Management of Patients On Dialysis And With Kidney Transplant During SARS-COV-2 (COVID-19) Epidemic In Italy

Supplementary Material

A. Proposal For A Therapeutic Management Plan For Haemodialysis And Transplant Patients With SARS-COV-2 Infection

Our recommendations for therapeutic management of haemodialysis and transplant patients with sars-cov-2 infection are based on our experience in management of the disease and the available literature. Within each clinical scenario, a case-by-case assessment needs to be considered.

1. Asymptomatic/paucisymptomatic haemodialysis patients (body temperature <38°C, cough, WITHOUT dyspnoea) and negative chest X-ray

Consider home management, if compatible with transport-related logistics. The patient must wear a surgical mask at all times.
Body temperature and O2 saturation must be checked at the dialysis center and, if applicable, at home.
Antiviral therapy (duration: 5-20 days to be determined based on clinical progression)*

- Lopinavir/ritonavir 200/50 mg 2 tabs x2/day **OR**
- Darunavir 800 mg 1 tab/day + ritonavir 100 mg 1 tab/day **OR**
- Darunavir/cobicistat 800/150 mg 1 tab/day

DOSAGE ADJUSTMENT NOT NECESSARY IN PATIENTS WITH RENAL IMPAIRMENT
SCREEN ONGOING THERAPY FOR INTERACTIONS (http://www.covid19-druginteractions.org/)

Hydroxychloroquinine

200 mg after each dialysis session (three times a week in patients on twice-weekly regimen)

Empirical antibiotic therapy

Consider a course of azythromycin 500 mg/day

Dialysis therapy

In patients undergoing hemodiafiltration, continue the existing dialysis method. In patients undergoing dialysis, the use of medium cut-off membranes may be considered with the aim of increasing the efficiency of removal of middle size molecules and, therefore, inflammation mediators.

NOTE: outpatients antiviral therapy, although in our opinion advisable, may not be feasible due to the high rate of adverse events(13); if employed liver enzymes should be checked regularly.

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2. Asymptomatic/paucisymptomatic transplant patients (body temperature <38°C, cough, cold WITHOUT dyspnoea) and negative chest X-ray

Hospitalization or home management, to be clinically decided on a case-by-case basis.

We advise to monitor body temperature and O2 saturation (if applicable) at home. We advise transplant center medical personnel to perform daily telephone visits.

Immunosuppressive therapy:

- Stop MMF or azathioprine immediately after the confirmation of SARS-Cov-2 infection
- Stop calcineurin inhibitor immediately after the confirmation of SARS-Cov-2 infection
- Glucocorticoids: initiation of methylprednisolone 16 mg

NOTE: If progression is favourable, the timing of and methods for immunosuppressive therapy resumption are not yet clear and should be evaluated by carefully weighing the benefit-risk ratio in the individual patient.
Our proposed approach is to resume the calcineurin inhibitor at half of the previous dosage, starting at least 15 days after disappearance of symptoms and swab negativization, with the aim of gradually reaching a blood level of 3-5 ng/ml of tacrolimus and 200-300 ng/ml of cyclosporine at the second hour.
Further increase in the calcineurin inhibitor dosage should be considered after at least another 15 days with no symptoms and an additional negative swab. In the calcineurin inhibitor re-titration period, it is recommended to maintain the dose of methylprednisolone at 8-16 mg/day, based on clinical judgement.
Case-by-case evaluation of subsequent re-initiation of MMF, azathioprine and m-TOR inhibitors.

Antiviral therapy (duration: 5-20 days to be determined based on clinical progression)*

- Lopinavir/ritonavir 200/50 mg 2 tabs x2/day **OR**
- Darunavir 800 mg 1 tab/day + ritonavir 100 mg 1 tab/day **OR**
- Darunavir/cobicistat 800/150 mg 1 tab/day

DOSAGE ADJUSTMENT NOT NECESSARY IN PATIENTS WITH RENAL IMPAIRMENT
THERAPY FOR INTERACTIONS (http://www.covid19-druginteractions.org/)

NOTE: outpatients antiviral therapy, although in our opinion advisable, may not necessarily be feasible due to the high rate of adverse events(13) and difficulties in performing regular monitoring of blood tests in this context; if employed, liver enzymes should be checked regularly and the potentially benefits weighted against the potential risks.

Hydroxychloroquinine

- 200 mg x2/day if GFR >30 ml/min
- 200 mg/day if GFR >15 ml/min and <30 ml/min
- 200 mg every other day if GFR <15 ml/min

Empirical antibiotic therapy

Consider a course of azythromycin 500 mg/day

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3. Haemodialysis patients with severe symptoms (body temperature >38°C, cough, dyspnoea) and/or positive chest X-ray

Hospitalization
Antiviral therapy (duration: 5-20 days to be determined based on clinical progression)*

- Lopinavir/ritonavir 200/50 mg 2 tabs x2/day **OR**
- Darunavir 800 mg 1 tab/day + ritonavir 100 mg 1 tab/day **OR**
- Darunavir/cobicistat 800/150 mg 1 tab/day

NO ADJUSTMENT FOR RENAL FUNCTION NECESSARY IN ANY CIRCUMSTANCES
SCREEN ONGOING THERAPY FOR INTERACTIONS (http://www.covid19-druginteractions.org/)

Hydroxychloroquinine

200 mg every other day (three times a week in patients under dialysis twice weekly)

Empirical antibiotic therapy

Consider a course of azythromycin 500 mg/day

Dialysis therapy (quarantine area)

In patients undergoing hemodiafiltration, continue with the existing dialysis method. In patients undergoing dialysis, the use of medium cut-off membranes is recommended with the aim of increasing the efficiency of removal of middle size molecules and, therefore, inflammation mediators.

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4. Transplanted patients with severe symptoms (body temperature >38°C, cough, dyspnoea) and/or positive chest X-ray

Hospitalization

Immunosuppressive therapy:

- Stop MMF or azathioprine immediately after the confirmation of SARS-CoV-2 infection
- Stop calcineurin inhibitor immediately after the confirmation of SARS-CoV-2 infection
- Glucocorticoids: initiation of methylprednisolone 16 mg

Antiviral therapy (duration: 5-20 days to be determined based on clinical progression)*

- Lopinavir/ritonavir 200/50 mg 2 tabs x2/day **OR**
- Darunavir 800 mg 1 tab/day + ritonavir 100 mg 1 tab/day **OR**
- Darunavir/cobicistat 800/150 mg 1 tab/day

NO ADJUSTMENT FOR RENAL FUNCTION NECESSARY IN ANY CIRCUMSTANCES

SCREEN ONGOING THERAPY FOR INTERACTIONS (http://www.covid19-druginteractions.org/)

Hydroxychloroquinine

200 mg x2/day if GFR >30 ml/min

200 mg/day if GFR >15 ml/min and <30 ml/min

200 mg every other day if GFR <15 ml/min

Empirical antibiotic therapy

Consider a course of azythromycin 500 mg/day

NOTE: If progression is favourable, the timing of and methods for immunosuppressive therapy resumption are not yet clear and should be evaluated by carefully weighing the benefit-risk ratio in the individual patient.

Our proposed approach is to resume the calcineurin inhibitor at half of the previous dosage, starting at least 30 days after clinical resolution (apyrexial patient, no need for oxygen therapy, negative chest X-ray) and after two negative swabs (one at discharge and one at 30 days), with the aim of gradually reaching a level of 3-5 ng/ml of tacrolimus and 200-300 ng/ml of cyclosporine at the second hour.

Resumption of full-dose calcineurin inhibitor dosage and maintenance of the methylprednisolone dose at 8-16 mg/day (based on clinical judgement) after 15 days free of symptoms and an additional negative swab.

Case-by-case evaluation of re-initiation of MMF, azathioprine and m-TOR inhibitors.

***:** Remdesivir should theoretically be considered as first-line in all patients or at least in patients with rapid clinical deterioration or patients with severe pneumonia, ARDS or global respiratory failure, hemodynamic decompensation, needing mechanical (or non-invasive) ventilation. Drug currently not routinely available in Italy.

Dose: 200 mg IV as loading dose in 30 minutes on Day 1, thereafter 100 mg/day IV (Days 2-10).

5. Hospitalised (transplant, dialysis) patient with clinical deterioration

COVID-19 patients deserve special respiratory surveillance. Respiratory exchanges may worsen even several days after the symptoms onset and may worsen rapidly. The need for O2 therapy may require a quick escalation and the nephrologist should be ready to interface with colleagues (pulmonologists, resuscitation team) for ventilatory support.

If Brescia-COVID respiratory severity scale **≥2 (see appendix) AND IF, AT THE SAME TIME:**

- The high viral load phase can be considered to be overcame (e.g. no fever for >72h and/or at least 7 days from symptoms onset)
- Ongoing superimposed bacterial infection can be ruled out clinically (patients at this stage of the disease usually present elevated CRP; a negative procalcitonine may be helpful in ruling out bacterial infection)
- Worsening of respiratory exchanges and/or significant worsening of chest imaging

A cytokine release syndrome may be assumed as cause the cause of the evolving clinical scenario. We recommend:

Dexamethasone (Brescia-COVID respiratory severity scale≥2)

20 mg/day for 5 days, thereafter 10 mg/day for 5 days

CONSIDER COMBINATION WITH

Tocilizumab (Brescia-COVID respiratory severity scale≥3)

In case of drug shortage, put cases with rapidly and significantly increasing of the D-Dimer levels first.
Requires in Italy signing of informed consent.
Perform quantiferon and viral marker assay for occult HBV hepatitis and if feasible monitor IL-6 levels.

Exclusion criteria:

- AST/ALT 5 times higher than normal.
- Neutrophils below 500 cells/mmc.
- PLT below 50,000 cells/mmc.
- Documented sepsis due to pathogens other than COVID-19.
- Presence of comorbidities associated with unfavourable outcome based on clinical judgement
- Complicated diverticulitis or bowel perforation
- Ongoing skin infection (e.g. antibiotic-induced uncontrolled dermopanniculitis)
- On-going anti-rejection immunosuppressive therapy

Dosages of tocilizumab per body weight in COVID-19

Max 3 infusions at a dose of 8 mg/kg of body weight (maximum dose per infusion 800 mg). Second infusion at an interval of 12-24 hours

PATIENT WEIGHT	TOCILIZUMAB DOSE	Dose Range mg/Kg
35-45 kg	320 mg (4 x 80 mg bottles)	9.1-7.1
46-55 kg	400 mg (1 x 400 mg bottle)	8.7- 7.3
56-65 kg	480 mg (1 x 400 mg bottle + 1 x 80 mg bottle)	8.6-7.4
66-75 kg	560 mg (1 x 400 mg bottle + 2 x 80 mg bottles)	8.5-7.5

76-85 kg	600 mg (1 x 400 mg bottle + 1 x 200 mg bottle)	7.9-7.0
>86 kg	800 mg (2 x 400 mg bottles)	9.3

Empirical antibiotic therapy and antiviral therapy
When tocilizumab is employed, empirical antibiotic therapy with piperacillin+tazobactam is advised.
Consider a course of azythromycin 500 mg/day if not already performed.
In this context maintenance of the antiviral therapy should be consider.

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6. COVID-19 patients with Acute Kidney Injury (AKI) requiring continuous renal replacement therapy (CRRT)

Indication: patients with stage 3 AKI (defined as a 3-fold increase in creatinine levels from baseline or creatinine ≥4.0 mg/dl or defined based on amount of diuresis: diuresis <0.3 ml/kg/h for ≥24 h or anuria for ≥12 h) hospitalized in ICU

Method: CVVH pre- and post-dilution with a prescribed dose >25 ml/kg/h (to obtain an administered dose ≥25 ml/kg/h).

Anticoagulation:

First choice: regional citrate anticoagulation (RCA).
Second choice: systemic heparinization with unfractionated heparin (UFH).
Third choice: treatment with no anticoagulants.
NOTE: most SARS-CoV-2 infected patients requiring intensive care management show altered liver function values secondary to drug-induced hepatotoxicity as well as due to possible liver involvement. In case of severe liver dysfunction, citrate clearance may be reduced of the 50% with risk of accumulation in 12% of the patients; of note the bleeding risk appear to be low and observed in 5% of the patients(S1). Nevertheless, we recommend in such patients close monitoring for signs of citrate accumulation.

Monitoring: See appendix for details concerning suggested monitoring in these patients.

Cartridges for cytokine adsorption (for example in Brescia, as per previous clinical practice, CytoSorb®): owing to the aforementioned role of proinflammatory cytokines in the pathogenesis of ARDS, we recommend the use of cartridges for cytokine adsorption if the patient has not already been treated with tocilizumab for ineligibility (case 1) or organizational/technical reasons (case 2).

- Case 1, patients ineligible for tocilizumab: we suggest using cartridges for cytokine adsorption as per manufacturer.
- Case 2, patients scheduled for therapy with tocilizumab, which has no yet been administered at the time of CVVH initiation, we believe that the use of the cartridges for cytokine adsorption should be continued 24 hours after tocilizumab administration or up to the point of reaching the completion of the suggested cycle as per manufacturer.

Note: patients with SARS-CoV-2 infection seem to be at higher risk of developing clothing during CVVH and therefore treatment with regional or systemic anticoagulation should be employed.
Some cartridges for cytokine adsorption may result in reduced blood levels of antibiotic (please, consult manufacturer manuals for adjustment in the antibiotics dose).

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7. COVID-19 patients with AKI requiring renal replacement therapy with haemodialysis

For AKI patients requiring intermittent haemodialysis, we recommend using as filters medium cut-off membranes in order to increase the clearance of pro-inflammatory molecules.
Use of bilumen CVC is necessary to increase treatment efficiency.

B. FURTHER CONSIDERATIONS FOR DIAGNOSIS AND TREATMENT

Considerations on chest imaging: due to the significant pressure on the health care system, chest x-ray is the first line imaging approach. Chest CT has the advantage of a greater sensitivity in detecting abnormalities in the lung structure and therefore may be a key step in the diagnostic definition of such patients; reports suggest for the chest CT an even higher diagnostic sensitivity compared to the RT-PCR (S2). Once the diagnosis has been established, chest x-ray represents the most effective and sustainable approach to monitor patients.

Considerations on RAS blockade: there is no evidence supporting a particular focus on RAS blockade in this context. Of note, patients with COVID-19 may develop dehydration secondary to diarrhoea as well as low fluid intake due to nausea as consequence of the disease itself and of the antiviral therapy. In this scenario, the use of RAS blockade should be weight against the potential negative effects.

Antipyretic in haemodialysis and transplant patients: we recommend the use of paracetamol.

Medium cut-off membranes for haemodialysis: although weak, evidence is in support for an anti-inflammatory effect of medium cut-off membranes; their use may in fact induce effective removal of uremic toxins of large-medium cut-off with a proven *in vivo* effect on CRP reduction and *in vitro* reduction of ROS, TNF-alpha and IL-6 production(S3).

CytoSorb® cartridge: when employed, CytoSorb filter is inserted in series with the hemofilter in a post filter position. The Cytosorb cartridge use is recommended for 48 hours with set and cartridge to be replaced after the first 24 hours. The CytoSorb cartridge should not increase *per se* the risk of circuit coagulation, however patients with SARS-CoV-2 infection seem to be at higher risk of developing clothing and therefore treatment with regional or systemic anticoagulation should be employed.
The CytoSorb cartridge may result in reduced blood levels of antibiotic (see below for dosing adjustments).

Antibiotic therapy management during use of CytoSorb cartridge: When possible, measure blood levels of antibiotics used. According to the literature, the most commonly used antibiotics (e.g. imipenem,

meropenem, piperacillin/tazobactam and linezolid) present limited reduction during treatment. Aminoglycosides are the antibiotics that are most subject to removal.

Recommended doses of main antibiotics:

- Piperacillin/tazobactam (removal insignificant): 4.5 g every 8 hours
- Cephalosporin (removal insignificant): doses close to maximum limit of recommended dosage.
- Linezolid: 600 mg every 12 hours.
- Meropenem: 1 g every 8 hours for the duration of CytoSorb.
- Imipenem/cilastatin (removal insignificant): 500 mg every 8 hours (doses close to maximum limit of recommended dosage).
- Fluoroquinolones (removal insignificant): doses close to maximum limit of recommended dosage.
- Aminoglycosides and vancomycin: administer loading dose (e.g. for amikacin 15 mg/kg followed by 7.5 mg/Kg/day; for vancomycin 15mg/kg/day followed by 7.5 mg/Kg/day) and daily monitoring of TDM.

Brescia-COVID respiratory severity scale

The scale consists of four testing criteria:

a) The patient has dyspnoea or **STACCATO SPEECH** (inability to count rapidly to 20 after taking a deep breath) at rest or after minimum activity (sitting down on bed, standing up, speaking, swallowing, coughing)
b) Respiratory rate > 22
c) PaO2 <65mmHg or SpO2<90%
d) Significant worsening of chest x-ray (increased compactness and extension of infiltrate)

The presence of two criteria confers a score of 2, the presence of more than 2 criteria a score of 3.

Note: the Brescia-COVID respiratory scale is a non-validated tool meant for internal use only. Other scales for defining the degree and severity of respiratory involvement may be employed. No prognostic role for this scale has been so far investigated in patients affected by SARS-CoV-2 infection. We suggest daily assessment of the scale in stable patients and re-assessment of the scale in case of signs of clinical deterioration or increase in oxygen supplementation requirement.

Off Label Drugs: in Italy, for lopinavir/ritonavir and hydroxychloroquine an “off-label” form should be used and the patient has to sign an informed consent form.

Suggested monitoring for patients with AKI treated with CVVH:

Regional citrate anticoagulation (RCA): important to closely monitor citrate accumulation risk parameters.

Monitor every 12 hours Total systemic calcium to Systemic Ca^{++} ratio, which should be less than 2.5
Assess lactic acid levels (if there are increased lactates not attributable to worsening of hemodynamic parameters/worsening of sepsis, consider citrate accumulation)
Assess changes in arterial pH.

Systemic heparinization with unfractionated heparin (UFH): monitor aPTT with the aim of maintaining it within therapeutic range that is 1-1.4 times normal. Dosage should be carried out 2 hours after the start of treatment and every 4 hours until target is reached, then every 8 hours (unless otherwise indicated). Monitor antithrombin-III every 48 hours.

General monitoring:

Every 24/h: body weight, fluid input/output, kidney function, electrolytes, acid-base balance, ionised calcium, cytolitic activity score and liver function.
Every 48/h: total calcium, serum phosphorus, magnesium

Supplementary References

S1. Zhang W, Bai M, Yu Y, et al. Safety and efficacy of regional citrate anticoagulation for continuous renal replacement therapy in liver failure patients: a systematic review and meta-analysis. *Crit Care.* 2019;23:22.
S2. Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RTPCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases [e-pub ahead of print]. Radiology. https://doi.org/10.1148/radiol.2020200642. Accessed March 22, 2020.
S3. Cantaluppi V, Marengo M, Quercia A, et al. Removal of large-middle molecules, inhibition of neutrophil activation and modulation of inflammation-related endothelial dysfunction during expanded hemodialysis (HDx). *Nephrol Dial Transplant.* 2019;34(Suppl 1):gfz096.FO048.