



# MANAGING COVID -19 KIDNEY TRANSPLANT RECIPIENTS A CHALLENGING SITUATION -A REVIEW

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## Abstract

COVID-19 is impacting provision of renal transplantation in the UK with a reduction in clinical activity. Publicly available Renal Registry and NHS Blood and Transplant reports were analysed to model the number of missed transplant opportunities, waiting list size and change in dialysis population over a six-month period starting 5 March 2020. An estimated 1,670 kidney transplant opportunities may be lost, which will lead to 6,317 active patients on the kidney-alone waiting list, compared to 4,649 based on usual activity estimates. This will result in 1,324 additional patients on dialysis who would otherwise have been transplanted. COVID19 will lead to a marked loss of transplant opportunities and a significantly larger national waiting list. The existing strain on dialysis capacity will be exacerbated as patients remain on dialysis as the only available form of renal replacement therapy. These findings will help inform policy and service specific strategy.

**Keywords :** Kidney transplantation, Covid19, managing COVID-19, Kidney transplant recipients, a challenging situation.

## Introduction<sup>[1,2]</sup>

The new coronavirus disease 2019 (COVID-19) infection, emerged in Wuhan city, China, in December 2019, has close genomic structural similarities with the severe acute respiratory syndrome coronavirus (SARS-CoV) that caused the SARS pandemic in 2003 and the middle east respiratory syndrome coronavirus (MERS-CoV) that caused (MERS) epidemic in 2012 . By April 26, 2020, infections related to COVID-19 affected people from 210 countries and caused 203,818 reported deaths worldwide. In the UK, mortality cases exceeded 30,000 so far. There is a common belief among transplant clinicians that kidney transplant recipients have a high risk of infection due to long-term immunosuppression and associated comorbidities. Data, clinical picture, and outcomes of COVID-19 in kidney transplant recipients are scarce . Therefore, we report 8 cases of kidney transplant recipients infected with COVID-19.

## Kidney transplantation<sup>[3]</sup>

A kidney transplant is a surgery to place a healthy kidney from a living or diseased donor into a person whose kidneys no longer function properly.

### Types of Kidney transplantation:

1. Diseased donor kidney transplantation.
2. Living donor kidney transplantation.
3. Pre-emptive kidney transplantation

### ***Living donor kidney transplantation***

A living donor kidney transplantation is when your kidney from a living donor is removed and placed into a recent who kidney no longer functions properly.

### ***Diseased Donor Kidney Transplantation.***

A diseased donor kidney transplantation is when you a kidney from someone who has recently died is removed with consent of the family or from a donor card and placed recipient who is kidney have failed and no longer function properly and this in need of kidney transplantation.

### ***Pre-emptive kidney transplant***

A pre-emptive kidney transplant is when the patient receives a kidney transplant before the patient's kidney function deteriorates to the point of needing dialysis to replace the normal filtering function of the kidneys.

### **Test's to be done before transplantation<sup>[4]</sup>**

There are three main blood tests that will determine if a patient and a potential donor are a kidney match.

They are:

1. *Blood typing.*
2. *Tissue typing.*
3. *Cross-matching.*

### ***Blood typing:***

Blood typing is the first blood test that will determine if the patient's blood is compatible with potential donor's blood. This test measures blood antibodies that react with different blood groups. If the donor's blood type works with patient's blood type, the donor will take the next blood test. The RH factor of blood doesn't matter.

### ***Tissue Typing:***

The first blood test is to determine the tissue type of the patient and the potential donor to see how well they match. Each person's tissues, except for identical twins, are usually different from everyone else's. It is believed that the better the HLA match, the more successful the transplant will be over a long period of time. Because of the way chromosomes/DNA are inherited or passed down in a family, a parent and child who have at least a 50% chance of matching, siblings could have a 0 to 100% match and unrelated donors would be less likely to match at all.

### ***Cross-Matching:***

A serum crossmatch is a blood test you and the donor will have multiple times, including right before the transplant surgery. To do the test, cells from the donor are mixed with your serum. If your serum has antibodies against the donor's cells, the antibodies will bind the donor cells and be detected using a fluorescent detection method. If these antibodies are at high levels, the donor cells will be destroyed.

### **Procedure<sup>[5]</sup>**

In most cases the barely functioning existing kidneys are not removed, as removal has been shown to increase the rates of surgical morbidity. Therefore, the kidney is usually placed in a location different from the original kidney. Often this is in the iliac fossa so it is often necessary to use a different blood supply:

- The renal artery of the new kidney, previously branching from the abdominal aorta in the donor, is often connected to the external iliac artery in the recipient.
- The renal vein of the new kidney, previously draining to the inferior vena cava in the donor, is often connected to the external iliac vein in the recipient.

The donor ureter is anastomosed with the recipient bladder. In some cases, a ureteral stent is placed at the time of the anastomosis, with the assumption that it allows for better drainage and healing. However, using a modified Lich-Gregoir technique, Gaetano Ciancia developed a technique which no longer requires ureteral stenting, avoiding many stents related complications.

## Complications<sup>[6,7]</sup>

- Post operative complications, such as bleeding, infection, vascular thrombosis and urinary complications
- Transplant rejection (hyperacute, acute or chronic)
- Infections and sepsis due to the immunosuppressant drugs that are required to decrease risk of rejection.
- Post-transplant lymphoproliferative disorder (a form of lymphoma due to the immune suppressants). This occurs in about 2% of patients, occurring especially in the first 2 years post-transplant
- Skin tumours
- Imbalances in electrolytes including calcium and phosphate which can lead to bone problems
- Proteinuria
- Hypertension
- Recurrence of original cause of kidney failure

## Drug to be used after transplantation:<sup>[8]</sup>

### Depleting Antibodies:

*Anti thymocyte Globulin*

*Alemtuzumab and Rituximab*

### Nondepleting Antibodies:

*Daclizumab*

### Antiproliferative Or Antimetabolite Agents:

*Azathioprine*

### Calcineurin Inhibitors:

*Cyclosporine And*

*Tacrolimus*

### Corticosteroids

### Tocilizumab

Tocilizumab, sold under the brand name Actemra among others, is an immunosuppressive drug, used for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis, a severe form of arthritis in children. It is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R). Interleukin 6 (IL-6) is a cytokine that plays an important role in immune response and is implicated in the pathogenesis of many diseases, such as autoimmune diseases, multiple myeloma and prostate cancer. Tocilizumab was jointly developed by Osaka University and Chugai, and was licensed in 2003 by Hoffmann-La Roche.<sup>[22]</sup> Tocilizumab was granted an emergency use authorization (EUA) for the treatment of COVID-19 in the United States in June 2021.<sup>[4]</sup>

### Bebtelovimab

Bebtelovimab is a monoclonal antibody medication that's injected into your vein.

Bebtelovimab is another medication that can treat mild-to-moderate COVID-19 in certain people ages 12 and older who aren't in the hospital. If you have COVID-19, are at high risk developing severe illness, and can't use or access other treatments, bebtelovimab may be another option for you.

How it's taken: Bebtelovimab is injected into your vein as a single dose. It takes about 30 seconds to infuse it into your body. If your healthcare provider recommends it for you, you should get it within 7 days of getting symptoms.

Effectiveness: Official product labelling states that bebtelovimab "may be effective" at treating mild-to-moderate COVID-19. Its clinical trials were conducted before Omicron was predominant. But Eli Lilly (the manufacturer of bebtelovimab) expects it to work against Omicron and its "stealth" sub variant. Other considerations: You won't be able to give yourself this medication. Since it's injected into your vein, you'll need to receive it from a healthcare provider.

## Sotrovimab

Sotrovimab is a monoclonal antibody medication. Monoclonal antibodies (mAbs) are human-made antibodies that help fight illnesses like COVID-19.

REGEN-COV currently isn't recommended due to resistance concerns against the Omicron BA.2 subvariant. It was previously recommended as a second-choice option for mild-to-moderate COVID-19 in certain people ages 12 and older who aren't in the hospital.

How it's taken: Sotrovimab is infused into your vein as a single dose. If your healthcare provider recommends it for you, you should get it within 10 days of getting symptoms.

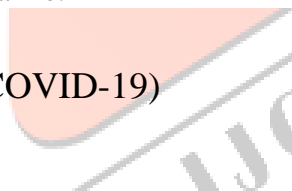
Effectiveness: In a clinical trial of non-hospitalized adults with COVID-19, sotrovimab was found to lower the risk of hospitalization or death by about 85%. But this was before the Omicron BA.2 sub variant became predominant.

## Favipiravir<sup>[9]</sup>

Favipiravir is an antiviral drug approved for the treatment of influenza in Japan. There is limited evidence suggesting that, compared to other antiviral drugs, favipiravir might improve outcomes for people with COVID-19, but more rigorous studies are needed before any conclusions can be drawn. Chinese clinical trials in Wuhan and Shenzhen claimed to show that favipiravir was "clearly effective". Of 35 patients in Shenzhen tested negative in a median of 4 days, while the length of illness was 11 days in the 45 patients who did not receive it. In a study conducted in Wuhan on 240 patients with pneumonia half were given favipiravir and half received umifenovir. The researchers found that patients recovered from coughs and fevers faster when treated with favipiravir, but that there was no change in how many patients in each group progressed to more advanced stages of illness that required treatment with a ventilator. On 22 March 2020, Italy approved the drug for experimental use against COVID-19 and began conducting trials in the three regions most affected by the disease. The Italian Pharmaceutical Agency reminded the public that the existing evidence in support of the drug is scant and preliminary. On 30 May 2020, the Russian Health Ministry approved a generic version of favipiravir named *Avifavir*, which proved highly effective in the first phase of clinical trials. In June 2020, India approved the use of a generic version of favipiravir called FabiFlu, developed by Glenmark Pharmaceuticals, in the treatment of mild to moderate cases of COVID-19. On 26 May 2021, a systematic review found a 24% greater chance of clinical improvement when administered in the first seven days of hospitalization, but no statistically significant reduction in mortality for any of the groups, including hospitalized.

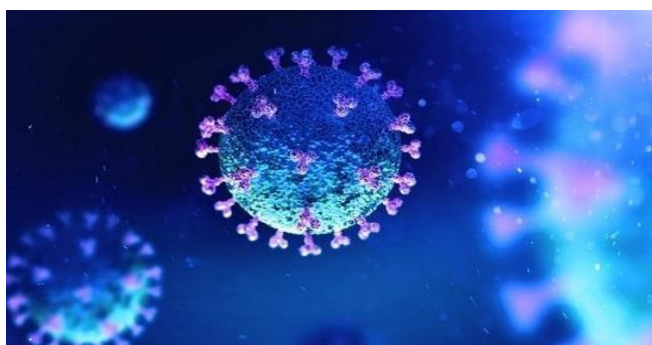


## CORONA VIRUS (COVID-19)



## Introduction<sup>[10]</sup>

The COVID-19 pandemic, also known as the coronavirus pandemic, is an ongoing global pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The novel virus was first identified from an outbreak in Wuhan, China, in December 2019. Attempts to contain it there failed, allowing the virus to spread to other areas of China and later worldwide. The World Health Organization (WHO) declared the outbreak a public health emergency of international concern on 30 January 2020 and a pandemic on 11 March 2020. As of 14 September 2022, the pandemic had caused more than 609 million cases and 6.51 million confirmed deaths, making it one of the deadliest in history.



## Epidemiology<sup>[11,12]</sup>

Epidemiology is the study of how diseases affect the health and illness of groups of people. Background on 31 December 2019, Chinese health authorities reported to the World Health Organization (WHO) a cluster of viral pneumonia cases of unknown cause in Wuhan, and an investigation was launched in early January 2020. On 9 June 2020, a Harvard University study suggested that COVID-19 may have been spreading in China as early as August 2019, based on hospital car park usage and web search trends.

### Cases

Cases means the number of people who have been tested for COVID-19 and have tested positive. These cases are according to Johns Hopkins University.

### Deaths

Deceased in a 16 m (53 ft) "mobile morgue" outside a hospital in Hackensack, New Jersey in April 2020. Most people who contract COVID-19 recover. For those who do not, the time between the start of symptoms and death usually ranges from 6 to 41 days, but most of the time about 14 days. This data is recorded by WHO.

### Variants<sup>[13]</sup>

There are many variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). Some are believed, or have been stated, to be of particular importance due to their potential for increased transmissibility, increased virulence, or reduced effectiveness of vaccines against them. These variants contribute to the continuation of the COVID-19 pandemic. As of July 2022, only the Omicron variant is designated as a circulating variant of concern by the World Health Organization.

### Etiology<sup>[14]</sup>

The pandemic is known by several names. It is sometimes referred to in news media as the "coronavirus pandemic" despite the existence of other human coronaviruses that have caused epidemics and outbreaks. During the initial outbreak in Wuhan, the virus and disease were commonly referred to as "coronavirus", "Wuhan coronavirus", "the coronavirus outbreak" and the "Wuhan coronavirus outbreak", with the disease sometimes called "Wuhan pneumonia". In January 2020, the WHO recommended 2019-nCoV and 2019-nCoV acute respiratory disease as interim names for the virus and disease per 2015 international guidelines against using geographical locations (e.g. Wuhan, China), animal species, or groups of people in disease and virus names in part to prevent social stigma. WHO finalized the official names COVID-19 and SARS-CoV-2 on 11 February 2020. Tedros Adhanom explained: CO for *corona*, VI for *virus*, D for *disease* and 19 for when the outbreak was first identified.

### Pathophysiology<sup>[15]</sup>

COVID-19 is most known for affecting the upper respiratory tract (sinuses, nose, and throat) and the lower respiratory tract (windpipe and lungs). The lungs are the organs most affected by COVID-19 because the virus accesses host cells via the receptor for the enzyme angiotensin-converting enzyme 2 (ACE2), which is most abundant on the surface of type II alveolar cells of the lungs. The virus uses a special surface glycoprotein called a "spike" to connect to the ACE2 receptor and enter the host cell.

#### 1) Respiratory tract

Following viral entry, COVID-19 infects the ciliated epithelium of the nasopharynx and upper airways.

#### 2) Gastrointestinal tract

The virus also affects gastrointestinal organs as ACE2 is abundantly expressed in the glandular cells of gastric, duodenal and rectal epithelium<sup>[108]</sup> as well as endothelial cells and enterocytes of the small intestine

### Diagnosis<sup>[16]</sup>

COVID-19 can provisionally be diagnosed on the basis of symptoms and confirmed using reverse transcription polymerase chain reaction (RT-PCR) or other nucleic acid testing of infected secretions. Along with laboratory testing, chest CT scans may be helpful to diagnose COVID-19 in individuals with a high clinical suspicion of infection. Detection of a past infection is possible with serological tests, which detect antibodies produced by the body in response to the infection.

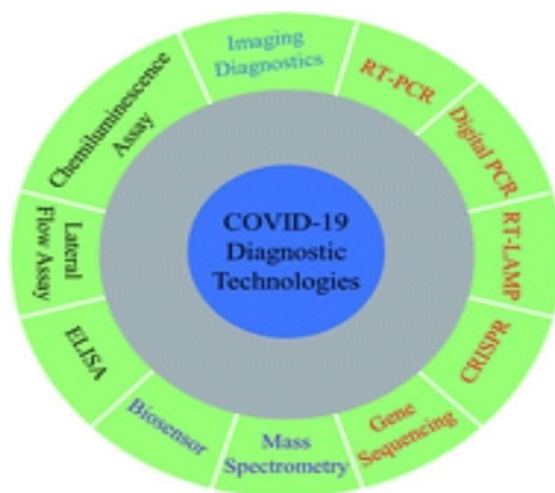


Fig : (c)

## Treatment<sup>[17]</sup>

Prior to April 2022, there were no specific, effective treatments or cures for coronavirus disease 2019 (COVID-19), the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. Although several medications have been approved in different countries as of April 2022, not all countries have these medications. Patients with mild to moderate symptoms who are in the risk groups can take nirmatrelvir/ritonavir (marketed as Paxlovid) or remdesivir, either of which reduces the risk of serious illness or hospitalization. In the US, the Biden Administration COVID-19 action plan includes the Test to Treat initiative, where people can go to a pharmacy, take a COVID test, and immediately receive free Paxlovid if

## Vaccine<sup>[18]</sup>

A vaccine is a biological preparation that provides active acquired immunity to a particular infectious disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as a threat, destroy it, and to further recognize and destroy any of the microorganisms associated with that agent that it may encounter in the future. Vaccines can be prophylactic (to prevent or ameliorate the effects of a future infection by a natural or "wild" pathogen), or therapeutic (to fight a disease that has already occurred, such as cancer). Some vaccines offer full sterilizing immunity, in which infection is prevented complet.

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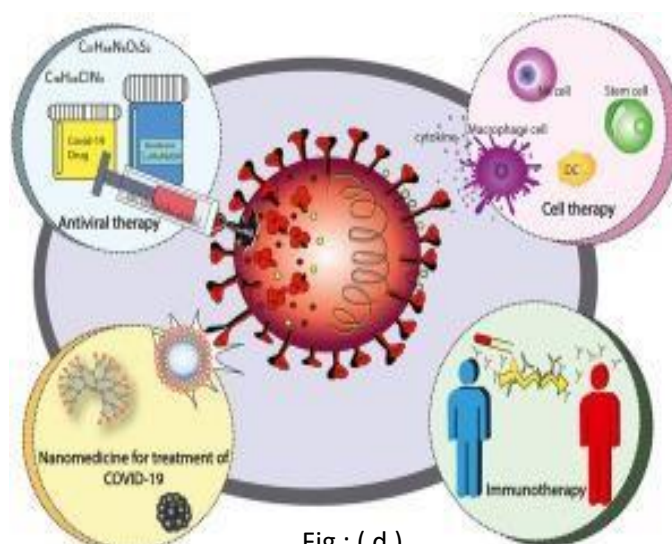


Fig : (d)

## Impact of COVID 19 on Kidney transplant recipients<sup>[19]</sup>

### Introduction

The 2019 novel coronavirus disease (COVID-19) pandemic has transformed lives throughout the globe and affected the medical community in immeasurable ways. The field of kidney transplantation experienced disruptions to the established models of care with transplant organizations and centers rapidly attempting to adjust their policies in response to the pandemic. Initially, almost universally, kidney transplantation was halted. This response was based on multiple factors, but was mainly an attempt to minimize the risk of transmission of a life-threatening, novel, and poorly understood infectious disease to an immunosuppressed population. Perhaps more pressingly, it was a response to the anticipated COVID-19-related surge in hospital admissions and strain on the healthcare system that prevented the safe performance of transplant surgeries. Since March 2020, we have come a long way in understanding the impact of these early practice changes on the field of kidney transplantation and the effect of therapeutic strategies on the mortality of kidney transplant recipients.

### Transplantation During The COVID-19 Pandemic<sup>[20]</sup>

There has been no national policy to halt organ donation and transplantation across the UK. At the time of analysis, however, national activity has come to a near stand-still. This study shows that from 5 March 2020 onwards, between 1000 and 1672 transplant opportunities will be missed over 3–6 months. This will greatly impact patients and families. Concerted efforts must be made to provide communication and support during the pandemic. Using digital technology and telemedicine is proving crucial in maintaining patient contact and health service delivery. Transplant patients have been shown to have favourable attitudes towards using health information technology and COVID-19 may be a stimulus to drive change in the way services are delivered. Transplantation provides superior outcomes and quality of life parameters for ESRD; however, the adjuvant immunosuppression required during and after the surgical procedure may expose recipients to additional risk. Recent case series from the UK and Italy have reported a mortality of 7–25% of COVID-19 in posttransplant patients, adding to the concern that these patients suffer significantly adverse outcomes.

### Kidney Transplant Recipient Survival After COVID-19<sup>[21]</sup>

Worldwide reports have consistently shown that hospitalized kidney transplant recipients infected with COVID-19 had high mortality rates approaching 20-30%. In Italy, mortality rates of transplant recipients infected with SARS-CoV-19 reached 33%, and were mainly attributed to respiratory failure. An initial report from the French registry reported a mortality of up to 30%. This was followed by the French IMPORTANT study which compared the impact of COVID-19 on mortality by comparing the mortality of kidney transplant recipients during the pandemic with previous years. The authors noted that the absolute number of deaths in April 2020 was more than twofold higher than the number of deaths in recipients in April 2018 or April 2019. Between March and June 2020, 44% of kidney recipient deaths were attributed to COVID-19, and as a result, COVID-19 was overwhelmingly responsible for the excess mortality in this population as compared to previous years.

### Clinical Management of The Transplant Recipient With COVID-19<sup>[22]</sup>

In general, kidney transplant recipients infected with COVID-19 present with the same signs and symptoms as those of the general population. These include fever, cough, respiratory failure, fatigue, myalgias, and gastrointestinal symptoms. Management of kidney transplant recipients has included antimetabolite withdrawal in most patients, and calcineurin inhibitor (CNI) and/or mTOR inhibitor withdrawal in a smaller number of patients.

Hydroxychloroquine and azithromycin were used ubiquitously in the early months of the pandemic. However, this practice has been abandoned given the overwhelming evidence failing to support any benefit and, in some instances, indicating harm. In Italy, antivirals such as lopinavir, ritonavir, and darunavir were being given, though these drugs ultimately did not prove effective in treating COVID-19. Of note, these antivirals interact with CNIs and therefore patients who received them may have had detectable CNI levels for several days after CNIs were withdrawn. Remdesivir is an inhibitor of the viral RNA-dependent

### Treating COVID-19 in Transplant Recipients<sup>[23]</sup>

Currently, remdesivir is the only antiviral drug that is approved by the Food and Drug Administration for the treatment of COVID-19 in both non hospitalized and hospitalized patients. Outpatient transplant recipients who are immunosuppressed or who have certain underlying comorbidities are candidates for several other therapeutic agents that are available through Emergency Use Authorizations (EUs). See Therapeutic Management of No Hospitalized Adults With COVID-19 for more information.

When treating hospitalized patients with mild to moderate, symptomatic COVID-19, clinicians should consider administering the therapeutics used in non-hospitalized patients with similar disease severity. Data from a large randomized controlled trial found that a short course of dexamethasone (6 mg once daily for up to 10 days) improved survival in hospitalized people with severe COVID-19 who were mechanically ventilated or who required supplemental oxygen.<sup>36</sup> Tocilizumab or baricitinib used in combination with dexamethasone is recommended for some patients with severe or critical COVID-19 who exhibit rapid respiratory decompensation.

### Covid-19 Vaccination in Transplanted Patient<sup>[24]</sup>

In the absence of a definitive cure for COVID-19, all eyes are on vaccine development and distribution. In nontransplant patients with COVID-19, serologic studies have indicated that immunoglobulin (Ig)M levels rise within 5–10 days of infection onset. IgG response typically follows with most patients developing an IgG response within 12–14 days of symptom onset. Follow-up studies indicate that these responses last for at least 5 months following infection and can confer immunity against recurrent COVID-19 infections. Very few studies have evaluated the serologic response of transplant recipients to COVID-19. SARS-CoV-2 IgG serology turned positive in 7 kidney transplant patients who were hospitalized with COVID-19 with seroconversion occurring between 4 and 38 days after infection. Interestingly, one patient who was less than 6 months from transplantation was able to seroconvert. In a different study, 855 consecutive kidney transplant recipients had their sera tested for the presence of nucleocapsid protein (NP) antibodies of those 855, 33 had been previously diagnosed with COVID-19 as confirmed by RT-PCR. 66.6% of those who had proven infection had evidence of IgG at a median time of testing of 36 days following their diagnosis.










### Symptoms<sup>[25]</sup>

Signs and symptoms of coronavirus disease 2019 (COVID-19) may appear 2 to 14 days after exposure. This time after exposure and before having symptoms is called the incubation period. You can still spread COVID-19 before you have symptoms. Common signs and symptoms can include:  Fever

- Cough
- Tiredness
- Early symptoms of COVID-19 may include a loss of taste or smell.

### Other Symptoms Can Include:

- Shortness of breath or difficulty breathing
- Muscle aches
- Chills
- Sore throat
- Runny nose
- Headache
- Chest pain
- Pink eye (conjunctivitis)

COVID-19 Identifying the symptoms			
Symptoms	Covid-19 Symptoms range from mild to severe	Cold Gradual onset of symptoms	Flu Abrupt onset of symptoms
 Fever	Common	Rare	Common
 Cough	Common (usually dry)	Mild	Common (usually dry)
 Fatigue	Sometimes	Sometimes	Common
 Aches and pains	Sometimes	Common	Common
 Sore throat	Sometimes	Common	Sometimes
 Headaches	Sometimes	Rare	Common
 Shortness of breath	Sometimes	No	No
 Runny or stuffy nose	Rare	Common	Sometimes
 Diarrhoea	Rare	No	Sometimes for children
 Sneezing	No	Common	No

Source: WHO, Centers for Disease Control and Prevention



## Conclusion

It is difficult to compare and draw conclusions regarding optimal immunosuppressant management in renal transplant recipients treated for SARS-CoV-2 from the limited data presented in currently published cases along with significant confounding variables. Most of the cases have relied on corticosteroid monotherapy for maintaining immunosuppression while treating SARS-CoV-2 in renal transplant recipients; however, the routine use of corticosteroids to treat patients with SARS-CoV-2 is not recommended. Renal transplant recipients with moderate oxygen requirements may be able to be managed successfully with steroid-sparing modifications to immunosuppression including modest reductions in calcineurin inhibitor trough concentrations and antiproliferative dosing. Further data are needed to determine optimal immunosuppressant management in this patient population, including if a corticosteroid-sparing strategy is viable in patients who present with severe clinical disease, such as those requiring ventilator support, or for those who are on steroid-containing regimens at baseline

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