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

Updated 25th March 2020

AIMS

To provide therapeutic 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 unit.

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

At the time of writing, there are no randomised controlled trials of additional therapy that show any benefit above standard supportive care.

The guidance is correct as of March 25th 2020 and may be updated further.

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
    - can be counterproductive in early disease
    - may be considered in progressive pulmonary disease/ARDS
- Antivirals, chloroquine/hydroxychloroquine or biologics should be used in line with local protocols or research studies
- Monitor inpatients closely for rapid deterioration
- Avoid excessive fluid administration
- Cases 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
- Naso pharyngeal swab for PCR analysis should be performed if:
    - Staff are trained in acquisition and have appropriate PPE
    - An alternative treatable cause is considered (eg Influenza)
    - Is required for diagnostic certainty – in admitted or deteriorating patients
    - Is required for purposes of isolation
- A negative swab result requires repeat if clinical suspicion is high
- All proven or suspected cases should be reported to NHS BT
    - https://www.odt.nhs.uk/deceased-donation/covid-19-advice-for-clinicians/

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

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. 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].
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

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 insufficient data to draw a conclusion on the course of transplanted patients, although anecdotal evidence from Italy would suggest a worse prognosis. 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 an increasingly recognised course for COVID.
Excessive fluid administration may worsen the pulmonary injury.
The decision to escalate patients to critical care should be 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

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 increasing steroids if currently taking them.
    - There is no evidence for benefit of high dose steroids at this stage
- Oxygen therapy to achieve saturations over 94% (unless COPD)
- Regular observations, especially saturations, to monitor for rapid deterioration
- Conservative fluid administration
- 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 should start at an early stage. 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 high dose steroids in discussion with ITU team
- 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.
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

References

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Appendix 1: Flow chart