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

Updated 9th July 2020

AIMS

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

OVERVIEW OF GUIDANCE

This is a consensus opinion of a group of transplant professionals. The guidance is based on the sparse 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 and all cases must be discussed with their paediatric transplant centres first.

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
- High dose steroid and Dexamethasone
    - can be counterproductive in early disease
    - Dexamethasone may be considered in progressive pulmonary disease/ARDS
- Antivirals (including Remdesivir) or biologics should only be used in line with local protocols or research studies
- Initial studies of Hydroxychloroquine have not shown benefit and may cause harm, this agent can not be recommended as part of a treatment regimen
- Monitor inpatients closely for rapid deterioration
- Maintain circulating volume but avoid excessive fluid administration
- Early thromboprophylaxis is strongly recommended, unless contraindicated
- All cases in transplanted or waiting list patients should be reported to NHS BT

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) and have a low threshold for considering COVID
- perform nasopharyngeal swab for PCR analysis in all potential cases
- only perform swabbing if they are trained in acquisition and have appropriate PPE. See NHS BT guidance
- A negative swab result requires repeat if clinical suspicion is high
- 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:
https://www.england.nhs.uk/coronavirus/

Detailed clinical guidance from the WHO can be found here:
https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

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

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 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 grown 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.

High dose steroids have previously been suggested as therapy for coronavirus lung injury but are associated with prolonged viral shedding[3] and may have deleterious effect in experimental models[4]. Early use of hydrocortisone in SARS CoV1 was associated with higher viral loads[5] and more recent analysis does not support their use, unless required for other indications [6].
Early results from the recovery trial suggest a benefit of Dexamethasone in managing patients with COVID pneumonia who require respiratory support, although there was no benefit in patients who did not require respiratory support [18].

Patients in the early phase may have false negative naso pharyngeal swab results (~30%) 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:

- 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
- Patients should self-isolate in line with national guidance
- Closely monitor patients remotely for change in symptoms
- Consider restarting immunosuppression 14 days after onset of symptoms if symptom free in absence of anti-pyretics for 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.

2: Patients who are unwell and admitted to hospital

Initial reports from the Chinese Centre for Disease Control and prevention suggest that 81% of non-immunosuppressed patients 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.

There is limited data on the course of transplanted patients with COVID, although one study from Spain[14] and another from New York[17] in a variety of transplant recipients recorded inpatient case fatality rates of 27.8% and 24%, respectively. UK data in renal transplant recipients suggests an overall mortality of 27% [15].

In a further 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 suggests a significantly higher rate of AKI which may, in part, reflect over cautious fluid replacement in patients with significant insensible fluid losses (eg patients with poor oral intake, fever and GI 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.

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].

Early reports from the RECOVERY trial suggest a 20% reduction in mortality for oxygen dependent patients who received Dexamethasone 6mg daily for ten days [18].

Remdesivir, which has now been granted conditional marketing authorisation as a licenced product, has been shown to reduce supportive measures including mechanical ventilation and time to recovery in patients with mild to moderate or severe COVID-19 disease who are on supplemental oxygen treatment (no significant effect on mortality has been reported) [19]. Treatment may be considered for adults and adolescents aged ≥ 12 years who weighing at least 40 kg and are hospitalised with suspected or laboratory confirmed SARS-CoV-2 infection with an SpO2 ≤ 94% on room air or requiring supplemental oxygen, ventilatory support or extracorporeal membrane oxygenation (ECMO). Treatment is only available in intravenous form and is not recommended in patients with eGFR less than 30 mL/min. Liver function needs to be monitored before initiation of Remdesivir and during treatment [20]. See gov.uk guidance on use of Remdesivir

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
- Consider Dexamethasone 6mg daily for 10 days
- Consider Remdesivir
- 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
- 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:
https://www.nice.org.uk/guidance/ng159
The mortality of all patients requiring critical care support is close to 50%.
There may be a role for the use of methyl prednisolone in patients who develop ARDS[9]

Recommendation:

- Stop antiproliferative agents (MMF/azathioprine)
- Dramatically reduce or stop CNI
- Consider Dexamethasone, as above
- Consider Remdesivir, as above
- Ventilatory support in line with local or national guidance
- Adjunctive support or antivirals in line with local practice or clinical trials

4: Additional agents, antivirals and other considerations

At present, there is no high level evidence of benefit for specific treatments for COVID 19.
The use of adjunctive agents or antivirals should be considered in conjunction with local practice or as part of clinical trials.

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:
https://renal.org/covid-19/ra-resources-renal-professionals/renal-association-uk-position-statement-patients-novel-corona-virus-infection-use-blood-pressure-medications/

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: https://www.gov.uk/government/news/ibuprofen-use-and-covid19coronavirus

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.
Anti-virals e.g. lopinavir/ritonavir (boosted protease inhibitor) have been used in other countries as a possible treatment for COVID 19 and is a treatment arm in RECOVERY trial. These medicines significantly interact with tacrolimus, ciclosporin, sirolimus and should not be used in combination. The degree of cytP450 enzyme inhibition is profound and can be seen within a few days. Contact transplant specialist for advice.

References

1. Javier Carbajo-Lozoyaa, Virus Res 165 (2012) 112–117
2. Ma-Lauer Y, Antiviral Res. 2020 Jan;173
3. Ogimi C J Infect Dis. 2017 Jul 15;216(2):203-209
4. Zhang X J Virol. 2008 May;82(9):4420-8.
5. Lee N J Clin Virol. 2004 Dec;31(4):304-9
6. Russell CD Lancet. 2020 Feb 15;395(10223):473-475.
7. Wu Z, JAMA. 2020 Feb 24 epub.
8. Wang D, JAMA. 2020 Feb 7, epub
9. Wu C, JAMA Intern Med. 2020 Mar 13
10. Yichun Cheng, https://www.medrxiv.org/content/10.1101/2020.02.18.20023242v1.article-info
11. S Chiu, Journal of Thrombosis and Haemostais https://doi.org/10.1111/jth.14830
12. FA Klok, Thrombosis Research https://doi.org/10.1016/j.thromres.2020.04.013
13. Tang, Journal of Thrombosis and Haemostais. doi:10.1111/JTH.14817
14. M Fernandez-Ruiz. AJT. 2020. https://doi.org/10.1111/ajt.15929
15. NHS BT weekly reports of COVID 19.
16. Clinical guide for the optimal use of Oxygen therapy during the coronavirus pandemic https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/04/C0256-specialty-guide-oxygen-therapy-and-coronavirus-9-april-2020.pdf
17. Pereira, M. R. AJT 2020. https://doi.org/10.1111/ajt.15941
18. https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_v2final.pdf
19. https://www.nice.org.uk/advice/es27/chapter/Key-messages
20. https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-remdesivir-in-the-treatment-of-patients-hospitalised-with-suspected-or-laboratory-confirme/treatment-protocol-for-healthcare-professionals

Transplant patient with symptoms compatible with COVID-19

Follow local guidelines for use of PPE

Assess patient, swab for SARS-Cov-2 and exclude other causes for symptoms (e.g. CMV, pneumocystis, community or hospital acquired pneumonia, influenza, urinary sepsis, lymphoma and fluid overload)

Patients who do not require hospital admission

- 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
- Patients should self isolate in line with national guidance
- Closely monitor patients remotely for change in symptoms
- Consider restarting immunosuppression 14 days after onset of symptoms if symptom free in absence of anti-pyretics for minimum of 3 days
- Consider early monitoring of graft function when safe to do so and risk of transmission to others is low

Patients who are unwell and admitted to hospital

- Stop antiproliferative agents (MMF/azathioprine)
- Consider reducing or stopping CNI
- Consider Dexamethasone 6mg od for 10 days
- Consider Remdesivir
- Oxygen therapy to achieve saturations between 92-96% (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
- Consider adjunctive antibiotics if superadded bacterial infection is suspected
- Early discussion of ceilings of care

Patients who are progressively unwell and require ventilatory support

- Stop antiproliferative agents (MMF/azathioprine)
- Dramatically reduce or stop CNI
- Consider Dexamethasone and Remedesivir
- Ventilatory support in line with local or national guidance
- Adjunctive support or antivirals in line with local practice or clinical trials