapy		
		range 12-39d. In the other study (Myers n=8, age 69 (43 – 75)), 6 received pulse-dose steroids (defined as at least 3 days of >/=125mg daily of methylprednisolone) and in 2 others IS regimen was not changed, CNI was titrated to appropriate therapeutic levels. However, outcomes were reported for the cohort as a whole. As well, 3/8 pts had negative swab test despite a clinical diagnosis. All patients were hospitalized and LOS was mean of 8 d with range 12-16 d.			

1. Primary study Supporting references [21]. [22].
2. Primary study Supporting references [21].
3. Primary study Supporting references [22]. [21].
4. Primary study Supporting references [21]. [22].
5. Systematic review Supporting references [22]. [21].
6. Primary study Supporting references [21]. [22].
7. Primary study Supporting references [22]. [21].
8. Primary study Supporting references [22]. [21].
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Population: Adult heart transplant recipients with known or suspected COVID-19
Intervention: Adjustment to maintenance immunosuppression therapy
Comparator: Routine care (no adjustment to maintenance immunosuppression therapy)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment)	Adjustment to maintenance immunosuppression therarpy		
In-Hospital Survival	Based on data from 52 patients in 5 studies[1] Follow up 15 d, 54d, NS in 3	Five observational studies reported on cohorts of patients with COVID-19, admitted to transplant programs. Four of these studies (Fernandez-Ruiz, Ketcham, Latif and Zhou, total n=48) reported that they reduced or paused immunosuppression for the majority of their patients from the standard immunosuppression protocol that is expected in the transplant population. The most common immunosuppression withdrawn or reduced was anti-metabolite or mycophenolate. Other immunosuppressive agents such as prednisone or calcineurin and mammalian target		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy improves or worsens in-hospital survival.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment)	Adjustment to maintenance immunosuppression therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
		of rapamycin (mTOR) inhibitors, were not withdrawn, but rather their dose reduced. In-hospital survival ranged from 68% to 100%. Specifically, the largest cohort (n=28, age= 64.0 (IQR 53.5-70.5), sex=21% female), in which M was discontinued in 16 patients (70%), CNI dose reduced in 6 (26%) and high-dose corticosteroids in 8 patients (47%), reported the lowest survival (68%). One other case series of 4 young patients (Lee) reported that all patients survived; mycophenolate sodium and valganciclovir were held for 6 weeks in 1 patient (15 yr female) while no change in immunosuppression was made in the other 3 (1/3 who was hospitalized, 13 mo-25 yrs, 67% female).			
30-Day Survival	Based on data from 28 patients in 1 studies[2] Follow up 54 d	1 observational study reported on cohorts of patients with COVID-19, followed by transplant program. In 30 day survival was 68% in this cohort (n=28, age= 64.0 (IQR 53.5-70.5), sex=21% female), in which M was discontinued in 16 patients (70%), CNI dose reduced in 6 (26%) and high-dose corticosteroids in 8 patients (47%).		**Very Low** 1 small observational study without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy improves or worsens 30 day survival.
In-Hospital Graft Survival	Based on data from 52 patients in 5 studies[3] Follow up 15d, 54d, NS in 3	Five observational studies reported on cohorts of patients with COVID-19, admitted to transplant programs. Four of these studies (Fernandez-Ruiz, Ketcham, Latif and Zhou, total n=48) reported that they reduced or paused immunosuppression for the majority of their patients from the standard immunosuppression protocol that is expected in the transplant population. The most common immunosuppression withdrawn or reduced was anti-metabolite or mycophenolate. Other immunosuppressive agents such as prednisone or calcineurin and mammalian target of rapamycin (mTOR) inhibitors, were not withdrawn, but rather their dose reduced. In-hospital there were no reports of graft loss. One other case series of 4 young patients (Lee) did not report any graft loss in the 15 yr old female pt where mycophenolate sodium and valganciclovir were held for 6 weeks or in the 3 pts (1/3 who was hospitalized, 13 mo-25 yrs, 67% female) where no change in immunosuppression was made.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy impacts in-hospital graft survival.
30-Day Graft Survival	Based on data from 28 patients in 1 studies[4] Follow up 54 day	1 observational study reported on cohort of patients with COVID-19, followed by transplant program. There were no reports of 30 d graft loss in this cohort (n=28, age= 64.0 (IQR 53.5-70.5), sex=21% female), in which M was		**Very Low** Single observational study without a control group of patients who had no	We are uncertain whether adjustment to maintenance immunosuppression

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment)	Adjustment to maintenance immunosuppression therarpy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
		discontinued in 16 patients (70%), CNI dose reduced in 6 (26%) and high-dose corticosteroids in 8 patients (47%).		changes to their immunosuppressive agents.	therapy impacts 30 day graft survival.
Renal Failure	Based on data from 41 patients in 2 studies[5] Follow up 15 days; 54 days	Two of the observational studies (n=41) that reported on cohorts of patients with COVID-19, admitted to transplant programs reported on renal failure. These studies reported that they reduced or paused immunosuppression for the majority of their patients from the standard immunosuppression protocol that is expected in the transplant population. The most common immunosuppression withdrawn or reduced was anti-metabolite or mycophenolate. Other immunosuppressive agents such as prednisone or calcineurin and mammalian target of rapamycin (mTOR) inhibitors, were not withdrawn, but rather their dose reduced. Latif (n=28/22 in hospital) reported in-hospital and 30 day renal failure of 14% and 11% and Ketcham (n= 13) reported in-hospital and 30 day renal failure of 85% and 0%		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy improves or worsen in-hospital and 30 day renal failure.
Mechanical Ventilation	Based on data from 48 patients in 4 studies[6] Follow up 15 days, 54 days, NS in 2	Four observational studies (n=48) reported on cohorts of patients with COVID-19, admitted to transplant programs. All studies reported that they reduced or paused immunosuppression for the majority of their patients from the standard immunosuppression protocol that is expected in the transplant population. The most common immunosuppression withdrawn or reduced was anti-metabolite or mycophenolate. Other immunosuppressive agents such as prednisone or calcineurin and mammalian target of rapamycin (mTOR) inhibitors, were not withdrawn, but rather their dose reduced. Patient requiring mechanical ventilation ranged from 0% to 38%. Specifically, the largest cohort (n=28, age= 64.0 (IQR 53.5-70.5), sex=21% female), in which M was discontinued in 16 patients (70%), CNI dose reduced in 6 (26%) and high-dose corticosteroids in 8 patients (47%), reported 32% of pts required mechanical ventilation.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy improves or increases the risk of requiring mechanical ventilation.
Hospital Admission	Based on data from 52 patients in 5 studies Follow up 15 days, 54 days, NS in 3	Five observational studies reported on cohorts of patients with COVID-19, admitted to transplant programs. Four of these studies (Fernandez-Ruiz, Ketcham, Latif and Zhou, total n=48) reported that they reduced or paused immunosuppression for the majority of their patients from the standard immunosuppression protocol that is expected in the transplant population. The most		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therapy improves or worsens in-hospital survival.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment)	Adjustment to maintenance immunosuppression therarpy		
		common immunosuppression withdrawn or reduced was anti-metabolite or mycophenolate. Other immunosuppressive agents such as prednisone or calcineurin and mammalian target of rapamycin (mTOR) inhibitors, were not withdrawn, but rather their dose reduced. Hospital admission ranged from 79% to 100%. Specifically, the largest cohort (n=28, age= 64.0 (IQR 53.5-70.5), sex=21% female), in which M was discontinued in 16 patients (70%), CNI dose reduced in 6 (26%) and high-dose corticosteroids in 8 patients (47%), hospital admission of 79%. One other case series of 4 young patients (Lee) reported that all patients survived; mycophenolate sodium and valganciclovir were held for 6 weeks in 1 patient (15 yr female) who was hospitalized while no change in immunosuppression was made in the other 3 (13 mo-25 yrs, 67% female) 1/3 who was hospitalized.		

1. Primary study Supporting references [57]. [13]. [14]. [16]. [33].
2. Primary study Supporting references [14].
3. Primary study Supporting references [33]. [14]. [13]. [16]. [57].
4. Primary study Supporting references [14].
5. Primary study Supporting references [13]. [14].
6. Primary study Supporting references [13]. [75]. [57]. [14].

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Population: Adult liver transplant recipients with known or suspected COVID-19
Intervention: Adjustment to maintenance immunosuppression therapy
Comparator: Routine care (no adjustment to maintenance immunosuppression therapy)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment)	Adjustment to maintenance immunosuppression therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
In-Hospital Survival	Based on data from 42 patients in 5 studies[1]	Only two studies compared change to no change in baseline immunosuppression. In one study, only 1 patient had changes in their immunosuppression (MMF and Prednisone changed to Prednisone alone at a higher dose). The other four patients had no changes. The survival was 100% in both groups. In the second study 7 patients had stopped, reduced, or increase prednisone (variable across patients), whereas 3 patients had no changes in their immunosuppression. Across those with change, the survival was 71% whereas in the three with no change, survival was 100%. None of the remaining three studies identified a separate group of patients who maintained the standard immunosuppression protocol that is expected in the transplant population. Across these studies, there was either a complete withdrawal of immunosuppression or reduction in dose. Survival across these studies ranged from 67% to 77%. There was discernable pattern to explain the variability in observed survival rates.		**Very Low** Observational studies with small sample size, large variability across studies, and in some cases, lack of a control group.	We are uncertain whether adjustment to maintenance immunosuppressi on therarpy increases or decreases in-hospital survival
30-Day Survival	Based on data from 13 patients in 1 studies	One single study evaluated 30-day survival. Immunosuppression was maintained in some patients and changed in others. The change was not uniform across all patients. Outcomes were only reported for the entire cohort. The survival rate reported was 77%.		**Very Low** Observational study with small sample size. Lack of a control group and poor reporting creating great deal of uncertainty.	We are uncertain whether adjustment to maintenance immunosuppressi on therarpy increases or decreases 30-day survival
In-Hospital Graft Survival	Based on data from 6 patients in 1 studies	One single study evaluated graft survival. Calcineurin and mammalian target of rapamycin (mTOR) inhibitors were temporarily discontinued on initiation of LPV/r and trough serum levels were obtained after 48-72 hours, with close therapeutic drug monitoring (TDM) thereafter. Baseline daily prednisone dose was usually reduced by 50%. Mycophenolate mofetil/mycophenolic acid (MMF/MPA) was also decreased in patients receiving LPV/r The QT interval was regularly assessed in patients treated with HCQ. The graft survival was 100%.		**Very Low** Observational study with very few patients and lack of a control group.	We are uncertain whether adjustment to maintenance immunosuppressi on therarpy increases or decreases in-hospital graft survival
In-Hospital Renal Failure	Based on data from 24 patients in 1 studies	Variable practice of reduction in all patients. Reduction in overall immunosuppression regimen in 19 (79%); Calcineurin inhibitor 15 (63%); Mycophenolic acid 13 (100%); Corticosteroid 2 (17%). Rate of in-hospital renal failure was 54%.		**Very Low** Small observational study without a control group.	We are uncertain whether adjustment to maintenance immunosuppressi on therarpy

Outcome Timeframe	Study results and measurements	Absolute effect estimates Routine care (no adjustment)	 Adjustment to maintenance immunosuppression therapy	Certainty of the Evidence (Quality of evidence)	Plain text summary
					increases or decreases in-hospital renal failure
In-Hospital Fungal infection	Based on data from 5 patients in 1 studies	One patient had maintenance IS changed from MMF/ P to P alone at a higher dose. The other 4 had no change in IS. In the patient with change, no fungal infection was observed. Across the four with change, only one developed fungal infection (25%).		**Very Low** Very small sample size. Observational study.	We are uncertain whether adjustment to maintenance immunosuppression therarpy increases or decreases in-hospital fungal infection
In-Hospital Supplemental Oxygen	Based on data from 29 patients in 4 studies	Only one study reported outcomes separately across patients with and without change. 7 patients had a change in IS (Stop T (4), Reduce T (1), reduce M (1), stop M (1), stop MPA (1), Increase in P (1)). 3 had no change. Across the 7 with change the rate of need for supplemental oxygen was 86% whereas it was 33% in those without change. Across the remaining three studies, There was either a reduction or withdrawal of IS. The rate of need for supplemental oxygen was 0% to 75%.		**Very Low** Observational studies with small sample size, large variability across studies, and in some cases, lack of a control group.	We are uncertain whether adjustment to maintenance immunosuppression therarpy increases or decreases in-hospital supplemental oxygen
30-Day Supplemental Oxygen	Based on data from 13 patients in 1 studies	One study with very variable practice of managing IS. In some patients IS was stopped, in other dose was reduced. The rate of need for supplemental oxygen was 38%.		**Very Low** Observational study with small sample size. Lack of a control group and poor reporting creating great deal of uncertainty.	We are uncertain whether adjustment to maintenance immunosuppression therarpy increases or decreases 30-day supplemental oxygen
In-Hospital Mechanical Ventilation	Based on data from 41 patients in 4 studies	Only one study reported outcomes separately across patients with and without change. 7 patients had a change in IS (Stop T (4), Reduce T (1), reduce M (1), stop M (1), stop MPA (1), Increase in P (1)). 3 had no change. In both groups, there was no need for mechanical ventilation. In the remaining studies There was either a reduction or withdrawal of IS. The rate of need for mechanical ventilation ranged from 0 - 33%.		**Very Low** Observational studies with small sample size, large variability across studies, and in some cases, lack of a control group.	We are uncertain whether adjustment to maintenance immunosuppression therarpy increases or decreases in-hospital mechanical ventilation
30-Day Mechanical Ventilation	Based on data from 13 patients in 1 studies	One study with very variable practice of managing IS. In some patients IS was stopped, in other dose was reduced. The rate of need for mechanical ventilation was 8%.		**Very Low** Observational study with small sample size. Lack of a control group and poor	We are uncertain whether adjustment to maintenance immunosuppressi

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no adjustment)	Adjustment to maintenance immunosuppression therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
				reporting creating great deal of uncertainty.	on therarpy increases or decreases 30-day mechanical ventilation
In-Hospital Non-Invasive Ventilation	Based on data from 28 patients in 3 studies	Only two studies compared change to no change in baseline immunosuppression. In one study, only 1 patient had changes in their immunosuppression (MMF and Prednisone changed to Prednisone alone at a higher dose). The other four patients had no changes. The rate of non-invasive ventilation was 100% in the patient with change and 0% in patients with no change. In the second study 7 patients had stopped, reduced, or increase prednisone (variable across patients), whereas 3 patients had no changes in their immunosuppression. Across those with change, the rate was 29% whereas in the three with no change, rate was 0%. In the one remaining study, the management of IS was variable and the rate of non-invasive ventilation was 23%.		**Very Low** Observational studies with small sample size, large variability across studies, and in some cases, lack of a control group.	We are uncertain whether adjustment to maintenance immunosuppression therarpy increases or decreases in-hospital non-invasive ventilation
In-Hospital ARDS	Based on data from 6 patients in 1 studies	One single study evaluated ARDS. Calcineurin and mammalian target of rapamycin (mTOR) inhibitors were temporarily discontinued on initiation of LPV/r and trough serum levels were obtained after 48-72 hours, with close therapeutic drug monitoring (TDM) thereafter. Baseline daily prednisone dose was usually reduced by 50%. Mycophenolate mofetil/mycophenolic acid (MMF/MPA) was also decreased in patients receiving LPV/r The QT interval was regularly assessed in patients treated with HCQ. There were no cases of ARDS.		**Very Low** Observational study with very few patients and lack of a control group.	We are uncertain whether adjustment to maintenance immunosuppression therapy increases or decreases in-hospital ARDS
In-Hospital ICU Admission	Based on data from 30 patients in 2 studies	In one study, Calcineurin and mammalian target of rapamycin (mTOR) inhibitors were temporarily discontinued on initiation of LPV/r and trough serum levels were obtained after 48-72 hours, with close therapeutic drug monitoring (TDM) thereafter. Baseline daily prednisone dose was usually reduced by 50%. Mycophenolate mofetil/mycophenolic acid (MMF/MPA) was also decreased in patients receiving LPV/r The QT interval was regularly assessed in patients treated with HCQ. In the other, Reduction in overall IS regimen 19 (79%); Calcineurin inhibitor 15 (63%); Mycophenolic acid 13 (100%); Corticosteroid 2 (17%). The rate of need for ICU admission was 17 - 33%.		**Very Low** Observational studies with small sample size, large variability across studies, and in some cases, lack of a control group.	We are uncertain whether adjustment to maintenance immunosuppression therapy increases or decreases in-hospital ICU admission
Length of Hospital Stay	Based on data from 24 patients in 1 studies	One study observed reduction in overall IS regimen 19 (79%); Calcineurin inhibitor 15 (63%); Mycophenolic acid 13 (100%); Corticosteroid 2 (17%). The median length of stay was 9 days, ranging from 4 to 22 days.		**Very Low** Observational study with very few patients and lack of a control group.	We are uncertain whether adjustment to maintenance immunosuppression therarpy

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment)	Adjustment to maintenance immunosuppression therapy		
					increases or decreases length of hospital stay

1. Systematic review Supporting references [7]. [15]. [30]. [11]. [24].

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Population: Adult kidney transplant recipients with known or suspected COVID-19
Intervention: Adjustment to maintenance immunosuppression therapy
Comparator: Routine care (no adjustment to maintenance immunosuppression therapy)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment)	Adjustment to maintenance immunosuppression therarpy		
In-Hospital Survival	Based on data from 432 patients in 18 studies[1]	All studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. In-hospital survival ranged from 33% to 100%. Specifically, two studies (total n of 18) reported survival rates of 33% (one reported reducing doses but not withholding immunosuppressive agents. The other reported with-holding all immunosuppressive agents). Two other studies (n of 45) reported survival rates of 50% and both with-held immunosuppressive agents. The remaining studies reported survival rates between 75% to 100%		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppressio n therapy improves or worsen in-hospital survival.
30-Day Survival	Based on data from 243	All studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all		**Very Low**	We are uncertain whether

Outcome Timeframe	Study results and measurements	Absolute effect estimates Routine care (no adjustment)	 Adjustment to maintenance immunosuppression therarpy	Certainty of the Evidence (Quality of evidence)	Plain text summary
	patients in 6 studies	modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. 30-day survival ranged from 33% to 100%. Specifically, one study (total n of 6) reported survival rates of 33% (reported with-holding all immunosuppressive agents). One other study (n of 16) reported survival rates of 50% after withholding all immunosuppressive agents. The remaining studies reported survival rates between 75% to 100%		Observational studies without control group of patients who had no changes to their immunosuppressive agents.	adjustment to maintenance immunosuppressio n therapy improves or worsen in-hospital survival.
In-Hospital Graft Survival	Based on data from 142 patients in 5 studies	All studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. In-hospital graft survival ranged from 92% to 100%.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppressio n therarpy improves or worsen in-hospital graft survival
30-Day Graft Survival	Based on data from 81 patients in 4 studies	All studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. 30-day graft survival was 100% in all studies.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppressio n therarpy improves or worsen 30-day graft survival
In-Hospital Renal Failure	Based on data from 167 patients in 8 studies	All studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. The rate of in-hospital mortality ranged from 5% to 56%. The higher rates of renal		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppressio n therarpy improves or worsen in-hospital renal failure

Outcome Timeframe	Study results and measurements	Absolute effect estimates Routine care (no adjustment)	 Adjustment to maintenance immunosuppression therarpy	Certainty of the Evidence (Quality of evidence)	Plain text summary
		failure were observed in 2 studies with a total sample size of 64 patients. In one study, the authors withheld immunosuppression. The practice of withholding immunosuppressive agents was variable across patients. This observation was similar to that seen in studies reporting lower rates of in-hospital renal failure.			
30-day Renal Failure	Based on data from 6 patients in 1 studies	One single study in which the authors withheld tacrolimus in all patients and myfortic in one patient. The authors observed 30-day (long-term) renal failure in 2 patients (33%).		**Very Low** One single observational study without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppressio n therarpy increases or decreases 30-day renal failure
In-Hospital Bacterial Infection	Based on data from 86 patients in 4 studies	All studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. The rate of in-hospital bacterial infection ranged from 6 to 62%. There was no discernable trend in withdrawal or reduction of immunosuppression contributing to the wide range of risk of in-hospital bacterial infections.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppressio n therarpy increases or decreases in-hospital bacterial infection
In-Hospital Supplemental Oxygen	Based on data from 245 patients in 10 studies	All studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. The rate of need for supplemental oxygen ranged from 17 to 100%. There was no discernable trend in withdrawal or reduction of immunosuppression contributing to the wide range of need for supplemental oxygen.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppressio n therarpy increases or decreases in-hospital supplemental oxygen
30-Day Supplemental Oxygen	Based on data from 96 patients in 2 studies	Both studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the		**Very Low** Observational studies without control group of patients who had no	We are uncertain whether adjustment to maintenance immunosuppressio

Outcome Timeframe	Study results and measurements	Absolute effect estimates Routine care (no adjustment)	 Adjustment to maintenance immunosuppression therarpy	Certainty of the Evidence (Quality of evidence)	Plain text summary
		transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. The rate of need for supplemental oxygen ranged from 29 - 50%. There was no discernable trend in withdrawal or reduction of immunosuppression contributing to the wide range of need for supplemental oxygen.		changes to their immunosuppressive agents.	n therarpy increases or decreases 30-day supplemental oxygen
In-Hospital Mechanical Ventilation	Based on data from 361 patients in 16 studies	All studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. The rate of need for mechanical ventilation ranged from 0 to 75%. There was no discernable trend in withdrawal or reduction of immunosuppression contributing to the wide range of need for mechanical ventilation		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppressio n therarpy increases or decreases in-hospital mechanical ventilation
In-Hospital Non-Invasive Ventilation	Based on data from 204 patients in 8 studies	All studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. The rate of need for non-invasive ventilation ranged from 3 to 50%. There was no discernable trend in withdrawal or reduction of immunosuppression contributing to the wide range of need for non-invasive ventilation.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppressio n therarpy increases or decreases in-hospital non-invasive ventilation
30-Day Non-Invasive Ventilation	Based on data from 112 patients in 2 studies	Three studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. The rate of need for non-invasive ventilation ranged from 11 to 50%. There		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppressio n therarpy increases or decreases 30-day non-invasive ventilation

Outcome Timeframe	Study results and measurements	Absolute effect estimates Routine care (no adjustment)	 Adjustment to maintenance immunosuppression therarpy	Certainty of the Evidence (Quality of evidence)	Plain text summary
		was no discernable trend in withdrawal or reduction of immunosuppression contributing to the wide range of need for non-invasive ventilation.			
In-Hospital ARDS	Based on data from 146 patients in 10 studies	All studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. The rate of need for ARDS ranged from 0 to 67%. There was no discernable trend in withdrawal or reduction of immunosuppression contributing to the wide range of ARDS risk.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therarpy increases or decreases in-hospital ards
30-Day ARDS	Based on data from 6 patients in 1 studies	One single study in which the authors withheld tacrolimus in all patients and myfortic in one patient. The authors observed no cases of 30-day ARDS.		**Very Low** One single observational study without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppression therarpy increases or decreases 30-day ards
In-Hospital ICU Admission	Based on data from 270 patients in 12 studies	All studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. The rate of need for ICU ranged from 0 to 83%. There was no discernable trend in withdrawal or reduction of immunosuppression contributing to the wide range of risk for ICU admission		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents	We are uncertain whether adjustment to maintenance immunosuppression therarpy increases or decreases in-hospital icu admission
30-Day ICU Admission	Based on data from 106 patients in 2 studies	Both studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus,		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents	We are uncertain whether adjustment to maintenance immunosuppression therarpy increases or decreases 30-day icu admission

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		Routine care (no adjustment)	Adjustment to maintenance immunosuppression therarpy		
		and Prednisone were not withdrawn, but rather their dose reduced. The rate of 30-day ICU admission ranged from 26 - 38%. There was no discernable trend in withdrawal or reduction of immunosuppression contributing to the wide range of need for 30-day ICU admission.			
Length of Hospital Stay	Based on data from 177 patients in 11 studies	All studies reported on cohorts of patients with COVID-19, admitted to transplant programs who all modified the patient's immunosuppression. None of the identified studies maintained the standard immunosuppression protocol that is expected in the transplant population. Most common immunosuppression withdrawn was anti-metabolite or mycophenolate. Other immunosuppressive agents such as Tacrolimus, Sirolimus, Everolimus, and Prednisone were not withdrawn, but rather their dose reduced. The mean/median length of hospital stay ranged from 4.5 to 27 days. There was no discernable trend in withdrawal or reduction of immunosuppression contributing to the wide range of mean/median length of hospital stay.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents	We are uncertain whether adjustment to maintenance immunosuppressio n therarpy increases or decreases length of hospital stay
In-Hospital Thrombosis	Based on data from 26 patients in 1 studies	One single study in which the authors withheld myfortic in 50% of patients, tacrolimus in 15% and mTOR inhibitors in 8%. The authors observed no cases of in-hospital thrombosis.		**Very Low** ne single observational study without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppressio n therarpy increases or decreases in-hospital thrombosis

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Population: Paediatric kidney transplant recipients at risk for COVID-19
Intervention: Adjustment to maintenance immunosuppression therapy
Comparator: Routine care (no adjustment to maintenance immunosuppression therapy)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
		Routine care (no adjustment)	Adjustment to maintenance immunosuppression therarpy		
COVID-19	Based on data from 64 patients in 1 studies[1]	A cohort of 64 children with stable graft function, transplanted between 2010 to 2020, were prospectively followed. No change was made to their immunosuppression. None of the children developed clinical symptoms of COVID-19. Two children lived in a household in which a member was diagnosed with COVID-19. Both children were tested for COVID-19. The tests were negative and their Anti-SARS-CoV-2 antibody test was also negative. These two children also did not have any modification to their immunosuppression.		**Very Low** Observational studies without control group of patients who had no changes to their immunosuppressive agents.	We are uncertain whether adjustment to maintenance immunosuppressi on therarpy increases or decreases COVID-19

1. Primary study Supporting references [4].

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[4] Angeletti A., Trivelli A., Magnasco A., Drovandi S., Sanguineri F., Santaniello M., Ferrando G., Forno R., Cipresso G., Tripodi G., Riella LV, Cravedi P., Ghiggeri GM : Risk of COVID-19 in young kidney transplant recipients. Results from a single-center observational study. Clin Transplant 2020; e13889

7. Decision to proceed with organ transplant or organ replacement therapy in the setting of COVID-19

PICO Question:

In adult and pediatric transplant waitlist patients in areas with high COVID-19 incidence, does **organ transplantation** vs **organ replacement therapies** (e.g. dialysis, left ventricular assist devices, ventricular assist devices, extra-corporeal membrane oxygenation) /no organ transplant, improve patient outcomes (e.g. hospitalization, respiratory failure, days in ICU, mortality, development of COVID-19).

Reviewers:

A. Wright, L. Hornby, A. Malik, F Foroutan

Literature Search:

Citations Screened: 1900 Citations Included: 26

Recommendation:

7.1 We suggest proceeding with transplantation over remaining on organ replacement therapies in the setting of COVID-19 activity in the community (weak recommendation, very low certainty of evidence).

Key Literature and Rationale:

This recommendation is based on several studies encompassing both renal and liver specific groups as well as several large studies of all SOT recipients.[18,30,45,48,53,56,65–73] These studies were primarily retrospective cohorts from single centres. However, more recent reports included in the last iteration of the literature search included higher quality prospective cohorts.[74–76] There is currently more literature for the renal group than other SOT groups.

In the renal group, we identified 7 studies following 104,811 patients who were either on the waitlist / renal replacement therapy (RRT) or underwent transplantation.[1-7] Some of the studies reported the incidence of COVID-19 in each group separately, whereas others conducted a direct comparison between the two groups. We combined all of the studies in a meta-analysis of proportions and subgrouped the studies/cohorts based on the patient group (transplant vs waitlist/RRT). Among the patients on waitlist/RRT, the risk of COVID-19 was 93 per 1000 persons followed compared to 43 per 1000 in the transplant group (Figure 1). The absolute risk difference between the two groups was 50 fewer cases of COVID-19, with a 95% CI of 117 fewer cases to 9 more cases per 1000 persons followed.

Among the patients who were diagnosed with COVID-19, the risk of mortality (16 studies following 8,186 patients[1-16]) and admission to the ICU (11 studies following 1,839 patients[4,5,8-11,13-17]) was similar between patients undergoing transplantation as compared to those remaining on the waitlist/RRT. In the waitlist/RRT group, the risk of mortality was 199 per 1000 persons followed compared to 214 per 1000 in the transplant recipient group (Figure 2) with an absolute risk difference of 15 more cases in the transplant groups (95% CI of 59 fewer to 86 more cases per 1000 persons). Similarly, the incidence of

ICU admission was 163 per 1000 in the waitlist/RRT group (Figure 3), but 160 per 1000 in the transplant group (absolute risk different of 3 fewer per 1000 in the transplant group, 95% CI 343 fewer to 229 more per 1000 persons followed).

Meta-analysis was not possible for data from other organ groups. Based on a small number of studies,[6,17-22] liver recipients affected with COVID-19 appear to have low mortality than other organ recipient groups. Mortality was higher in those who were longer post-transplantation which may be confounded by the impact of age on COVID-19 mortality risk.[18] Most of the infections early post-transplantation were mild and all patients survived. This was in stark contrast to the cohorts of patients with end-stage liver disease based on one study.[20]

Limited data from pediatric heart and renal recipients indicated survival was 100% for children affected with COVID-19 even in the setting of transplantation.[23-26]

For the renal group specifically, based on the meta-analysis performed, there does not appear to be a trend towards transplant improving or worsening the risk of COVID-19. Among those with COVID-19, the meta-analysis did not show a difference in mortality or admission to the ICU between individuals undergoing transplantation compared to those on the waitlist/RRT. We acknowledge that there is imprecision around the point estimates and the indirect nature of our comparisons. However, despite the low certainty in the evidence, the panel felt that the overall balance of benefits, however, favoured continuing with transplantation, particularly if it could reduce the patients overall need to access healthcare. For the other organ groups, the panel reached the same conclusions and rationales and favoured proceeding with transplantation. This includes pediatric patients, though data was even more limited for this group.
The panel, however, felt that the decision to proceed with transplantation may vary across different transplant programs and across different candidates in need of transplantation. The decision to proceed with transplantation will also be dependent on the local status of the epidemic. Although at the individual patient level, we favor proceeding with transplant, this may not be feasible if healthcare resources are overwhelmed by the pandemic response. Local hospital administration will need to be involved in the allocation of surgical and medical resources and ultimately in the decision as to whether proceeding with transplantation is feasible for the system. To reflect this variability in practice and values and preferences, the strength of the recommendation remains weak.

In an effort to optimize transplant outcomes and maintain transplant activity, centers should have a planned COVID-19 free pathway which minimizes the risk of nosocomial COVID-19 infection. This should include pre-transplant testing of the recipient, isolation precautions for staff and recipient while in hospital, minimization of laboratory testing post-discharge, and post-discharge virtual care when feasible.

<u>Knowledge Gaps/Research Considerations:</u>

Significant knowledge gaps are present given the quality of the literature to date.

Evidence is limited in certain groups – specifically candidates for lung, heart and pancreas transplant. Most of these patients were only studied in cohorts with multiple different solid organ transplant groups. There were no patient cohorts of end-stage lung disease (which may be a mixture of COPD, IPF, cystic fibrosis), end stage heart-disease, or pure diabetes mellitus type 1. In addition, some of these groups have fewer options for organ replacement therapies or may potentially have higher risks from

COVID-19 infection (specifically lungs) There were no specific trials for lung transplant candidates but ECMO is a therapy that is generally restricted to an ICU setting and results in potential increased risk for complications the more transplant is delayed. Specific study in this candidates and recipients would be valuable. There is also limited data on pediatric candidates who have different risks from COVID-19 infection and limited data for renal transplant candidates who are not on in-centre hemodialysis who may have different risks for COVID-19 exposure (i.e. home hemodialysis or PD dialysis).

Any developed therapies or vaccination may change these recommendations, particularly to strengthen the recommendation to continue with transplantation.

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Evidence Profiles:

Population: Adult kidney transplant candidates in areas with COVID 19
Intervention: Transplant
Comparator: Remain on dialysis/waitlist

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Remain on dialysis/waitlist	Transplant	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
COVID-19 Un-specified	(CI 95% -) Based on data from 104811 patients in 7 studies[1] Follow up Not Reported	**93** per 1000	**43** per 1000 Difference: **50 fewer per 1000** (CI 95% 117 fewer - 9 more)	**Very Low** Due to very serious risk of bias, Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[2]	We are uncertain whether transplant improves or worsen the risk of covid-19

1. Systematic review . **Baseline/comparator** Control arm of reference used for intervention . Supporting references [90]. [99]. [77]. [100]. [93]. [98]. [101].
2. **Risk of bias: Serious.** Observational data; **Imprecision: Serious.** If 117 fewer is the truth, folks may make a different management decision as opposed to 9 more. ;

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Population: Adult kidney transplant candidates with COVID-19
Intervention: Transplant
Comparator: Remain on dialysis/waitlist

Outcome Timeframe	Study results and measurements	Absolute effect estimates Remain on dialysis/waitlist	 Transplant	Certainty of the Evidence (Quality of evidence)	Plain text summary
Mortality Un-specified	(CI 95% -) Based on data from 8186 patients in 16 studies[1] Follow up Not Reported	**199** per 1000	**214** per 1000 Difference: **15 more per 1000** (CI 95% 59 fewer - 86 more)	**Very Low** Due to very serious risk of bias, Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[2]	We are uncertain whether transplant recipients are at an increased or decreased risk of mortality post COVID-19 infection
ICU Admission Un-specified	(CI 95% -) Based on data from 1839 patients in 11 studies[3]	**163** per 1000	**160** per 1000 Difference: **3 fewer per 1000** (CI 95% 343 fewer - 229 more)	**Very Low** Due to very serious risk of bias, Due to serious risk of bias, Due to serious imprecision[4]	We are uncertain whether transplant recipients are at an increased or decreased risk of icu admission

1. Systematic review . **Baseline/comparator** Control arm of reference used for intervention . Supporting references [105]. [76]. [83]. [99]. [100]. [107]. [94]. [77]. [103]. [106]. [98]. [101]. [104]. [93]. [102]. [90].
2. **Risk of bias: Serious.** Observational data; **Imprecision: Serious.** If 117 fewer is the truth, folks may make a different management decision as opposed to 9 more. ;
3. Systematic review . **Baseline/comparator** Control arm of reference used for intervention . Supporting references [100]. [94]. [102]. [106]. [83]. [103]. [105]. [76]. [107]. [90]. [92].
4. **Risk of bias: Serious.** Observational studies and no direct comparison; **Imprecision: Serious.** 95CI confidence leads to completely different conclusions and management strategies ;

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Population: Adult lung transplant candidates in areas with COVID 19
Intervention: Transplant
Comparator: Remain on organ replacement/waitlist

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Remain on organ replacement/waitlist	Transplant	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality	Based on data from 884 patients in 2 studies[1] Follow up 14 days-4 months	There were no studies with n>2 that reported on outcomes specific to lung recipients 1 Large national retrospective database review (Ravanan) in UK that included 597 COVID+ Tx recipients and 197 waitlist pts (2.2.% of recipients were lung and 1 % of waiting list were waiting for a lung; 80 transplanted in 2019, 41 in 2020) reported mortality of 25.8% for all Tx (8/41, 19.5% Tx done in 2020; 16/80 20% done in 2019) and 10.2% for waitlist. MVA did not show any association with time from Tx. Increasing recipient age was the only variable independently associated with death after positive SARS-CoV-2 test. One study (Pereira) reported mortality in a cohort of 90 organ recipients (46 kidney, 17 lung, 13 liver, 9 heart, 3 heart-kidney, 1 liver-kidney, 1 kidney-pancreas; only 17.8% =< 1year post Tx) as 18% overall and 24% of hospitalized pts but 15 still in hospital, 9 of these in ICU		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[2]	We are uncertain whether transplant increases or decreases mortality
Patient Survival - 30 day	Based on data from 794 patients in 1 studies[3] Follow up Median (IQR) was 36 (13-47) for wait-listed and 44 (30-52) days for SOT recipients	Only 1 study calculated 30 day % survival in 597 COVID+ Tx recipients and 197 waitlist pts (2.2.% of recipients were lung and 1 % of waiting list were waiting for a lung; 80 transplanted in 2019, 41 in 2020) and reported as 89.5 (84.2-93.1) for waitlist and 73.6 (69.8-77.0) for organ recipients (not specific to lung)		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[4]	We are uncertain whether transplant increases or decreases patient survival - 30 day
ICU Admission	Based on data from 90 patients in 1 studies[5] Follow up Median 20 (14-24) days	Pereira reported ICU admission in a cohort of 90 organ recipients (46 kidney, 17 lung, 13 liver, 9 heart, 3 heart-kidney, 1 liver-kidney, 1 kidney-pancreas; only 17.8% =< 1year post Tx) as 26% (4 patients declined intubation/ICU admission)		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[6]	We are uncertain whether transplant increases or decreases icu admission

1. Primary study Supporting references [92]. [93].
2. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
3. Primary study Supporting references [93].
4. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
5. Primary study Supporting references [92].
6. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;

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Population: Adult pancreas transplant candidates in areas with COVID 19
Intervention: Transplant
Comparator: Remain on organ replacement/waitlist

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Remain on organ replacement/waitlist	Transplant	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality	Based on data from 894 patients in 3 studies[1] Follow up 14 days-4 months	Dube reported a case series of 4 (2< 1 yr post Tx) pancreas recipients who were COVID+. 1 patient who was <1yr post Tx died. 1 Large national retrospective database review (Ravanan) in UK that included 597 COVID+ Tx recipients and 197 waitlist pts(0.5% of recipients were pancreas and 3.2% SPK and 4.6 % of waiting list were waiting for SPK but 0% for pancreas; 80 transplanted in 2019, 41 in 2020) reported mortality of 25.8% for all Tx (8/41, 19.5% Tx done in 2020; 16/80 20% done in 2019) and 10.2% for waitlist. MVA did not show any association with time from Tx. Increasing recipient age was the only variable independently associated with death after positive SARS-CoV-2 test. One study (Pereira) reported mortality in a cohort of 90 organ recipients (46 kidney, 17 lung, 13 liver, 9 heart, 3 heart-kidney, 1 liver-kidney, 1 kidney-pancreas; only 17.8% =< 1year post Tx) as 18% overall and 24% of hospitalized pts but 15 still in hospital, 9 of these in ICU		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[2]	We are uncertain whether transplant increases or decreases mortality
Patient Survival - 30 day	Based on data from 794 patients in 1 studies[3] Follow up Median (IQR) was 36 (13-47) for wait-listed and 44 (30-52) days for SOT recipients	Only 1 study calculated 30 day % survival in 597 COVID+ Tx recipients and 197 waitlist pts (0.5% of recipients were pancreas and 3.2% SPK and 4.6 % of waiting list were waiting for SPK but 0% for pancreas; 80 transplanted in 2019, 41 in 2020) and reported as 89.5 (84.2-93.1) for waitlist and 73.6 (69.8-77.0) for organ recipients (not specific to pancreas))		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[4]	We are uncertain whether transplant increases or decreases patient survival -30 day

Outcome Timeframe	Study results and measurements	Absolute effect estimates Remain on organ replacement/waitlist	Transplant	Certainty of the Evidence (Quality of evidence)	Plain text summary
ICU Admission	Based on data from 90 patients in 1 studies[5] Follow up Median 20 (14-24) days	Pereira reported ICU admission in a cohort of 90 organ recipients (46 kidney, 17 lung, 13 liver, 9 heart, 3 heart-kidney, 1 liver-kidney, 1 kidney-pancreas; only 17.8% =< 1year post Tx) as 26% (4 patients declined intubation/ICU admission)		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[6]	We are uncertain whether transplant increases or decreases icu admission

1. Primary study Supporting references [93]. [92]. [66].
2. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
3. Primary study Supporting references [93].
4. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
5. Primary study Supporting references [92].
6. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;

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[93] Ravanan RA-O, Callaghan CA-O, Mumford L., Ushiro-Lumb I., Thorburn D., Casey J., Friend P., Parameshwar J., Currie IA-O, Burnapp L., Baker R., Dudley J., Oniscu GC, Berman M., Asher J., Harvey D., Manara AA-O, Manas D., Gardiner D., Forsythe JLR : SARS-CoV-2 infection and early mortality of wait-listed and solid organ transplant recipients in England: a national cohort study. LID - 10.1111/ajt.16247 [doi]. (1600-6143 (Electronic)):

Population: Adult heart transplant candidates in areas with COVID 19
Intervention: Transplantation
Comparator: Remain on organ replacement/waitlist

Outcome Timeframe	Study results and measurements	Absolute effect estimates Remain on organ replacement/waitlist	Transplantation	Certainty of the Evidence (Quality of evidence)	Plain text summary
Mortality	Based on data from 895 patients in 3 studies[1] Follow up 14d-4months	Boffini (n= 11 transplants done during COVID era until April) reported 3 later tested + for COVID 19 but all survived after at least 3 weeks fo follow up. They also reported 1 death on the waiting list during this period (do not say if related to COVID) 1 Large national retrospective database review (Ravanan) in UK that included 597 COVID+ Tx recipients and 197 waitlist pts (3.9% of recipients were HT but none of waiting list were waiting for heart; 80 transplanted in 2019, 41 in 2020) reported mortality of 25.8% for all Tx (8/41, 19.5% Tx done in 2020; 16/80 20% done in 2019) and 10.2% for waitlist. MVA did not show any		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[2]	We are uncertain whether transplantation increases or decreases mortality

Outcome Timeframe	Study results and measurements	Absolute effect estimates Remain on organ replacement/waitlist	Transplantation	Certainty of the Evidence (Quality of evidence)	Plain text summary
		association with time from Tx. Increasing recipient age was the only variable independently associated with death after positive SARS-CoV-2 test. One study (Pereira) reported mortality in a cohort of 90 organ recipients (46 kidney, 17 lung, 13 liver, 9 heart, 3 heart-kidney, 1 liver-kidney, 1 kidney-pancreas; only 17.8% =< 1year post Tx) as 18% overall and 24% of hospitalized pts but 15 still in hospital, 9 of these in ICU			
Patient Survival - 30 day	Based on data from 794 patients in 1 studies[3] Follow up Median (IQR) was 36 (13-47) for wait-listed and 44 (30-52) days for SOT recipients	Only 1 study calculated 30 % survival in 597 COVID+ Tx recipients and 197 waitlist pts (3.9% of recipients were HT but none of waiting list were waiting for heart; 80 transplanted in 2019, 41 in 2020)and reported as 89.5 (84.2-93.1) for waitlist and 73.6 (69.8-77.0) for organ recipients (not specific to heart)		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[4]	We are uncertain whether transplantation increases or decreases patient survival -30 day
ICU Admission	Based on data from 90 patients in 1 studies[5] Follow up Median 20 (14-24) days.	Pereira reported ICU admission in a cohort of 90 organ recipients (46 kidney, 17 lung, 13 liver, 9 heart, 3 heart-kidney, 1 liver-kidney, 1 kidney-pancreas; only 17.8% =< 1year post Tx) as 26% (4 patients declined intubation/ICU admission)		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[6]	We are uncertain whether transplantation increases or decreases icu admission

1. Primary study Supporting references [79]. [92]. [93].
2. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
3. Primary study Supporting references [93].
4. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
5. Primary study Supporting references [92].
6. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;

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Population: Pediatric heart transplant candidates in areas with COVID 19
Intervention: Transplant
Comparator: Remain on organ replacement/waitlist

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Remain on organ replacement/waitlist	Transplant	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality	Based on data from 4 patients in 1 studies[1] Follow up not stated	Lee reported a case series of 4 (2<= 6 mo post Tx) recent pediatric heart Tx recipients who were COVID +. All patients survived. F/u period not specified.		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[2]	We are uncertain whether transplant increases or decreases mortality

1. Primary study Supporting references [60].
2. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;

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Population: Pediatric kidney transplant candidates in area with COVID 19
Intervention: Transplant
Comparator: Remain on dialysis/waitlist

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Remain on dialysis/waitlist	Transplant	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality	Based on data from 6 patients in 1 studies[1] Follow up Md 19 (1-32)	Only 1 study included outcomes of pediatric dialysis patients and kidney Tx patients with COVID 19. The study was of children with chronic kidney pathologies who contracted COVID 19, 3 were Tx recipients (all >1yr post Tx) and 3 on dialysis. All patients survived. Followup period was Median 19 days (1-32).		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[2]	We are uncertain whether transplant increases or decreases mortality
Graft Survival	Based on data from 6 patients in 1 studies[3] Follow up Md 19 (1-32)	Only 1 study included outcomes of pediatric dialysis patients and kidney Tx patients with COVID 19. The study was of children with chronic kidney pathologies who contracted COVID 19, 3 were Tx recipients (all >1yr post Tx) and 3 on dialysis. 100% graft survival. Followup period was Median 19 days (1-32).		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[4]	We are uncertain whether transplant increases or decreases graft survival
ICU Admission	Based on data from 6 patients in 1 studies[5] Follow up Md 19 (1-32)	Only 1 study included outcomes of pediatric dialysis patients and kidney Tx patients with COVID 19. The study was of children with chronic kidney pathologies who contracted COVID 19, 3 were Tx recipients (all >1yr post Tx) and 3 on dialysis. None of the patients were admitted to the ICU. Followup period was Median 19 days (1-32).		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[6]	We are uncertain whether transplant increases or decreases icu admission

Outcome Timeframe	Study results and measurements	Absolute effect estimates Remain on dialysis/waitlist	Transplant	Certainty of the Evidence (Quality of evidence)	Plain text summary
Hospital Stay	Based on data from 6 patients in 1 studies[7] Follow up Md 19 days (1-32)	Only 1 study included outcomes of pediatric dialysis patients and kidney Tx patients with COVID 19. The study was of children with chronic kidney pathologies who contracted COVID 19, 3 were Tx recipients (all >1yr post Tx) and 3 on dialysis. Length of hospital stay only reported for whole cohort (n=16) as 3 +/- 0.5 days for 8/16 hospitalized of entire cohort. Followup period was Median 19 days (1-32).		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[8]	We are uncertain whether transplant increases or decreases hospital stay

1. Primary study Supporting references [88].
2. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
3. Primary study Supporting references [88].
4. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available, Differences between the population of interest and those studied; **Imprecision: Very Serious.** Low number of patients;
5. Primary study Supporting references [88].
6. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
7. Primary study Supporting references [88].
8. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;

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Population: Adult kidney transplant candidates in areas with COVID 19
Intervention: Transplant
Comparator: Remain on dialysis/waitlist

NOTE: THIS INCLUDES ARTICLES FROM ORIGINAL SEARCH (WITHOUT META ANALYSIS) AND ATTEMPTED TO FOCUS ON RECIPIENTS EARLY AFTER TRANSPLANT

Outcome Timeframe	Study results and measurements	Absolute effect estimates Remain on dialysis/waitlist	Transplant	Certainty of the Evidence (Quality of evidence)	Plain text summary
Mortality[1]	Based on data from 1613 patients in 7 studies[2] Follow up < = 4 months	Seven studies total. 2 studies (Alberici, Trujillo) reported outcomes of COVID-19+ Tx recipients (N= 20;26) and those on dialysis (N=21;25). Mortality for Tx was 25% & 23%, and 24% & 28% for Dialysis. Neither of these studies reported specifically on Tx patients who were <1yr post tx. 1 Large national retrospective database review (Ravanan) in UK that included 597 COVID+ Tx recipients and 197 waitlist pts(81.9% of recipients were KT or SPK and 95.5% of waiting list were waiting for kidney or SPK; 80 transplanted in 2019, 41 in 2020) reported mortality of 25.8% for all Tx (8/41, 19.5% Tx done		**Very Low** Due to serious risk of bias, Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[3]	We are uncertain whether transplant increases or decreases mortality

Outcome Timeframe	Study results and measurements	Absolute effect estimates Remain on dialysis/waitlist	Absolute effect estimates Transplant	Certainty of the Evidence (Quality of evidence)	Plain text summary
		in 2020; 16/80 20% done in 2019) and 10.2% for waitlist. MVA did not show any association with time from Tx. Increasing recipient age was the only variable independently associated with death after positive SARS-CoV-2 test. Two other studies only included Tx patients; 1 (Fava) included 89 recipients, 11 that were <6 mo post Tx with 55% mortality in those and the other (Pascual) that focussed solely on pts <6 mo post transplant reported a 46% mortality in 24 COVID+ recipients. One study (Pereira) reported mortality in a cohort of 90 organ recipients (46 kidney, 17 lung, 13 liver, 9 heart, 3 heart-kidney, 1 liver-kidney, 1 kidney-pancreas; only 17.8% =< 1year post Tx) as 18% overall and 24% of hospitalized pts but 15 still in hospital, 9 of these in ICU). One study (Arlsan) reported on 602 hemodialysis patients from one centre, 7 became COVID + but none died.		
Patient Survival - 30 day	Based on data from 794 patients in 1 studies[4] Follow up Median (IQR) was 36 (13-47) for wait-listed and 44 (30-52) days for SOT recipients	Only 1 study calculated 30 day % survival in 597 COVID+ Tx recipients and 197 waitlist pts (81.9% of recipients were KT or SPK and 95.5% of waiting list were waiting for kidney or SPK; 80 transplanted in 2019, 41 in 2020)and reported as 89.5 (84.2-93.1) for waitlist and 73.6 (69.8-77.0) for organ recipients (not specific to kidney)		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[5]	We are uncertain whether transplant increases or decreases patient survival - 30 day
Renal Failure (in hospital)	Based on data from 75 patients in 2 studies[6] Follow up < = 1 month	Two studies reported on renal failure in Tx recipients.Trujillo (n= 26 Tx, 25 D) reported renal failure of 69% (78%, AKIN 1, 22% AKIN 2) none needed dialysis and Pascual (n=24 Tx) 54.2. Only Trujillo reported in dialysis as 0.		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[7]	We are uncertain whether transplant increases or decreases renal failure (in hospital)
ICU Admission	Based on data from 206 patients in 4 studies[8] Follow up < = 1 month	Only four studies (one that included all organ recipients not just kidney and not just early post Tx) reported on ICU admission and at times patients refused admission or were denied because of lack of resources. Pascual (n=24 <6 mo post Tx) reported that 4 pts were admitted to ICU and 2 of these died, ICU admission was denied in 9 others. Alberici (n= 20 Tx, 21 D)reported that 4 KT went to ICU and Trujillo (n= 26 KT; 25 D) reported that none of the pts could go to ICU because of resource restraints. Pereira reported ICU admission in a cohort of 90 organ recipients (46 kidney, 17 lung, 13 liver, 9 heart, 3 heart-kidney, 1 liver-kidney, 1 kidney-pancreas; only 17.8% =< 1year post Tx) as 26% (4 patients declined intubation/ICU admission).		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[9]	We are uncertain whether transplant increases or decreases icu admission

Outcome Timeframe	Study results and measurements	Absolute effect estimates Remain on dialysis/waitlist	 Transplant	Certainty of the Evidence (Quality of evidence)	Plain text summary
Hospital Stay	Based on data from 41 patients in 1 studies[10] Follow up < = 1 month	Alberici reported that hospital stay was mean of 13 days for Tx and 12 days for Dialysis		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[11]	We are uncertain whether transplant increases or decreases hospital stay

1. Mortality with COVID 19 for kidney transplant recipients compared to those on dialysis
2. Primary study Supporting references [90]. [77]. [92]. [83]. [94]. [93]. [76].
3. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
4. Primary study Supporting references [93].
5. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available, Differences between the population of interest and those studied; **Imprecision: Very Serious.** Low number of patients;
6. Primary study Supporting references [90]. [94].
7. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
8. Primary study Supporting references [76]. [90]. [92]. [94].
9. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available, Differences between the population of interest and those studied; **Imprecision: Very Serious.** Low number of patients;
10. Systematic review Supporting references [76].
11. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;

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[93] Ravanan RA-O, Callaghan CA-O, Mumford L., Ushiro-Lumb I., Thorburn D., Casey J., Friend P., Parameshwar J., Currie IA-O, Burnapp L., Baker R., Dudley J., Oniscu GC, Berman M., Asher J., Harvey D., Manara AA-O, Manas D., Gardiner D., Forsythe JLR : SARS-CoV-2 infection and early mortality of wait-listed and solid organ transplant recipients in England: a national cohort study. LID - 10.1111/ajt.16247 [doi]. (1600-6143 (Electronic)):

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Population: Adult liver transplant candidates in areas with COVID-19
Intervention: Transplantation
Comparator: Remain on organ replacement therapy/waitlist

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Remain on organ replacement therapy/waitlist — Transplantation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality	Based on data from 1161 patients in 6 studies[1] Follow up <= 4 months	Four studies reported on mortality in liver Tx recipients in early Tx period. Massoumi reported 5/13 recent liver recipients contracted COVID 19 but none died. Belli reported mortality for cohort 103 (21 recent Tx) COVID+ recipients as only observed in those 60 yrs or over (16[22%, 95% CI 13-33] of 73 patients vs none [0%, 0-13] of 27 patients <60 years. Mortality was in 15 [18%, 95% CI 11–28] of 82 patients with Tx >=2yrs vs one [5%, 0–24] of 21 patients with Tx <2yrs. Patrono (n=10 COVID+, 3 recent Tx) reported overall Mortality as 20%, 10% directly attributable to COVID. Colmenero (n=111, 15 recent Tx) reported overall Mortality as 18% and Standardized (by age and gender) Mortality Ratio of 95.55 (95%CI 94.25-96.85). No deaths in those <60 yrs old. One study (Lavarone) followed 50 hospitalized patients with cirrhosis and COVID19. They report 30-day cumulative probability of overall mortality as 34% [95% Confidence Interval (CI) 23-49] and show this is higher (p=.035) than for non cirrotic patients (n=399) which was [18% (95%CI 15-22). 1 Large national retrospective database review (Ravanan) in UK that included 597 COVID+ Tx recipients and 197 waitlist pts(Only 10.7% of recipients were liver and 3% of waiting list were waiting for liver; 80 transplanted in 2019, 41 in 2020) reported mortality of 25.8% for all Tx (8/41, 19.5% Tx done in 2020; 16/80 20% done in 2019) and 10.2% for waitlist. MVA did not show any association with time from Tx. Increasing recipient age was the only variable independently associated with death after positive SARS-CoV-2 test. One study (Pereira) reported mortality in a cohort of 90 organ recipients (46 kidney, 17 lung, 13 liver, 9 heart, 3 heart-kidney, 1 liver-kidney, 1 kidney-pancreas; only 17.8% =< 1year post Tx) as 18% overall and 24% of hospitalized pts but 15 still in hospital, 9 of these in ICU).	**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision, Due to very serious publication bias[2]	We are uncertain whether transplantation increases or decreases mortality
Patient Survival - 30 day	Based on data from 794 patients in 1 studies[3] Follow up Median (IQR) was 36 (13-47) for wait-listed and 44 (30-52)	Only 1 study calculated 30 day % survival in 597 COVID+ Tx recipients and 197 waitlist pts(10.7% of recipients were liver recipients and 3% of waiting list were waiting for liver; 80 transplanted in 2019, 41 in 2020)and reported as 89.5 (84.2-93.1) for waitlist and 73.6 (69.8-77.0) for organ recipients (not specific to liver)	**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[4]	We are uncertain whether transplantation increases or decreases patient survival -30 day

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Remain on organ replacement therapy/waitlist	Transplantation	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
	days for SOT recipients				
ICU Admission	Based on data from 140 patients in 2 studies[5] Follow up < 1 month	One study (Pereira) reported n=23 (26%; 4 patients declined intubation/ICU admission) ICU admission from a cohort of 90 organ recipients (46 kidney, 17 lung, 13 liver, 9 heart, 3 heart-kidney, 1 liver-kidney, 1 kidney-pancreas; only 17.8% =< 1year post Tx) . One study (Iavarone n=50 patients with cirrhosis and COVID19) reported that 2 patients were admitted to the ICU		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[6]	We are uncertain whether transplantation increases or decreases icu admission
Hospital Stay	Based on data from 50 patients in 1 studies[7] Follow up < 1 month	One study (Iavarone n=50 patients with cirrhosis and COVID19) reported that length of hospital stay as Md 15 days IQR 10-23		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[8]	We are uncertain whether transplantation increases or decreases hospital stay
ARDS[9]	Based on data from 50 patients in 1 studies[10] Follow up < 1 month	One study (Iavarone n=50 patients with cirrhosis and COVID19) reported that 52% of hospitalized patients developed ARDS		**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision[11]	We are uncertain whether transplantation increases or decreases ards

1. Primary study Supporting references [80]. [87]. [91]. [92]. [93]. [78]. [84].
2. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
3. Primary study Supporting references [93].
4. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
5. Primary study Supporting references [84]. [92].
6. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Low number of patients;
7. Primary study Supporting references [84].
8. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;
9. Acute Respiratory Distress Syndrome from COVID19
10. Primary study Supporting references [84].
11. **Risk of bias: Very Serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting; **Indirectness: Very Serious.** Direct comparisons not available; **Imprecision: Very Serious.** Only data from one study;

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8. Prophylaxis against COVID-19 in solid organ transplant recipients

PICO Question:

In adult and pediatric patients who have received a solid organ transplant or are currently on the waitlist for organ transplant, does prophylaxis (chemoprophylaxis) vs routine care (i.e. no prophylaxis) prevent infections with SARS-CoV2 and/or improve patient outcomes in those who are infected with SARS-CoV2 and develop COVID-19 disease.

Reviewers:

C. A. Buchan, T. M. Wilson

Literature Search:

Citations Screened: 1900 Citations Included: 0

Recommendations:

8.1 We make no recommendation for or against prophylactic treatment for SARS-CoV-2.

Good Practice Statement:

Transplant recipients and those waiting for transplant should follow public health guidance, including but not limited to, physical distancing, hand hygiene, and wearing a mask.

Key Literature and Rationale:

We are unable to recommend for or against prophylactic treatment for SARS-CoV-2 in transplant recipients due to a lack of evidence. There is one registered randomized control trial on prophylaxis for patients at risk of COVID-19, including solid organ transplant recipients. This trial is active and, thus, results are not yet published.

Since there is no available data on the use of chemoprophylactic strategies for prevention of infection with SARS-CoV2 in solid organ transplant recipients, at present time, prevention revolves around public health and infection control strategies. Adherence to public health guidance for physical distancing, mask wearing, and diligent hand hygiene is recommended.

Additionally, there are currently no chemoprophylaxis strategies recommended in the general population but several ongoing trials are underway. In the future, if supportive data does become available for chemoprophylaxis use, careful consideration will need to be paid to drug-drug interactions with agents used in transplantation, including immunosuppressive and other routine prophylactic regimens, when developing recommendations for solid organ transplant patients.

Knowledge Gaps/Research Considerations:

Considerable knowledge gaps exist. At present time, there are no specific studies published on prophylaxis of infection with SARS-CoV2 in solid organ transplant patients and only a very limited number, including one peer reviewed randomized control trial of hydroxychloroquine prophylaxis in occupational and household contacts, in the general population. At present time, prophylaxis, including pre- and post-exposure is not recommended outside of clinical trial. Currently there are multiple prophylactic strategies under investigation.

Future studies to optimally answer this question would be to randomize transplant recipients to receive chemo-prophylaxis compared to no prophylaxis (ie. current practice). Potential study designs could address pre-exposure prophylaxis in areas of high prevalence or post-exposure prophylaxis after a confirmed exposure. Studies would need to assess the success of preventing infection with SARS-CoV2 compared to standard of care, but would also need to assess impact of potential adverse outcomes including drug-drug interactions, graft dysfunction, etc.

9. Anti COVID-19 therapy in solid organ transplant recipients

PICO Question:

In adult and pediatric transplant recipients and waitlist patients with COVID-19, does anti-COVID treatment (e.g. lopinavir-ritonavir, hydroxychloroquine, remdesivir, tocilizumab, sarilumab, siltuximab, anakinra, convalescent serum) vs routine supportive care (no specific anti-COVID treatment) improve patient outcomes?

Reviewers:

ML. Luong, S. Shalhoub, S. Bernier

Literature Search:

Citations Screened: 1900 Citations Included: 12

Recommendation:

9.1 We make no recommendation for or against specific anti-COVID-19 treatment. We suggest following the national guidance available for the general population.

Key Literature and Rationale:

This recommendation is based on a review of 12 publications of small cohort studies.[1-12] Cohort size ranged from 10 to 29 SOT patients hospitalized with COVID infection. Treatment received were highly heterogenous and included a wide range of therapeutic agents: antiviral, anti-inflammatory, immunomodulators and convalescent plasma. Mortality outcome was reported for each treatment group however, outcome among untreated patients (standard of care) was often lacking, and when present, was confounded due to lack of randomization where the decision to withhold treatment was often due to relative stability compared to treated patients. The small number of patients, the heterogenous treatment modalities and the lack of standard of care-untreated group precludes any significant meaningful comparative analysis.

Given that the magnitude of the COVID pandemic transcends beyond the transplant population, we refer to the current treatment guidelines for COVID for both SOT and non-SOT patient population.

Knowledge Gaps/Research Considerations:

Research on treatment COVID is moving at an exceedingly fast pace and treatment guidelines for COVID change on a weekly basis. Therapeutic candidates include antivirals, anti-inflammatory agent, immunomodulators and passive immunotherapy such as convalescent plasma. Numerous large clinical trials are ongoing to determine the efficacy of each of these agents. Given the global magnitude of the pandemic, current research and large clinical trials are conducted in the general population. Conclusion of these trials will determine treatment guidelines. These guidelines will likely be applicable to all patients (both SOT and non-SOT).

SOT recipients are at higher risk of sever COVID disease. Therefore, it is important to understand how to optimize their management to improve outcome. While treatment data in SOT is limited, and that trials focused on SOT are unlikely to occur, it is worthwhile mentioning the importance to continue to conduct research in this at-risk patient population.

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Evidence Profiles:

Population: Adult kidney transplant recipients who have acquired COVID-19
Intervention: Anti-COVID-19 therapy
Comparator: Routine care (no specific anti-COVID-19 therapy)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no specific anti-COVID-19 therapy) Anti-COVID-19 therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
In-Hospital Survival[1]	Based on data from 167 patients in 10 studies[2] Follow up Ranges from (median) 7-43 days	In seven studies (Alberici, Columbia University, Crespo, Devresse, Nair, Rodriquez-Cubillo, Zhu) of 118 kidney transplant recipients, 62 of 77 (81%) recipients who received hydroxychloroquine survived. 15 of 19 (79%) of recipients who received hydrxychloroquine and LPV or darunavir survived. 14 of 18 (78%) recipients who received azithromycin survived. 1 of 5 (20%) of recipients who received LPV survived. 9 out of 10 (90%) who received umifenovir (6), oseltamivir (2), ribavirin (1), or ganciclovir (1) survived. 40 out of 57 (70%) of recipients who received corticosteroids survived. 6 out of 11 (55%) of recipients who received dexamethasone survived. 15 out of 20 (75%) of recipients who received tocilizumab survived. 11 out of 15 (73%) of recipients who received immunoglobulins survived. 5 of 6 (83%) recipients who did not receive anti-viral treatments survived. In all studies many treatments were given in combination. In three additional studies (Fernandez-Ruiz, Fung, Yi) of 49 transplant recipients (all organs, including kidney), 15 of 18 (83%) recipients who received hydroxychloroquine survived. 10 of 11 (91%) recipients who received hydroxychloroquine or azithromycin or a combination of both survived. 5 of 9 (56%) of recipients who received lopinavir-ritonavir survived. 1 of 3 (33%) of recipients who received interferon beta survived. 1 of 2 (50%) of recipients who received immunoglobulins survived. 5 of 6 (83%) recipients who received ribavirin survived. All recipients (100%) who received remdesivir (3), corticosteroids (2), tocilizumab (6), convalescent plasma (2), anakinra (1), and nebulized IFN (1) survived. In all studies many treatments were given in combination. 7 out of 8 (88%) recipients who did not receive anti-viral treatments survived.	**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision, Due to very serious inconsistency[3]	We are uncertain whether anti-covid-19 therapy improves or worsen in-hospital survival
30-Day Survival	Based on data from 110 patients in 7 studies[4]	In four studies (Alberini, Columbia University, Crespo, Zhu) of 61 kidney transplant recipients, 19 out of 26 (73%) recipients who received hydroxychloroquine survived. 15 out of 19 (79%) recipients who received hydroxychloroquine and	**Very Low** Due to very serious risk of bias, Due to very serious	We are uncertain whether anti-covid-19 therapy improves or worsen 30-day survival

Outcome Timeframe	Study results and measurements	Absolute effect estimates Routine care (no specific anti-COVID-19 therapy)	Anti-COVID-19 therapy	Certainty of the Evidence (Quality of evidence)	Plain text summary
	Follow up Ranges from (median) 7-43 days	boosted LPV or darunavir survived. 1 out of 5 (20%) of recipients who received LPV survived. 7 out of 9 (78%) of recipients who received azithromycin survived. 9 out of 10 (90%) recipients who received the following antivirals umifenovir (6), oseltamivir (2), ribavirin (1), or ganciclovir (1) survived. 6 out of 11 (55%) recipients who received dexamethasone survived. 21 out of 34 (62%) recipients who received corticosteroids survived. 6 out of 7 (86%) of recipients who received immunoglobulins survived. 8 out of 11 (73%) recipients who received tocilizumab survived. In all studies, many treatments were given in combination. 5 of 6 (83%) of patients who did not receive anti-viral treatment survived. In three additional studies (Fernandez-Ruiz, Fung, Yi) of 49 transplant recipients (all organs, including heart), 15 of 18 (83%) recipients who received hydroxychloroquine survived. 10 of 11 (91%) recipients who received hydroxychloroquine or azithromycin or a combination of both survived. 5 of 9 (56%) of recipients who received lopinavir-ritonavir survived. 1 of 3 (33%) of recipients who received interferon beta survived. 1 of 2 (50%) of recipients who received immunoglobulins survived. 5 of 6 (83%) recipients who received ribavirin survived. All recipients (100%) who received remdesivir (3), corticosteroids (2), tocilizumab (6), convalescent plasma (2), anakinra (1), and nebulized IFN (1) survived. In all studies many treatments were given in combination. 16 of 17 (94%) recipients who did not receive anti-viral treatments survived.		inconsistency, Due to very serious indirectness, Due to very serious imprecision[5]	

1. Add details of what this means here.
2. Primary study Supporting references [58]. [61]. [64]. [57]. [53]. [56]. [62]. [55]. [63]. [54].
3. **Risk of bias: Very Serious. Inconsistency: Very Serious. Indirectness: Very Serious. Imprecision: Very Serious.**
4. Primary study Supporting references [57]. [63]. [58]. [55]. [64]. [53]. [54].
5. **Risk of bias: Very Serious. Inconsistency: Very Serious. Indirectness: Very Serious. Imprecision: Very Serious.**

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Population: Adult liver transplant recipients who have acquired COVID-19
Intervention: Anti-COVID-19 therapy
Comparator: Routine care (no specific anti-COVID-19 therapy)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no specific anti-COVID-19 therapy)	Anti-COVID-19 therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
In-Hospital Survival	Based on data from 73 patients in 4 studies[1] Follow up Median 18 - 32 days	In one study (Lee) of 24 liver transplant recipients, 12 of 18 (67%) recipients who received hydroxychorloquine (some in combination with azithromycin; N is unknown) survived, while 1 of 5 (20%) of recipients who received corticosteroids survived. It is unclear whether 1 or 2 recipients did not receive anti-viral treatments. The survival rate of these patients is either 0% or 50%. In three studies (Fernandez-Ruiz, Fung, Yi) of 49 transplant recipients (all organs, including liver), 15 of 18 (83%) recipients who received hydroxychloroquine survived. 10 of 11 (91%) recipients who received hydroxychloroquine or azithromycin or a combination of both survived. 5 of 9 (56%) of recipients who received lopinavir-ritonavir survived. 1 of 3 (33%) of recipients who received interferon beta survived. 1 of 2 (50%) of recipients who received immunoglobulins survived. 5 of 6 (83%) recipients who received ribavirin		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[2]	We are uncertain whether anti-covid-19 therapy improves or worsen in-hospital survival

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no specific anti-COVID-19 therapy)	Anti-COVID-19 therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
		survived. All recipients (100%) who received remdesivir (3), corticosteroids (2), tocilizumab (6), convalescent plasma (2), anakinra (1), and nebulized IFN (1) survived. Of note, in all studies many treatments were given in combination. 7 out of 8 (88%) recipients who did not receive anti-viral treatments survived.			
30-Day Survival	Based on data from 49 patients in 3 studies[3] Follow up Median 18 - 32 days	The one study (Lee) of 24 liver transplant recipients, did not report 30-day survival rates. In three studies (Fernandez-Ruiz, Fung, Yi) of 49 transplant recipients (all organs, including heart), 15 of 18 (83%) recipients who received hydroxychloroquine survived. 10 of 11 (91%) recipients who received hydroxychloroquine or azithromycin or a combination of both survived. 5 of 9 (56%) of recipients who received lopinavir-ritonavir survived. 1 of 3 (33%) of recipients who received interferon beta survived. 1 of 2 (50%) of recipients who received immunoglobulins survived. 5 of 6 (83%) recipients who received ribavirin survived. All recipients (100%) who received remdesivir (3), corticosteroids (2), tocilizumab (6), convalescent plasma (2), anakinra (1), and nebulized IFN (1) survived. Of note, in all studies many treatments were given in combination. 16 of 17 (94%) recipients who did not receive anti-viral treatments survived.		**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[4]	We are uncertain whether anti-covid-19 therapy improves or worsen 30-day survival

1. Primary study Supporting references [60]. [63]. [58]. [57].
2. **Risk of bias: Very Serious. Inconsistency: Very Serious. Indirectness: Very Serious. Imprecision: Very Serious.**
3. Systematic review Supporting references [57]. [58]. [63].
4. **Risk of bias: Very Serious. Inconsistency: Very Serious. Indirectness: Very Serious. Imprecision: Very Serious.**

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Population: Adult heart transplant recipients who have acquired COVID-19
Intervention: Anti-COVID-19 therapy
Comparator: Routine care (no specific anti-COVID-19 therapy)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no specific anti-COVID-19 therapy) Anti-COVID-19 therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
In-Hospital Survival	Based on data from 49 patients in 3 studies[1] Follow up Median 18 - 32 days	In three studies (Fernandez-Ruiz, Fung, Yi) of 49 transplant recipients (all organs, including heart), 15 of 18 (83%) recipients who received hydroxychloroquine survived. 10 of 11 (91%) recipients who received hydroxychloroquine or azithromycin or a combination of both survived. 5 of 9 (56%) of recipients who received lopinavir-ritonavir survived. 1 of 3 (33%) of recipients who received interferon beta survived. 1 of 2 (50%) of recipients who received immunoglobulins survived. 5 of 6 (83%) recipients who received ribavirin survived. All recipients (100%) who received remdesivir (3), corticosteroids (2), tocilizumab (6), convalescent plasma (2), anakinra (1), and nebulized IFN (1) survived. Of note, in all studies many treatments were given in combination. 7 out of 8 (88%) recipients who did not receive anti-viral treatments survived.	**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[2]	We are uncertain whether anti-covid-19 therapy improves or worsen in-hospital survival
30-Day Survival	Based on data from 49 patients in 3 studies[3] Follow up Median 18 - 32 days	In three studies (Fernandez-Ruiz, Fung, Yi) of 49 transplant recipients (all organs, including heart), 15 of 18 (83%) recipients who received hydroxychloroquine survived. 10 of 11 (91%) recipients who received hydroxychloroquine or azithromycin or a combination of both survived. 5 of 9 (56%) of recipients who received lopinavir-ritonavir survived. 1 of 3 (33%) of recipients who received interferon beta survived. 1 of 2 (50%) of recipients who received immunoglobulins survived. 5 of 6 (83%) recipients who received ribavirin survived. All recipients (100%) who received remdesivir (3), corticosteroids (2), tocilizumab (6), convalescent plasma (2), anakinra (1), and nebulized IFN (1) survived. Of note, in all studies many treatments were given in combination. 16 out of 17 (94%) recipients who did not receive anti-viral treatments survived; 9 recipients were out-patients.	**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[4]	We are uncertain whether anti-covid-19 therapy improves or worsen 30-day survival

1. Primary study Supporting references [57]. [63]. [58].
2. **Risk of bias: Very Serious. Inconsistency: Very Serious. Indirectness: Very Serious. Imprecision: Very Serious.**
3. Primary study Supporting references [63]. [58]. [57].
4. **Risk of bias: Very Serious. Inconsistency: Very Serious. Indirectness: Very Serious. Imprecision: Very Serious.**

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Population: Adult lung transplant recipients who have acquired COVID-19
Intervention: Anti-COVID-19 therapy
Comparator: Routine care (no specific anti-COVID-19 therapy)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Routine care (no specific anti-COVID-19 therapy) Anti-COVID-19 therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
In-Hospital Survival	Based on data from 31 patients in 2 studies[1] Follow up Median 18 - 32 days	In two studies (Fung, Yi) of 31 transplant recipients (all organs, including lung), 13 out of 14 (93%) recipients who received hydroxychloroquine, azithromycin, or a combination of both survived. 5 out of 6 (83%) of recipients who received ribavirin survived. All recipients (100%) who received remdesivir (3), corticosteroids (2), tocilizumab (5), convalescent plasma (2), anakinra (1), and nebulized IFN (1) survived. Of note, in all studies many treatments were given in combination. 6 out of 6 (100%) recipients who did not receive anti-viral treatments also survived.	**Very Low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious inconsistency, Due to very serious imprecision[2]	We are uncertain whether anti-covid-19 therapy increases or decreases in-hospital survival
30-Day Survival	Based on data from 31 patients in 2 studies[3] Follow up Median 18 - 32 days	In two studies (Fung, Yi) of 31 transplant recipients (all organs, including lung), 13 out of 14 (93%) recipients who received hydroxychloroquine, azithromycin, or a combination of both survived. 5 out of 6 (83%) of recipients who received ribavirin survived. All recipients (100%) who received remdesivir (3), corticosteroids (2), tocilizumab (5), convalescent plasma (2), anakinra (1), and nebulized IFN (1) survived. Of note, in all studies many treatments were given in combination. 15 out of 15 (100%) recipients who did not receive anti-viral treatments also survived; 9 of the recipients were out-patients.	**Very Low** Due to very serious risk of bias, Due to very serious inconsistency, Due to very serious indirectness, Due to very serious imprecision[4]	We are uncertain whether anti-covid-19 therapy improves or worsen 30-day survival

1. Primary study Supporting references [63]. [58].
2. **Risk of bias: Very Serious. Inconsistency: Very Serious. Indirectness: Very Serious. Imprecision: Very Serious.**
3. Systematic review Supporting references [58]. [63].
4. **Risk of bias: Very Serious. Inconsistency: Very Serious. Indirectness: Very Serious. Imprecision: Very Serious.**

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