Evidence summary

Clinical care of people with a kidney or kidney-pancreas transplant during a COVID-19 pandemic

Developed on 11 May 2020 version 1.0

The target audience for this set of guidelines is for health professionals. The consumer version of this guidance will be available soon. Coronaviruses are a large family of viruses that cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS).(1, 2) The newest member of the coronavirus family is the novel coronavirus SARs-CoV-2 which causes coronavirus disease (COVID-19).(1) The symptoms of COVID-19 include cough, fever and shortness of breath.(3-5) Both the new virus and the disease were unknown before the outbreak began in December 2019.

As the COVID-19 pandemic continues, a large volume of research and guidelines have been released in response to emerging evidence.

KHA-CARI is producing a limited number of evidence summaries related to clinical care related to COVID-19 in people with kidney disease including acute kidney injury, kidney/kidney-pancreas transplantation, dialysis and earlier stages of chronic kidney disease. It is anticipated these summaries will be reviewed and updated on a fortnightly basis and any new changes are highlighted.

KHA-CARI welcomes any clinician and public feedback on these summaries. Comments can be emailed to cari.schn@health.nsw.gov.au

Ungraded evidence

Risk of severe disease with COVID-19 in kidney/kidney-pancreas transplant recipients

> Kidney/kidney-pancreas transplant recipients may have increased risk of severe disease from COVID-19, with possible additional increased risk among those with a long-term transplant and other comorbidities

Transplant recipients have an increased risk of respiratory infections because of their suppressed immune system. While there is little published evidence on COVID-19, transplant recipients have a greater risk of severe disease requiring intensive care admission and ventilatory support, and higher mortality, with other respiratory viruses including SARS.(6)

The risk factors for severe COVID-19 disease in transplant recipients are not yet well understood. However, accumulating case reports and case series suggest that the transplant recipients most at risk may be chronic (long-term) recipients on stable, lower doses of immunosuppression with concurrent comorbidities including diabetes, cardiovascular disease and inflammatory bowel disease and/or a failing graft.(7-10)

Measures to reduce transmission of 2019 novel coronavirus in kidney/kidney-pancreas transplant recipients

Measures to minimise acquiring and spreading 2019 SARS-CoV-2 infection include physical distancing, hand hygiene using soap where possible, cough and sneeze etiquette, staying home, telehealth consultations for transplant care and self-isolation following contact with a person with probable or confirmed COVID-19 or if COVID-19 symptoms. Follow the advice available at https://www.health.gov.au/ and https://covid19.govt.nz/.

COVID-19 is primarily spread person to person from respiratory droplets which can be either be inhaled through the cough or sneeze of an infected close contact, or through touching a surface contaminated with infected respiratory droplets followed by touching eyes, nose or mouth.(11)

Wearing mask/face coverings for kidney/kidney-pancreas transplant recipients

In kidney/kidney-pancreas transplant recipients with new respiratory symptoms, a surgical mask may reduce transmission of 2019 SARS-CoV-2 infection and other viral infections to others.

Appropriate surgical mask usage in a person with 2019 SARS-CoV-2 infection will reduce the risk of transmission of infection of viral illnesses to others.(12) A face mask is worn after performing hand hygiene, removing any jewellery, and tying hair back.(13) Surgical masks should be changed when moistened or damaged and should not left be undone with the ties dangled around the neck. Inappropriate use of a mask may lead to an increased risk of disease transmission.(13-15). There is no evidence to suggest a respirator (N95 or P2) mask should be worn in community settings.

Delayed access to health advice for non-COVID-19 illness

People with a kidney/kidney-pancreas transplant should be encouraged to seek health advice for non-COVID-19 symptoms.

There is emerging evidence that some people delay accessing health care when they develop non-COVID-19 symptoms including serious symptoms such as acute chest pain, which can lead to poor outcomes.(16) It is important that people with a kidney/kidney-pancreas transplant are advised to access health advice (including telehealth) for any new symptoms or illness within the same time frame as they would have prior to COVID-19. This may include seeking advice from a telehealth service (https://www.health.gov.au/ and https://covid19.govt.nz/).

Diagnosis of 2019 SARS-CoV-2 infection in kidney/kidney-pancreas transplant recipients

A negative nasopharyngeal swab does not rule out infection and should not be used as the sole basis for patient management decisions. A positive test is indicative of the presence of 2019 SARS-CoV-2 RNA, although clinical correlation with patient history and other diagnostic information is necessary to determine clinical management. A positive nasopharyngeal swab for 2019 SARS-CoV-2 does not rule out co-infection with other viral, bacterial, fungal or parasitic organisms.

The SARS-CoV-2 RNA is generally detectable in respiratory specimens during the acute phase of infection.(17) While the virus can be detected in specimens from a number of sites, the detection rates vary considerably depending on where they were taken from. An observational study of 205 COVID-19 positive patients indicated bronchoalveolar lavage fluids show the highest positive rates (93%), followed by sputum (72%), nasal swabs (63%), fibro-bronchoscope brush biopsy (46%), pharyngeal swab (32%), faeces and blood (1%).(17)

The cycle threshold values of the RT-PCR are an indicator of viral load, with lower cycle threshold values corresponding to higher viral copies. A cycle threshold (CT) of less than 40 cycles is considered a positive result.(17)

It is important to note that having a negative test does not rule out SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions.(18) Negative results must be combined with clinical observations, patient history, and epidemiological information. While a positive test is indicative of the presence of SARS-CoV-2 RNA, clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status and clinical decision-making.

Immunosuppression management of kidney/kidney-pancreas transplant recipient with documented 2019 SARS-CoV-2 infection/COVID-19

Recipients of a kidney/kidney-pancreas transplant should continue immunosuppression therapy unless advised by the transplant team. In moderate to critical COVID-19 illness, higher dose of steroids and reduction in antiproliferative agents (mycophenolate mofetil or azathioprine) and calcineurin inhibitor dose may be considered, in conjunction with knowledge of comorbidities and weighing the risks and benefits of continuing immunosuppression.

The current evidence pertaining to immunosuppression management in COVID-19 patients is limited to case reports and series.(9, 10) There are few data regarding the potential impact of immunosuppression on COVID-19 disease and outcomes. Transplant recipients should not stop taking their immunosuppression abruptly because it may lead to acute rejection and other systemic disease such as hypotension (as in the case of corticosteroids). It may be prudent to consider judicious reduction of immune suppressant medications, such as the anti-proliferative agents as well as those that affect T-cells, on a case by case basis, with specific consideration of the recipients' age and existing co-morbidities. In critical COVID-19 illness, consider ceasing antimetabolite and calcineurin inhibitor agents and using steroids as a single agent for immunosuppression therapy.

Use of ACE inhibitors or angiotensin receptor blockers (ARBs) in kidney/kidney-pancreas transplant recipients

Treatment decisions about ACE inhibitors or ARBs remain than same? as for non-COVID-19 care unless stated otherwise by the treating nephrologist. There is no high certainty evidence that ACE inhibitors or ARBs should be modified to manage COVID-19 risk or infection.

It is not recommended to cease ACEI/ARBs unless indicated for the management of an existing condition such as hypertension or acute kidney injury. No change to ACEI/ARB therapy should be made purely for COVID-19 risk or infection.(19)

Antiviral and other disease modifying therapies for kidney/kidney-pancreas transplant recipient with documented COVID-19

For kidney/kidney-pancreas transplant recipients, antiviral medications and other disease-modifying treatments should be administered in the context of clinical trials with appropriate ethical approval.

To date, there is no proven effective anti-viral therapy for SARS-CoV-2 infection. Apart from supportive care, such as supplemental oxygen for patients with moderate symptoms and extracorporeal membrane oxygenation for critically ill patients, all interventions are experimental. Hydroxychloroquine may be considered for transplant recipients with COVID-19 in the context of an appropriately conducted clinical trial. Clinicians should also be mindful of the potential interaction with calcineurin inhibitors, as well as the risk of QT-prolongation in at-risk individuals, particularly for those who are receiving concomitant medications that may prolong the QTc (such as tacrolimus). There is no conclusive evidence to suggest a combination of lopinavir/ritonavir should be recommended in recipients with COVID-19.(20) There is no conclusive evidence to suggest remdesevir should be recommended for transplant recipients with COVID-19.

Hydroxychloroquine (an analogue of chloroquine) has been demonstrated to have an anti-SARS-CoV-2 activity *in vitro*.(21) It has been routinely used for the treatment of rheumatoid arthritis and systemic lupus erythematous. A recent single-arm study from France examined the treatment efficacy of hydroxychloroquine and azithromycin in a cohort of COVID-19 positive patients.(22) A total of 26 patients received the combination therapy and 10 were treated as controls. After 6 days of treatment, 70% of those who received the combination therapy were virologically cured compared with 12.5% in the control arm (p=0.001).(22) However, this study is limited by the very small sample size, very short follow-up time, high attrition rates and the lack of blinding.

The combined lopinavir/ritonavir (human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor) may have some *in vitro* inhibitory activity against SARS-CoV-2, the virus that causes SARS in humans. However, a recently published open labelled randomised controlled trial of *Lopinavir/Ritonavir* compared with standard care found no differences between the treatment and standard care arms in terms of clinical improvement, 28-day mortality and viral loads detected on throat swab.(20) Given the potential drug-drug interactions with calcineurin inhibitors and mammalian target of rapamycin (mTORI)s, these agents should not be used cautiously in transplant populations in the context of a clinical trial with appropriate ethical approval.

Remdesevir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination, has been developed for the treatment of Ebola virus infections. Remdesevir has *in vitro* inhibitory activity against SARS-CoV-2.(23) Currently, there are 9 registered (6 recruiting)

clinical trials to test the efficacy of remdesevir in adult hospitalised COVID-19 patients.(24) The primary outcomes of these trials varied considerably between trials. Improvement in clinical status assessed using an ordinal scale at the specified time (commonly 15 days) after admission is the most frequently reported primary outcome. The scale included: 1) Death; 2) Hospitalised, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalised, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalised, requiring supplemental oxygen; 5) Hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalised, limitation on activities and/or requiring home oxygen; 8) Not hospitalised, no limitations on activities.

Ungraded evidence

Supportive therapies for kidney/kidney-pancreas transplant recipients with documented COVID-2019

For kidney/kidney-pancreas transplant recipients, supportive therapies including intravenous immunoglobulin, convalescent plasma and tocilizumab should be administered in the context of clinical trials with appropriate ethical approval.

Intravenous immunoglobulins (IVIG) may be beneficial for recipients with hypogammaglobulinemia, however, there is no conclusive evidence to recommend IVIG for routine use in transplant recipients with COVID-19.

Convalescent plasma is being investigated as a treatment to aid recovery in patients with COVID-19. One small uncontrolled case series of 5 critically unwell ventilated COVID-19 patients showed clinical improvement following administration of convalescent plasma.(25, 26)

There is no conclusive evidence to suggest high dose steroids improves survival in patients with severe acute respiratory distress syndrome. In those with MERS or SARS, there was evidence of harm including delayed viral clearance and increased likelihood of requiring mechanical ventilation.(27-29) There is inconclusive evidence to suggest high-dose corticosteroids may exacerbate COVID-19 associated lung injury.(29)

Tocilizumab may be considered in transplant recipients with severe interstitial pneumonitis requiring ventilatory support. Note that while tocilizumab is suggested in many guidelines and is currently undergoing clinical trials and there is no clinical trial evidence to support its use.

Explanation of ungraded recommendation

An ungraded recommendation is given when there is not enough evidence to give an evidence-based recommendation, but the guideline panel regards it as important to provide a recommendation. Additional information and a review of the recommendation strength will be added as recommendations are updated.

Using this summary

This evidence summary is based on the best information available at the time of writing. The summary is intended to provide information. The summary is not intended to define a standard of care or be considered to represent a standard. The evidence summary is not intended to define a course of clinical management which should take into account the needs of individual patients and health resources. All healthcare professionals using this evidence summary remains responsible for clinical decision making in all clinical situations.

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