

MANAGEMENT OF PATIENTS ON DIALYSIS AND WITH KIDNEY TRANSPLANT DURING COVID-19 CORONAVIRUS INFECTION

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Introduction

The COVID-19 epidemic in Lombardy requires the development of a protocol for nephropathic patients, particularly those undergoing dialysis and carriers of renal transplants.

The China CDC has recently published the largest COVID-19 case series, which includes 44,672 cases. This study shows an overall mortality rate of 2.3%. Beside age (1.3% mortality in the 50-59 age group, 3.6% in the 60-69 age group, 8% in the 70-79 age group and 14.8% in the ≥ 80 age group), the main risk factors are the presence of cardiovascular diseases (10.5% mortality), diabetes (7.3% mortality), chronic respiratory diseases (6.3% mortality), high blood pressure (6% mortality) and cancer (5.6% mortality) (1,2). In the Lombardy region, however, the disease seems to have much higher mortality rates than reported in China and this should lead us to investigate carefully all factors potentially responsible for this trend.

The comorbidities associated with increased mortality during COVID-19 infection are very common in patients with Chronic Kidney Disease (CKD) as well as in patients undergoing renal replacement therapy with haemodialysis. In addition, there are currently no solid data on COVID-19-positive patients undergoing dialysis or with kidney transplant having a condition of reduced immunocompetence, besides various cardiovascular risk factors.

In these weeks, we have followed 21 transplanted patients and 17 dialysis patients at our institution in Brescia. Our initial experience suggests that the disease has a severe progression, with a potentially life-threatening outcome especially in the subgroup of kidney-transplanted patients. Furthermore, a significant number of nephropathic patients with COVID-19 have been managed at sites in Lodi, Cremona, Manerbio, Montichiari and Chiari, which are part of the Brescia task force. The Chinese experience suggests that the disease has a less severe course in dialysis patients, compared not only to kidney transplant patients but also to non-nephropathic patients. This is also our initial experience in Brescia, although not confirmed by all sites participating in our task force. Obviously, the lack of adequate data both in the general population (proportion of asymptomatic subjects) and in nephropathic patients means that there are no data to allow us to draw any final conclusions.

For this reason, we are collecting detailed clinical and laboratory data from our patients with the aim of sharing the clinical and outcome characteristics of the disease in nephropathic patients with the nephrology community.

In general terms, optimal disease management is still being debated and the therapeutic approach still lacks significant evidence. The indication for anti-retroviral therapy is uncertain and to date there is no registered drug for the treatment of COVID-19 infections (3). However, experience can be drawn from the use of antiviral agents on viruses belonging to the same family of Betacoronaviruses (SARS and MERS). Nevertheless, the emergency provides the rationale for using antivirals notwithstanding preliminary scientific evidence. In patients with advanced CKD, there is also the problem of adjusting therapy based on the degree of renal function. Conversely, in kidney transplanted patients, there is a need to carefully modulate immunosuppressive therapy. To date, no clear guidelines exist for the management of these patients (4).

Brescia is currently the second largest area affected after Bergamo (2,918 cases as of 17 March 2020). A working group consisting of infective disease specialists and intensivists from Lombardy has developed a therapeutic protocol in COVID-19 patients based on disease severity (Guidelines on the Therapeutic and Support Management of Patients with COVID-19 Coronavirus Infection. Edition 2.0, 12 March 2020). Partly borrowing the infectiological and intensivist approach of the protocol, we have adapted that approach to our dialysis and kidney-transplanted patients. We will also provide some logistics considerations resulting from our direct experience in the management of patient flows during the COVID-19 epidemic.

Pharmacological treatment

Chloroquine – hydroxychloroquine: investigational evidence seems to support the role of antiviral activity of chloroquine towards the SARS and avian influenza viruses in *in vitro* and animal models. A panel of Chinese experts supports the use of this drug in consideration of a benefit observed in terms of patient hospitalizations and overall outcomes (5).

Lopinavir/ritonavir: second-generation anti-retroviral. Anecdotal evidence seems to support its possible role in COVID-19 infection.

Darunavir ritonavir and darunavir/cobicistat: potential alternatives to lopinavir/ritonavir based on the similar mechanism of action.

Remdesivir: nucleotide analogues whose mechanism of action consists in incorporating the drug into newly synthesized RNA chains. It has been suggested that it plays a role in reducing viral load and improving lung function parameters in animal and *in vitro* models (6,7). Two clinical trials are ongoing in China.

Corticosteroids: the use of corticosteroids would be contraindicated in the early phases of the disease. However, data suggest their role in the management of acute respiratory distress syndrome (ARDS) with a significant impact on the survival curves of treated patients (8).

Tocilizumab: in consideration of the central role that IL-6, in combination with other pro-inflammatory cytokines, seems to have in the development of COVID-19-induced ARDS, tocilizumab could play a role in the management of selected cases in the absence of major contraindications.

Logistics considerations

Proper logistic planning is considered necessary in the management of this health emergency. The management of these patients make it necessary to reconcile infection protocols (e.g. isolation) with needs that are intrinsic to our specialty (e.g. the need to move patients for haemodialysis). Our experience, though still limited, seems to suggest a better outcome in transplanted patients directly managed in a nephrology ward compared to the group managed in other general COVID areas and evaluated by the nephrologist only in consultation.

The particular logistic organization of our institution has allowed us to implement an efficient organizational model. A summary of our institution is presented here:

1st Floor:

Male ward	Haemodialysis, peritoneal dialysis, outpatient offices	Female ward
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2nd Floor:

Dialysis	Transplant ward and outpatient offices
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On 27-28 February, we started reducing the number of beds in the female ward and increasing discharges from the male ward, subsequently transferring female patients that could not be discharged to the male ward. In the night between 27 and 28 February, we admitted the first (kidney-transplanted) positive female patient, subsequently transferred to the ICU due to clinical deterioration. As of 28 February, the logistic situation was as follows. To be noted, the COVID area was equipped with dialysis machines and equipment.

1st Floor:

Male and female ward	Haemodialysis, peritoneal dialysis, outpatient offices	COVID
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2nd Floor:

Dialysis	Transplant ward and outpatient offices
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Between 2-4 March we admitted the first positive patients to the COVID area. At this stage, the need was almost only for transplanted patients, as our site covers a large community which also includes the areas of Lodi and Codogno. The progressive inflow of COVID-positive patients into our hospital, together with the need to receive haemodialysis patients, has therefore led us to move the male and female ward to the 2nd floor, close the transplant centre and rearrange the ward's central spaces to create haemodialysis rooms, intended partially for COVID-positive patients and partially for COVID-negative patients.

1st Floor:

COVID HAEMODIALYSIS INPATIENTS	HAEMODIALYSIS COVID INPATIENTS	HAEMODIALYSIS COVID- NEGATIVE	HAEMODIALYSIS COVID TRANSPLANT	COVID TRANSPLANT INPATIENTS
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2nd Floor:

Dialysis	COVID-negative nephrology ward
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PROPOSAL FOR A THERAPEUTIC MANAGEMENT PLAN FOR HAEMODIALYSIS AND TRANSPLANT PATIENTS WITH COVID-19 INFECTION

1. Asymptomatic/paucisymptomatic haemodialysis patients (fever >37.5°C but <38°C, cough, cold WITHOUT dyspnoea) and negative chest X-ray

Possible home management, if compatible with transport-related logistic management. The patient must wear a surgical mask at all times.

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/>)

Hydroxychloroquine

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

Empirical antibiotic therapy

Only in the presence of bacterial superinfection

Dialysis therapy

In patients undergoing hemodiafiltration, continue the existing dialysis method. In patients undergoing dialysis, the use of the **Theranova** filter is recommended with the aim of increasing the efficiency of removal of middle size molecules and, therefore, inflammation mediators.

2. Asymptomatic/paucisymptomatic transplant patients (with mild symptoms: fever >37.5°C but <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. Daily monitoring when at home, of fever and O2 saturation (if possible) with daily telephone visit by the transplant centre.

Immunosuppressive therapy:

- Stop MMF or azathioprine
- Stop calcineurin inhibitor
- 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

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

Hydroxychloroquine

- 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

Only in the presence of bacterial superinfection

3. Haemodialysis patients with severe symptoms (fever >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/>)

Hydroxychloroquine

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

Empirical antibiotic therapy

Only in the presence of bacterial superinfection

Dialysis therapy (quarantine area)

In patients undergoing hemodiafiltration, continue with the existing dialysis method. In patients undergoing dialysis, the use of the **Theranova** filter is recommended with the aim of increasing the efficiency of removal of middle size molecules and, therefore, inflammation mediators.

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

Hospitalization

Immunosuppressive therapy:

- Stop MMF or azathioprine
- Stop calcineurin inhibitor
- 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/>)

Hydroxychloroquine

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

Only in the presence of bacterial superinfection

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 (transplanted, dialysis) patient with clinical deterioration

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 finished (e.g. no fever for >72h and/or at least 7 days from symptoms onset)
- Ongoing superbacterial infection can be ruled out clinically
- There is ongoing worsening of respiratory exchanges and/or significant worsening of chest X-ray

Dexamethasone

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

CONSIDER COMBINATION WITH

Tocilizumab

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.

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 dermatitis)
- 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

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 COVID-19-infected patients requiring intensive care management show altered liver function values secondary to drug-induced hepatotoxicity as well as due to possible liver involvement. This is associated with an increased risk for citrate accumulation.

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

CytoSorb: owing to the aforementioned role of proinflammatory cytokines in the pathogenesis of ARDS, we recommend the use of CytoSorb adsorbent cartridge 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 the routine approach with Cytosorb cartridge (duration 48 hours, set and cartridge must be replaced after the first 24 hours).

- Case 2, patients scheduled for therapy with tocilizumab, which has not yet been administered at the time of CVVH initiation, we believe that the use of CytoSorb should be continued 24 hours after tocilizumab administration or up to the point of reaching the total of 48 hours of Cytosorb treatment.

The CytoSorb cartridge should not increase *per se* the risk of circuit coagulation, however patients with COVID-19 infection seem to be at higher risk of developing clotting in this context and therefore treatment with regional or systemic anticoagulation should be employed.

The CytoSorb cartridge may result in reduced blood levels of antibiotic (see Appendix for dosing adjustments).

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

For AKI patients requiring intermittent haemodialysis, we recommend using the TheraNova filter in order to increase the clearance of pro-inflammatory molecules.

Use of bilumen CVC is necessary to increase treatment efficiency.

APPENDIX

Brescia-COVID respiratory severity scale	
0	Ambient air
1	Oxygen therapy
2	Oxygen therapy plus 1 of the following 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 with >6L/minute O ₂ c) PaO ₂ <65mmHg with >6L/minute O ₂ d) Significant worsening of chest x-ray (increased compactness and extension of infiltrate)
3	The patient requires high-frequency nasal ventilation (HFNC), CPAP or NIV
4	The patient is intubated for CPAP or pressure support
5	The patient is under controlled mechanical ventilation; PaO ₂ /FiO ₂ >150 mmHg
6	The patient is under controlled mechanical ventilation; PaO ₂ /FiO ₂ ≤150 mmHg
7	The patient is under controlled mechanical ventilation; PaO ₂ /FiO ₂ ≤150 mmHg and intravenous infusion of neuromuscular blockers
8	The patient is under controlled mechanical ventilation; PaO ₂ /FiO ₂ ≤150 mmHg and one of the following: a) Prone position b) ECMO

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.

Monitoring suggested 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, cytotoxic activity score and liver function.
Every 48/h: total calcium, serum phosphorus, magnesium

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: 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.

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