Guidance on the management of transplant recipients diagnosed with or suspected of having COVID19

Updated 19th November 2021

AIMS

To provide guidance on the management of transplanted patients diagnosed with or suspected of having COVID 19, based on the available evidence.

OVERVIEW OF GUIDANCE

This is a consensus opinion of a group of transplant professionals. The guidance is based on the information available on transplant recipients in the literature and should be used in conjunction with local or national guidance. We understand that individual patients may need a bespoke plan but this is a general guideline which may help others when managing transplant recipients with, or suspected of having, COVID 19.

All unwell transplant recipients should be discussed with their usual transplant unit.

This guidance does not cover cardiothoracic or small bowel transplant recipients.

Caution must be exercised when reducing immunosuppression in paediatric recipients who appear to have a milder disease than adults. All cases must be discussed with their paediatric transplant centres first.

This guidance does not cover vaccination but all transplant patients should be encouraged to maintain COVID vaccination up to date in line with national guidance.

EXECUTIVE SUMMARY

- Exclude all other causes of fever and symptoms
- Discontinue antiproliferative agents (Aza/MMF) and restart after full recovery
- Calcineurin inhibitors
    - Review and minimise in early disease
    - Reduce or discontinue in severe or progressive disease
- Inhaled budesonide may be useful in reducing symptoms associated with early COVID 19
- High dose steroid and Dexamethasone
    - Can be counterproductive in early disease
    - Dexamethasone is advised in hospitalised patients with progressive pulmonary disease/ARDS
- Antivirals (including Remdesivir) or IL-6 inhibitors (Tocilizumab and Sarilumab) should be used in line with local protocols
- Oral antiviral agents such as Molnupiravir (recently MHRA approved) will shortly be made available by NHSE for patients at increased risk of severe disease (over 50 or one other risk factor for adverse outcome).
- anti-Sars-CoV-2 spike mAb combination, casirivimab/imdevimab (Ronapreve) should be used in hospitalised patients with negative serum anti-spike antibodies at baseline
- Monitor inpatients closely for rapid deterioration
- Maintain circulating volume but avoid excessive fluid administration
- Early thromboprophylaxis is strongly recommended, unless contraindicated
- Drug – drug interactions must be considered when initiating any new medication
- All cases in transplanted or waiting list patients should be reported to NHS BT
- Hydroxychloroquine has not shown benefit and may cause harm, this agent cannot be recommended as part of a treatment regimen
- The available evidence does not support the use of Ivermectin for the treatment or prophylaxis of COVID 19 outside of research trials
- Lopinavir and ritonavir/Azithromycin have not shown benefit in treating COVID 19

GENERAL PRINCIPLES

Staff evaluating transplant patients with fever or cough should:

- follow national or local guidelines on the use of personal protective equipment
- exclude other causes for symptoms (Eg CMV, pneumocystis, community or hospital acquired pneumonia, influenza, urinary sepsis, lymphoma and fluid overload; amongst other diagnoses)
- consider atypical presentations of COVID (eg loin pain in patients with lower lobe infection, unusual thrombotic events or acute delerium) and have a low threshold for considering COVID
- perform nasopharyngeal swab for PCR analysis in all potential cases
- only perform swabbing if staff are trained in acquisition and have appropriate PPE. See NHS BT guidance
- A negative swab result requires repeat if clinical or radiological suspicion is high
- Ask the patient to wear a fluid resistant surgical mask if they are in a clinical or communal area or being transported, to reduce the risk of droplet dispersal, unless wearing would compromise clinical care (ie delivery of oxygen)
- All proven or suspected cases to be reported to NHS BT and UK Renal Registry
    - https://www.odt.nhs.uk/deceased-donation/covid-19-advice-for-clinicians/
    - https://renal.org/covid-19/data/

USEFUL LINKS

The guidance is not intended to be comprehensive and UK national guidance links are below:
https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases

NHS England guidance to clinicians can be found here

Detailed clinical guidance from the WHO can be found here

COVID 19 rapid guideline: renal transplantation:
https://www.nice.org.uk/guidance/ng178

UK Corona virus data dashboard
https://coronavirus.data.gov.uk/

University of Liverpool COVID—19 Interaction Checker
https://www.covid19-druginteractions.org/

CLINICAL GUIDELINES FOR MANAGING PATIENTS WITH OR SUSPECTED OF HAVING COVID 19
See appendix 1 for flow chart

1: Patients who do not require hospital admission

The majority of patients will have mild symptoms and do not require hospital admission. Each patient should be considered individually regarding the risk of immunosuppression dose reduction. Particular care should be exercised in paediatric recipients who may have a milder illness.

Experience from international centres suggests the discontinuation of antiproliferatives, such as mycophenolate and azathioprine, in line with clearance of other viral pathogens. Experimental evidence suggests that coronavirus may require intact immunophilin pathways with a role for tacrolimus and cyclosporin to inhibit the growth of human coronaviruses[1,2]. This data would suggest that calcineurin inhibitors may be the agent of choice to continue but their potential benefit has to be balanced against their immunosuppressive effect. Levels should be reviewed and minimised in the face of active infection.

Inhaled budesonide has shown some benefit in terms of symptomatic recovery for patients over 65 years old or over 50 with other comorbidities who have onset of symptoms within the preceding 14 days. There was no significant benefit in terms of progression to hospitalisation or death (35). MHRA guidance

Results from the recovery trial suggest a benefit of Dexamethasone in managing patients with severe or critical COVID pneumonia [18] but early use of high dose steroids may be associated with higher viral loads[5] and more recent analysis does not support early use, unless required for other indications [6]. Dexamethasone is indicated in patients requiring admission for supplemental oxygen.

Molnupiravir is an oral antiviral agent which has been reported to half the risk of hospitalisation or death when compared to placebo in subjects with one risk factor for severe COVID who started therapy within 5 days of the onset of symptoms. The trial (36) excluded patients with eGFR under 15, patients with cirrhosis or hepatitis but the drug is promising and peer reviewed publication is awaited. Although the MHRA have authorised it use in patients with mild to moderate COVID-19 and at least one risk factor for developing severe disease, the drug is currently unavailable in the UK (37).

Patients in the early phase may have false negative naso pharyngeal swab results and repeat nasal swab may be required if first result is negative and clinical suspicion is high, particularly if a result is required for isolation protocols. It is important to review the naso pharyngeal swab result in conjunction with clinical suspicion and radiological changes.

Recommendation:

- Patients to self-isolate in line with national guidance
- Closely monitor patients remotely for change in symptoms
- Provide NHS patient information and consider supply of returnable oxygen saturation meters
- Stop antiproliferative agents (MMF/azathioprine)
- Review total burden of immunosuppression and consider reduction of CNI
- High or increased dose steroid is NOT recommended at this stage
- Consider inhaled budesonide 800mcg twice daily for up to 14 days in symptomatic patients
- Consider restarting immunosuppression 14 days after onset of symptoms if symptom free in absence of anti-pyretics for a minimum of 3 days
- Consider early monitoring of graft function when safe to do so and risk of transmission to others is low
- Due to prolonged viral shedding in immunosuppressed patients and the risk of disease transmission, post COVID transplant recipients must be reviewed in an area separate from non-affected individuals until confirmed non infectious.

2: Patients who are unwell and admitted to hospital

Initial reports in early 2020 from the Chinese Centre for Disease Control and Prevention suggested that in non-immunosuppressed patients, 81% of have a mild disease with 14% having severe disease and 5% requiring intensive care support[7]. The overall mortality was 2.3%, rising to 49% in patients requiring critical care.

Data on the course of unvaccinated transplant patients with COVID during the first wave from Spain[14] and New York[17] in a variety of transplant recipients recorded inpatient case fatality rates of 27.8% and 24%, respectively. Early UK data in unvaccinated renal transplant recipients in the first wave and second wave suggested an overall inpatient mortality of 27% [15]. Comparatively, data from the ISARIC database in a similar era also recorded an inpatient mortality of 27.6% in a non transplant specific population, although there may be a reporting bias to more severe cases [26]. As of October 6th October 2021, NHS BT reported COVID infection in 6,016 UK transplant recipients with a functioning graft of which 11% had died. In the post vaccine era, NHS BT data has shown that transplant recipients who are greater than two weeks post 2 doses of COVID vaccine have a mortality of 8% within 28 days of a positive COVID test compared to 17% in unvaccinated transplant patients.

In a further early study of 138 hospitalised patients from China, the median onset of dyspnoea from first symptoms was 5 days, with admission on day 7 and onset of ARDS at day 8[8]. The scenario of rapid deterioration and requirement for ventilation one week after onset of symptoms is a recognised clinical course for COVID.

Initial reports from China suggested Acute Kidney Injury rates around 3%[8,10] with higher mortality rates in patients with renal impairment [10]. See summary. Initial UK experience reported higher rates of AKI which may, in part, reflect over cautious fluid replacement in patients with significant insensible fluid losses. Although excessive fluid administration may worsen pulmonary injury, it is important to maintain circulating volume and renal perfusion, to reduce the potential for AKI.[23] See NICE guidance NG191

Severe COVID pneumonia is associated with abnormal clotting parameters and a higher rate of both venous (25-27%) and arterial (3.7%) thrombosis [11,12]. A significantly elevated D Dimer or prolonged PT/APTT may be associated with greater incidence of VTE [11,12]. The combination of COVID pneumonia and acute pulmonary emboli are likely to worsen hypoxia. Heparin use may reduce 28 day mortality in patients with severe COVID pneumonia and significant sepsis induced coagulopathy[13]. Patients who deteriorate should be considered for urgent imaging to exclude concomitant pulmonary emboli. See NICE guidance NG191

Report from the RECOVERY trial suggest a 20% reduction in mortality for oxygen dependent patients who received Dexamethasone 6mg daily for ten days [18]. Patients with severe or critical COVID 19 should be prescribed Dexamethasone – See NICE guidance NG191

Remdesivir was initially shown to reduce supportive measures and time to recovery in patients with mild to moderate or severe COVID-19 disease requiring supplemental oxygen treatment [20,25]. Subsequent data from the WHO SOLIDARITY trial[27] failed to show a mortality benefit from Remdesivir and treatment should be in line with local protocols or research trials. See gov.uk guidance on use of Remdesivir

Data on the use of one or two doses of Tocilizumab from the RECOVERY trial (38) has suggested benefit in reducing 28-day mortality (RR 0.85 p=0.028) and requirement for invasive mechanical ventilation (RR0.79 p=0.0019) for non immunosuppressed patients with hypoxia and CRP greater than 75. Patients also experienced a shorter length of stay (median 19 days for Tocilizumab vs over 28 days for standard care) and a greater proportion discharged within 28 days (RR 1.2 p= <0.0001). Although observational comparative data in transplant patients has not shown an improvement in survival with Tocolizumab (31,32), the criteria for administration and severity of disease was heterogenous in the two publications and further prospective randomised data is required in transplant patients before a firm conclusion on lack of benefit can be made.

NICE rapid guidance on managing COVID 19 recommend the use of a single-dose of Tocilizumab or Sarilumab for hypoxaeimic patients with a CRP >75 or within 48hrs of requiring high-flow nasal oxygen or invasive/non-invasive ventilatory support See NICE guidance NG191. Caution needs to be exercised when using in patients on active immune suppression therapy, baseline transaminases more than 5 times the upper limit of normal and in the presence of co-existing infection that may be worsened by IL-6 inhibition . See MHRA guidance on Tocolizumab

Data on combination casirivimab and imdevimab (Ronapreve) treatment from the RECOVERY trial suggests a 20% reduction in 28-day mortality and a reduction in progression to requiring ventilation in hospitalised COVID-19 patients with negative anti-spike antibodies (39). There was no benefit in patients with evidence of anti-spike antibodies at admission. The interim commissioning policy on casirivimab and imdevimab can be found here

Recommended indications for admission:

- Hypoxia (saturations under 95%)
- Significant chest X ray findings consistent with COVID
- Tachypnoea

Indicators of poor prognosis

- Older age
- Elevated CRP over 125
- Neutrophil to lymphocyte ratio over 3.1
- Significantly elevated troponin (see local ranges)
- Elevated D Dimer
- Platelets under 100
- Elevated ferritin

Recommendation:

- Stop antiproliferative agents (MMF/azathioprine)
- Consider reducing or stopping CNI
- Check for anti-spike antibodies
- Dexamethasone 6mg daily (or equivalent doses of hydrocortisone, prednisolone) for 10 days for patients requiring supplemental oxygen
- Remdesivir may be considered in line with local protocols..
- Tocilizumab or sarilumab as a single dose for those with hypoxaemia and a CRP >75 (in the absence of a co-existing infection that could be worsened by IL-6 inhibition and in accordance with local policies)
- A single infusion of casirivimab/imdevimab (Ronapreve) for those with negative serum anti-spike antibodies at baseline who have not been previously treated.
- Oxygen therapy to achieve saturations of 92-96%[16] (unless COPD)
- Regular observations, especially saturations, to monitor for rapid deterioration
- Fluid administration to maintain circulating volume but avoid significant overload
- Consider stopping ACEi/ARB in patients at risk of AKI
- Early VTE prophylaxis with heparin, if no contra-indication.
- VTE prophylaxis should continue for a minimum of 7 days, including after discharge.
- Consider adjunctive antibiotics if superadded bacterial infection is suspected
- Early discussion of ceilings of care

3: Patients who are progressively unwell and require ventilatory support

Deterioration to requirement for ventilation may occur precipitously and discussion of ceilings of care need to be considered at an early stage. The decision to escalate patients to critical care is made on an individual basis in line with national guidance and frailty scoring.
It is recommended to start the conversation at an early point in clinical care:
See NICE guidance NG191
The mortality of all patients requiring critical care support is close to 50%.
Dexamethasone is recommended in patients with severe COVID pneumonia[18,19]

Data from the immune modulation arm of the REMAP-CAP trial has indicated positive benefits with the use of tocilizumab or sarilumab in non immunosuppressed patients with COVID pneumonia within 24 hours of admission to intensive care unit, with an overall reduction in the risk of death of 24% (40). It is important to note that the trial excluded patients who had ongoing immune suppression or had been admitted for greater than 14 days prior to ICU admission.

Recommendation:

- Stop antiproliferative agents (MMF/azathioprine)
- Dramatically reduce or stop CNI
- Early initiation of discussions on outcome and ceilings of care
- Consider Dexamethasone, as above
- Consider therapeutic anticoagulation, if no contraindications
- Remdesivir may be considered in line with local protocols
- Tocilizumab or sarilumab may be used (in the absence of a co-existing infection that could be worsened by IL-6 inhibition) in accordance with local policies, if not given already.
- A single infusion of casirivimab/imdevimab (Ronapreve) for those with negative serum anti-spike antibodies at baseline, if not used already.
- Ventilatory support in line with local or national guidance
- Adjunctive support or antibacterial therapy in line with local practice or clinical trials

4: Additional agents, antivirals and other considerations

The use of adjunctive agents or antivirals should be considered in conjunction with local practice or as part of clinical trials.

Hydroxychloroquine/Lopinavir and ritonavir/Azithromycin

Data from RECOVERY trial has shown no effect on mortality in hospitalized patients with hydroxychloroquine, lopinavir and ritonavir or Azithromycin. (24,41,42)

ACEi and ARB

Angiotensin Converting Enzyme 2 (ACE 2) may play a role in coronavirus infection but there is conflicting evidence from basic science studies about the likely effect that modulation of the renin-angiotensin system would have on infection. A number of transplant recipients may be taking ACEi/ARB for their beneficial effect on proteinuria or management of cardiac failure. Therefore it is recommended that the standard advice on continuing or stopping ACEi/ARBs should be adhered to. Temporary discontinuation should be considered in patients who are at risk of Acute Kidney Injury.
The Renal Association guidance can be found here.

NSAIDs

Reports in the media suggested that NSAIDs, such as Ibuprofen, may worsen the outcome of patients with COVID 19 through the potentiation of ACE 2. Recent statements from international medicine regulators state that there is no evidence to link poor outcomes to NSAIDs and patients who require these agents should continue. As most transplant patients do not use NSAIDs and there are other available antipyretics, we would suggest not discontinuing these agents in patients who require them for their pain or anti-inflammatory properties.
The current UK government guidance on use of NSAIDS is here

Interactions with transplant immunosuppression

Tacrolimus, ciclosporin and sirolimus can interact with some antifungal and antibiotic medications - for example fluconazole and clarithromycin. Where possible use an alternative agent to avoid interaction or reduce dose of immunosuppressant.

University of Liverpool COVID—19 Interaction Checker
https://www.covid19-druginteractions.org/

COVID-19 convalescent plasma Use of COVID-19 convalescent plasma has been trialled in several studies. Currently there is no published scientific evidence to recommend its use. The RECOVERY trial suspended recruitment to the convalescent plasma arm of the study on 14th January 2021 after finding no difference in the primary outcome measure of 28 day mortality in the convalescent plasma group when compared to the usual care alone group.[34]Several other RCTs have shown no benefit of convalescent plasma in severe COVD-19.[22]

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Appendix 1: Flow chart (updated 19th November 2021)