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THE TORONTO TRANSPLANT ID PROGRAM *for infection-free transplantation*

Interim UHN Clinical Guidance for Solid Organ Transplant (SOT) Patients with COVID-19

Executive summary:

Solid organ transplant (SOT) recipients are expectedly at risk of COVID-19. During this current pandemic, many SOT recipients have been diagnosed with COVID-19. Treatment of COVID -19 in this population is challenging. Main issues that should be considered for the treatment of SOT patients include:

1. Currently, there is no proven treatment available for the management of COVID-19. We strongly recommend participation of SOT recipients with COVID-19 in randomized control trials.
2. Immunosuppression reduction is not routinely recommended for the management of COVID-19 in SOT recipients. However, in patients with progressive COVID-19, reducing the doses of antiproliferative agent can be considered.
3. Drug-drug interaction is a major issue that should be strongly considered in selection of therapeutic options and participation in clinical trials (Refer to Table 1).
4. Empiric antimicrobial therapy is recommended for the management of pneumonia or sepsis in SOT patients during the COVID-19 pandemic. Antibacterial/antifungal therapeutic options are provided on the antimicrobial stewardship website: https://www.antimicrobialstewardship.com/infectioninsot.

Introduction:

A new coronavirus (i.e., SARS-CoV-2) has been recently identified as the cause of COVID-19 which may be associated with severe acute respiratory infection. Number of confirmed cases with COVID-19 has been increasing across Canada in recent weeks[1]. SOT recipients appear to be at risk of severe illness with COVID-19[2]. COVID-19 in SOT recipients is likely associated with a higher rate of complications and mortality compared with immunocompetent patients[3,4]. Co-infections with other viral, bacterial and fungal infections have been shown in COVID-19 patients[5]. Thus, a positive test for other pathogens does not rule out COVID-19[5]. Due to low level of evidence, many recommendations are based on limited available information, case series and extrapolation of data from Middle East Respiratory Syndrome (MERS) and COVID-19 in immunocompromised patients.

Participation in Clinical Trials:

- Strongly consider enrollment of patients in COVID-19 clinical trials when eligibility criteria allows SOT recipients to participate.
- We recommend against participation of SOT recipients in clinical trials using traditional medicines, herbal drugs, interferon or protease inhibitors such as lopinavir/ritonavir or darunavir/cobicistat due to drug-drug interactions and the risk of allograft rejection[6–8].

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Case Definition[6-8]:

- Mild illness: uncomplicated upper respiratory tract infection with non-specific symptoms such as fever, fatigue, dry or productive cough, anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhoea, nausea, and vomiting.
- Moderate illness:
    - Pneumonia: SOT patient with pneumonia but no signs of severe illness and no need for supplemental oxygen.
- Severe illness:
    - Pneumonia plus one of the followings:
        1) Tachypnea (respiratory rate > 30 breaths/min)
        2) Respiratory distress
        3) SpO2 ≤ 93% on room air
- Acute respiratory distress syndrome (ARDS):
    - Onset: within 1 week of a known clinical insult or new or worsening respiratory symptoms.
    - Radiographic findings bilateral opacities, lobar or lung collapse, or nodules.
    - Rule out cardiac failure or fluid overload.

Management:

A. Immunosuppression Reduction:

- Immunosuppression reduction is NOT routinely recommended for all SOT patients with confirmed diagnosis of COVID-19[9]. However, immunosuppression reduction should be considered in patients with progressive COVID-19.
- Reducing the doses of antiproliferative agents (i.e., mycophenolate mofetil and azathioprine) may be considered in SOT patients with progressive COVID-19.
    - Animal data showed MMF significantly increases the risk of severe lung injury and mortality in MERS-CoV[10].
- We do NOT recommend routine reduction of the doses of calcineurin inhibitors (CNI)[11,12].
- We do NOT recommend increasing the dose of steroids for the management of COVID-19. The data on efficacy of corticosteroids in patients with COVID-19 is controversial. Corticosteroid therapies for COVID-19 should be only limited to the setting of clinical trials.

B. Inpatient vs Outpatient Treatment:

- Patients with mild illness may not require hospital admission. Self-quarantine at home with frequent follow-up via OTN or Telehealth is recommended.
- Provide symptomatic treatment such as antipyretics. Non-steroidal anti-inflammatory agents should be avoided.
- Counsel transplant patients about signs and symptoms of progressive disease. SOT recipients should seek urgent care in case of progressive symptoms and specifically shortness of breath.
- Treatment of pneumonia in SOT patients may require hospital admission.

C. Antibacterial Therapy:

1) We recommend empiric antimicrobial therapy for patients with pneumonia or sepsis.
    - See https://www.antimicrobialstewardship.com/infectioninsot
    - See SHS+UHN ASP: https://www.antimicrobialstewardship.com/covid19
2) Empiric antibiotic therapy should be adjusted considering history of colonization, clinical, radiographic and laboratory findings.
3) In patients with severe illness, empiric antibiotic treatment should be based on the clinical diagnosis such as community- acquired pneumonia, health care-associated pneumonia or sepsis[13].
    - De-escalate antimicrobial therapy based on microbiology results and clinical assessment.
4) In case of concomitant use of quinolones and hydroxychloroquine, monitor blood sugar and ECG changes due to risk of hypoglycemia and prolongation of QTc.

- Drug-drug interactions could be reviewed in the following websites:
    - http://www.covid19-druginteractions.org/
    - https://hivclinic.ca/wp-content/plugins/php/app.php

D. Medical Management of COVID-19:

a) Hydroxychloroquine

- We do NOT recommend routine use of hydroxychloroquine for treatment or prophylaxis due to lack of convincing data. This medication may provide some antiviral effects via several mechanisms (see table 1) [14–17], the clinical efficacy of this medication in COVID-19 has not been proven [14–19]. Chloroquine is currently unavailable in Canada.
    - Hydroxychloroquine is generally well tolerated. Although this medication is available in Canada, the supply chain appears to be impacted by global demand.
    - A small clinical trial at Shanghai Public Health Clinical Center showed the effect of hydroxychloroquine (n=30; 400 mg/day for 5 days) was similar to control group (n=30) who received conventional treatment. The primary endpoint was

negative throat swab 7 days following randomization (86.7% vs 93.3%). Median duration of hospitalization, time to defervescence and time to improvement of radiographic findings were similar in both groups[20]. The conventional treatment was not clearly explained in this study.

- Hydroxychloroquine was demonstrated to inhibit viral replication *in vitro* by different assays [21,22].
- Clinical and *In vivo* data are very limited at this point.
  - A case series (n=26) showed viral clearance at day 6 of treatment in 57% of patients using hydroxychloroquine(200 mg TID for 10 days), 100% of patients who used simultaneous azithromycin (n=6) and 12.5% of patients who did not receive treatment[23]. Study limitations included lack of blinding, non-randomized design, and lack of clinical outcome. 6 patients were excluded due to unavailable samples after being transferred to ICU. Controls were 16 patients who refused to participate or were treated at other hospitals.
  - Chloroquine/hydroxychloroquine has been recommended for the management of COVID-19 regardless of severity of illness by guidelines in China; however, human data were not provided[24,25].

b) Lopinavir/ritonavir

- We do NOT recommend routine use of this antiviral medication for the management of COVID-19 in SOT recipients[26,27].
- A significant drug-drug interaction is expected with calcineurin inhibitors (see table 1). Lopinavir/ritonavir should be generally avoided in SOT recipients[26,27]. In case of using lopinavir/ritonavir, the dose of tacrolimus should be reduced to 0.5 mg to 1 mg every week. Monitor tacrolimus/cyclosporine blood level daily.
- The level of evidence in efficacy of lopinavir/ritonavir in management of COVID-19 is poor.
  - *In-vitro* data showed activity of this antiviral against SARS, specifically when ribavirin was concomitantly used[28]. However, there is no similar data for COVID-19.
  - Animal data also supported activity of this antiviral against MERS-CoV[10]. No animal data is available for COVID-19.
  - A randomized controlled trial (lopinavir/ritonavir for 2 weeks vs standard of care) showed no significant difference in clinical improvement, mortality at 28 days and viralogical clearance among patients with COVID-19 and hypoxemia[29].
  - In a small cohort (n=18), 5 patients with hypoxemia received lopinavir/ritonavir (400 mg/100 mg BID for 2 weeks). Of these, 3 patients significantly improved in 3 days associated with viral clearance, but 2 patients deteriorated and one required mechanical ventilation[30].
  - Data in SARS outbreak showed efficacy [i.e., clinical and virologic outcome] of lopinavir/ritonavir plus ribavirin (n=41) vs ribavirin alone in a historical cohort

(n=111; 2.4% vs 29%)[28]. There is no comparative data to show the effect of lopinavir/ritonavir plus ribavirin in COVID-19.

- In SARS outbreak, a multicentre cohort showed efficacy of lopinavir/ritonavir combined with ribavirin (n=75 vs 634 matched controls) in reducing the risk of mortality (2.3% vs 15.6%) and mechanical ventilation (0% vs 11%)[31]. This regimen did not provide a benefit in rescue therapy. The study design was not clearly explained.

c) Remdesivir

- We do NOT recommend treatment with this antiviral for management of COVID-19 due to lack of sufficient evidence [22,32,33]. Treatment with this antiviral should be limited to randomized control trials.
- Remdesivir has been used on the basis of Compassionate Use application although obtaining the drug is not guaranteed. The pharmaceutical company is transitioning to "Expanded Access Program" (EAP) and no further information has been provided.
- Access to Remdesivir outside of clinical trials is currently limited to patients who are pregnant, or patients aged under 18 with confirmed COVID-19 and severe manifestations of disease.
  - See https://www.gilead.com/purpose/advancing-global-health/covid-19 for most up to date information.
- Our understanding of the adverse effects is limited to non-transplant patients who received this medication in previous trials for other viral illnesses[17]. Data related to long-term effects of remdesivir and drug-drug interaction with transplant medications are very limited.
- Currently, there is no clinical data showing the efficacy of remdesivir in treatment of COVID-19.
  - *In vitro* and animal data showed remdesivir has been highly effective against SARS-CoV-2 as prevention or treatment[22,33,34].
  - The mechanism of the effect of remdesivir has been well explained. RNA-dependent RNA polymerase (i.e., the target molecule of remdesivir) is 96% identical in sequence among MERS-CoV, SARS-CoV-1 and SARS-CoV-2[34]; thus, extrapolation of the findings of studies showing efficacy of remdesivir in MERS and SARS to COVID-19 is reasonable[35].

d) Tocilizumab

- We do NOT recommend routine use of tocilizumab for the management of COVID-19. Treatment with this medication should be limited to randomized control trials.
- It appears that some patients with severe COVID-19 develop features of hyperinflammation such as cytokine release syndrome[9]. Although IL-6 has been

repeatedly shown to play an important role in pathogenesis of severe COVID-19 [36–39], the efficacy of this drug has not been demonstrated.

- Some centres used IL-6 blood level >40 pg/ml or CRP> 10 mg/dl as an indicator to start tocilizumab. IL-6 blood level is not routinely available.
- Patients should be aware that there are no published data regarding the efficacy of in SOT recipients with COVID-19. Multicentre clinical trials are underway.

e) Convalescent Plasma:

- We do NOT recommend treatment with convalescent plasma outside of clinical trials. Due to the public health emergency, FDA facilitated access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections[40]. Convalescent plasma has not been shown to be effective in clinical trials yet.
- Patients with COVID-19 may develop neutralizing antibody response within 2 weeks after infection targeting nucleocapsid and S protein[41]. Five critically ill patients with ARDS significantly improved and discharged from ICU after receiving convalescent plasma (binding titer greater than 1:1000 end point dilution) that had been obtained from 5 patients who recovered from COVID-19[42].
- Despite considerable similarities between SARS-CoV and SARS-CoV-2, convalescent serum from patients with history of SARS may not provide protective effect (i.e., cross-neutralization) against COVID-19 [43].

f) Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Antagonists:

- We do NOT recommended switching these medications to other drugs[44]. It has been suggested that treatment with angiotensin converting enzyme inhibitors/angiotensin receptor antagonists may increase viral entry[45]. Further studies are required to support these findings.

E. Laboratory Monitoring

- Monitoring of viral shedding may be helpful to predict survival. Other markers that are helpful to monitor response to treatment during inpatient care include platelet count, albumin, ALT, serum Cr, creatine kinase, prothrombin time, D-dimer, high-sensitivity cardiac troponin I, serum ferritin and CRP[46].

F. Repeat COVID-19 Testing Following the Diagnosis:

1) Limited data is available to demonstrate the duration of viral shedding in immunocompromised patients[47]. However, long duration of viral shedding is expected[48].
2) Repeating the test may predict response to treatment. The median duration of viral shedding is 20 days while SARS-CoV-2 remains detectable until death in non-survivors[46].
3) Two consecutive negative tests (i.e., NP specimens collected ≥ 24 hours apart) are required at the time of discharge from hospital. Upper respiratory tract specimens

should be repeatedly collected in hospitalized patients with confirmed diagnosis of COVID-19 to prove viral clearance[13].

4) Physicians managing SOT patients under self-quarantine strategy (i.e., home isolation) should NOT discontinue isolation even after complete improvement of symptoms. Nasopharyngeal swabs should be repeated 7 days after the resolution of symptoms. At least, two consecutive nasopharyngeal swab specimens are required ≥24 hours apart[49].

Table 1: Medications that have been studied in small number of trials

Drug	Dose	Administration	Important Adverse Effects	Contraindication	Warning	Monitor	Dose Adjustment	Interaction
Hydroxychloroquine[Δ] Possible mechanisms: 1) Glycosylation of ACE2 receptor and subsequently decreasing of viral entry. 2)Reducing acidification of endosomes and interference with intracellular virus trafficking. 3)Immuno-modulatory effect and attenuation of cytokine storm reaction.	400 mg BID (day 1) then 200 mg BID for at least 5 days to a max of 10 days[*] Alternative regimens: 200 mg TID for up to 10 days[23] 600 mg BID on day one, then 400 mg daily on days 2-5[50]	Administer with food or milk. Do not crush or divide film-coated tablets. Before start, test G6PD and arrange for baseline ophthalmologic exam	Retinopathy (reversible early changes), Tinnitus, Hypoglycemia, Bone marrow suppression, Hemolysis, Bronchospasm	Pre-existing retinopathy QT > 500 ms, baseline ECG is preferred. Myasthenia gravis Porphyria Epilepsy Porphyria Pregnancy is not contraindication	Cardiomyopathy (discontinue if arrhythmia, or cardiac complication) Hypoglycemia Marrow suppression Proximal weakness Psychiatric effects History of psoriasis or porphyria may exacerbate underlying disease	Perform ECG daily if initial QT 450-500 ms CBC Liver function Renal function (in patients at risk for ocular toxicity) Blood glucose (only if symptoms of hypoglycemia occur) Muscle strength Ophthalmologic exam is NOT needed for short-term use specifically if the dose is <5 mg/Kg/day[51]	Not required in hepatic or renal insuffi-ciency	Risk of hypoglycemia: Antidiabetics, antipsychotics, SSRIs, quinolones, Salicylates Risk of arrhythmia, bradycardia: beta-blockers ** No significant interaction with transplant medications
Remdesivir (Investigational agent, not approved yet)[ΓΙ]	200 mg as a single dose on day 1, followed by 100 mg once daily for a total duration of 5 to 10 days	Please review the pharmaceutical company website: https://www.gilead.com/purpose/advancing-global-health/covid-19 If you plan to apply for compassionate use, an email should be sent to: CompassionateAccess@gilead.com. Once approved, confidential disclosure agreement (CDA) needs to be signed. Intravenous infusion for 30 minutes. No special training or equipment is required for the drug administration. Lyophilized formulation for injection is a preservative-free, white to off-white or yellow	Not available. Stroke, sepsis, hyperglycemia, urinary tract infection, brain edema, hypotension reported in Ebola RCTs. Transient adverse effects included constipation, heartburn, itching, unusual feelings in the ear, dizziness, loss of appetite, nausea, vomiting, shaking of the leg and arm, headache, loose stool, or upset stomach[52].	Not available	Not available. Patient should not drink alcohol for 14 days after you start receiving remdesivir.	If possible, daily monitoring or renal (creatinine and BUN) and liver (ALT, AST) functions should be performed.	Not available Hepatic or renal insuffi-ciency were not exclusion criteria in previous RCTs for Ebola[52]. Animal studies did not show significant renal side effects.	Data not available. Closely monitor trough levels of calcineurin inhibitors

		lyophilized solid containing 150 mg remdesivir that is to be reconstituted with 29 mL of sterile water for injection and diluted into intravenous infusion fluids prior to intravenous administration.						
Tocilizumab Only if CRP as surrogate marker is elevated (experimental therapy for COVID-19)	4-8 mg/kg (recommended dose: 400 mg, max: 800 mg) Repeat after 12 hours (same dose), if the response to the 1st dose was poor. In case of poor response, a third dose is given after 1 week.[δ]	Dilute with normal saline to 100 ml and infuse over the course of an hour.	Transaminitis (20-30%), neutropenia, thrombocytopenia HSV/VZV reactivation Sepsis, serious infections occurred in patients on concomitant immunosuppressive therapy. Demyelination disorders	Patients with active bacterial or fungal infections, specifically TB.	Use with caution in patients at increased risk for GI perforation In COVID-19 clinical trials, ALT / AST> 5 ULN, neutrophils <0.5, and platelets less than 50, definite diagnosis of rheumatic immune-related diseases are exclusion criteria.	ALT, AST, ALP, bilirubin, and latent TB screening (before or during treatment) CBC, ALT/AST, Bilirubin Median time to defervescence: 4 hours Blood pressure stabilization: 1-3 days	Liver enzymes>3 to 5 × ULN (confirmed with repeat testing): Interrupt until ALT/AST <3 × ULN For persistent increases >3 × ULN, discontinue. Liver enzymes>5 × ULN: Discontinue.	Enhances adverse effects of cyclosporine and tacrolimus. Patients on leflunomide, discontinue. Avoid in leukemic patients recently used cladribine
Lopinavir/ ritonavir Only for mild illness (Avoid in transplant patient and use ONLY IF there is no other option)	Lopinavir 400 mg/ritonavir 100 mg twice daily for 14 days[53]	Solution should be taken with food. Tablets: with or without food, swallow whole, do not break, crush, or chew.	Rash, diarrhea, vomiting, transaminitis, hyperglycemia, neutropenia, thrombocytopenia	Pregnancy; hepatic or renal failure; coadministration with metronidazole, venetoclax, salmeterol	Cardiac conditions: monitor QT Hepatotoxicity: monitor ALT	Triglycerides/cholesterol (prior to initiation), LFTs, electrolytes, glucose	No dose adjustment, Avoid once-daily dosing in hemo-dialysis patients	Significant interaction with transplant medications; Cyclosporine: Monitor cyclosporine trough level Consider empiric cyclosporine dose reduction. Monitor tacrolimus trough level. tacrolimus 0.5 mg to 1 mg every week may be adequate.

* American Academy of Ophthalmology (AAO) recommends not exceeding a daily hydroxychloroquine dosage of 5 mg/kg using actual body weight in most patients.

** Atenolol is safe and has no significant interaction.

δ Up to 4 doses have been administered (with at least an 8-hour interval between consecutive doses) in patients with cytokine release syndrome.

Π It was used in RCTs for Ebola and its effect was lower than monoclonal antibodies. Its safety has been approved in those trials.

Δ Chloroquine has been highly effective in the control of 2019-nCoV infection in vitro[19]. Hydroxychloroquine is preferred.

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