Recommendation of the Czech Society of Nephrology and the Czech Transplantation Society for the treatment of COVID-19 in patients after kidney transplantation

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COVID-19 is caused by a new coronavirus, SARS-CoV-2. Patients after kidney transplantation are a high-risk group for severe COVID-19, with frequent need for hospitalization (32%-78%) and mortality rates ranging from 18% to 30% in most studies, which, however, included mainly hospitalized patients.[1-5] International transplant societies have not yet published comprehensive recommendations for the treatment of COVID-19, nor have randomized trials been performed in the organ transplant population. Therefore, the recommendations of the CSN and CTS are based on updated guidelines for the general population with specifications for patients after kidney transplantation, if relevant.[6,7] Recommendations regarding ventilatory support and hemodynamics go beyond those of the CSN and CTS, and we refer to the consensus of international groups.[7,8] Most treatment recommendations are related to the severity of the course of COVID-19. The basic definitions of asymptomatic, mild, moderate, severe, and critical COVID-19 disease are shown in Table 1.[6,7]

Table 1: Clinical severity of COVID-19 in adults

Asymptomatic infection	• Positive virological evidence of SARS-CoV-2 (PCR, Ag test) • Absence of clinical symptoms compatible with COVID-19
Mild disease	• Presence of various COVID-19 symptoms (e.g., temperature, cough, sore throat, cephalea, fatigue, myalgia, nausea, vomiting, diarrhea, loss of smell or taste) • Absence of new-onset shortness of breath or reduced oxygen saturation • Absence of pathological findings on CT or lung X-ray
Moderate disease	• Evidence of lower respiratory tract disease by clinic and imaging and/or significant physical exhaustion with febrile illness >38°C • Oxygen saturation (SpO2) ≥94% in air at rest
Severe illness	• Pulmonary infiltrates >50% • Reduced oxygen saturation (SpO2) < 94% on air at rest • Breathing rate ≥30/min • Ratio of arterial partial pressure of oxygen to inspired oxygen fraction (PaO2/FiO2) <300
Critical illness	• Respiratory failure (PaO2/FiO2 <200, ARDS), including patients with deterioration despite advanced forms of ventilatory support (non-invasive ventilation, high-flow nasal oxygen therapy /HFNC/) and patients requiring artificial lung ventilation • Septic shock • Disorder of consciousness • Multiorgan failure

1. Antiviral treatment

1.1 Remdesivir

- We recommend remdesivir to hospitalized patients with moderate or severe disease requiring oxygen therapy but not mechanical ventilation.
- There are insufficient data to prefer 5- or 10-day treatment with remdesivir.
- We recommend considering remdesivir therapy in hospitalized patients with a moderate course without the need for oxygen therapy.
- We recommend monitoring liver and renal function during treatment with remdesivir.

Remdesivir is an adenosine analogue that inhibits SARS-CoV-2 replication after binding to viral RNA polymerase. It is likely to reduce the risk of death in hospitalized patients with moderate or severe COVID-19 requiring oxygen therapy but without the need for noninvasive or invasive pulmonary ventilation. Evidence is based on 4 randomized trials.[9-12] In the ACTT-1 trial, there was a 70% reduction in the risk of death in the first 28 days in the remdesivir-treated group compared with placebo in patients initially treated with oxygen (without the need for high-flow therapy or ventilation).[9] Remdesivir also led to a reduction in the time required for recovery by several days and improved clinical status.[9,11] The WHO-organized SOLIDARITY trial did not confirm a mortality benefit of remdesivir.[12] However, its results are limited by its open-label design and reporting of a number of clinically relevant endpoints without stratification according to initial disease severity.[6,7,12] There is no evidence for remdesivir monotherapy in patients requiring high-flow oxygen therapy; however, in combination with dexamethasone, the potential benefit of reducing viral load while controlling the exaggerated inflammatory response probably outweighs the potential benefit.[6,7] In post-transplant patients with problematic viral load control and an initially delayed anti-SARS-CoV-2 immune response, the benefit of remdesivir may be more pronounced.[13-15]

The results of remdesivir treatment in patients hospitalized for moderate COVID-19 without the need for oxygen therapy are inconsistent.[9,11,12] Remdesivir may be considered for patients at high risk of progression to a severe course.[6] These patients include post-transplant patients, especially the elderly (>65 years) and early (<6 months) post-transplant patients.[16]

Remdesivir is administered intravenously at an initial dose of 200mg, 100mg on subsequent days for a total of 5-10 days. There are probably no significant differences between 5- and 10-day treatment, although some studies show a benefit of 5-day treatment.[11,17] Insurance companies in the Czech Republic cover 5-day treatment. The maximum effect of remdesivir treatment can be achieved when administered early in the infection to reduce viral load and prevent a subsequent massive inflammatory response.[1] In post-transplant patients with prolonged replication, it is not possible to determine a cut-off time from symptom onset when it is still appropriate to administer remdesivir. In cases of prolonged symptom duration (>10 days), determination of viral load, e.g. by Ct (cycle treshold) for PCR detection or by quantification of SARS-CoV-2 Ag in serum by ELISA, may aid the decision.[14,18] Remdesivir contains renally excreted sodium sulfobutyl ether-beta-cyclodextrin and is therefore not recommended in patients with reduced renal function (eGFR <30ml/min) who have been excluded from the initial studies. However, later studies did not report an increased incidence of adverse events in patients with advanced renal dysfunction.[19-21]

1.2 Lopinavir-ritonavir

- We do not recommend lopinavir-ritonavir for the treatment of COVID-19.

Randomised trials have not shown a benefit of the HIV protease inhibitor lopinavir-ritonavir compared with standard treatment. Most of the data come from the RECOVERY and WHO SOLIDARITY trials, which included patients with moderate, severe, and critical disease.[12,22] In addition, interactions with immunosuppressive agents must be considered in post-transplant patients. Lopinavir-ritonavir is a potent cytochrome P450 3A4 inhibitor that leads to increased levels of calcineurin and mTOR inhibitors with subsequent toxicity and excessive immunosuppression.[23]

1.3 Experimental antiviral treatment

- We do not recommend favipiravir, chloroquine, hydroxychloroquine, azithromycin, or ivermectin for the treatment of COVID-19.

None of the above agents has been shown to have a significant benefit in the treatment of COVID-19.[6,7] Favipiravir has been tested without apparent effect in several randomized trials.[7,24] The risk of toxicity, especially QTc interval prolongation and ventricular arrhythmias, is predominant with chloroquine and hydroxychloroquine. In a large randomized trial, hydroxychloroquine treatment was associated with an increased risk of progression of COVID-19 to the need for mechanical ventilation and a numerically higher risk of death.[25]

2. Anti-SARS-CoV-2 antibody products

2.1 Convalescent plasma

- We do not recommend routine administration of convalescent plasma for the treatment of COVID-19.

Plasma from donors cured of COVID-19 may contain antibodies to SARS-CoV-2, which have the potential to reduce viral load and subsequent inflation.[6] However, a pooled analysis of 9 randomized trials did not demonstrate the efficacy of convalescent plasma in the treatment of COVID-19 compared with standard care.[7] In the largest RECOVERY trial using high-titre convalescent plasma with high antibody titres, there was no difference in 28-day mortality in patients with mild to moderate COVID-19, nor was there a difference when analysed in detail in different patient groups according to COVID-19 severity.[26] There are only case-control data in post-transplant patients.[1,27] In the absence of controlled studies, a beneficial effect of administering plasma with very high antibody titres early after symptom onset cannot be excluded in immunocompromised patients.[6] On the other hand, known adverse effects of treatment must be considered. These include allergic reactions, transmission of infections, transfusion-associated acute lung injury (TRALI) or circulatory overload (TACO) and others.[6]

2.2 Anti-SARS-CoV-2 monoclonal antibodies

- We recommend treating patients with mild to moderate COVID-19 with a combination of monoclonal antibodies: casirivimab (1200mg) + imdevimab (1200mg) (REGN-COV2).

- Treatment should be given as soon as possible after SARS-CoV-2 confirmation and within 10 days of the onset of clinical symptoms.
- We do not recommend administering monoclonal antibodies to patients hospitalized for COVID-19. Treatment may be considered in patients hospitalized for causes other than COVID-19.

Monoclonal antibodies currently in clinical use include bamlanivimab, etesivimab, casirivimab and imdevimab, all of which bind in different parts of the receptor-binding domain (RBD) S of the SARS-CoV-2 protein.[6] In phase 2/3 trials in outpatients with mild to moderate COVID-19, the combination of bamlanivimab + etesivimab or casirivimab + imdevimab resulted in a faster decline in viral load compared with placebo; the difference was not statistically significant with bamlanivimab monotherapy.[28,29] Previously unpublished results from phase 3 trials (summarized in Ref. 6) demonstrated a 70% reduction in the risk of hospitalization or death with both antibody combinations. Treatment with monoclonal antibodies has been approved for patients at high risk of progression to severe disease, which includes patients after kidney transplantation. Treatment must be initiated early, due to the production of self antibodies around day 10 of clinical symptoms.[30] Experience in patients after kidney transplantation is limited. In a small uncontrolled study, treatment with casirivimab + imdevimab was well tolerated and none of the 25 treated patients progressed to severe COVID-19.[31] The combination of bamlanivimab (700mg) + etesivimab (1400mg) is not yet available in the Czech Republic.

Bamlanivimab monotherapy has reduced efficacy in some new SARS-CoV-2 variants (e.g. B.1.351 - South African variant) compared to antibody combination[32] and is therefore not the preferred treatment, but can be used when other agents are not available. Treatment with monoclonal antibodies is not effective in patients with severe COVID-19 and may even be associated with a worse course in patients requiring mechanical ventilation or high-flow oxygen therapy.[33,34]

In patients treated with monoclonal antibodies, vaccination against COVID-19 (including administration of the second dose) should be delayed for at least 3 months due to possible interference with the immune response after vaccination. No data are available on the efficacy of monoclonal antibody treatment in patients after vaccination. It should be considered in patients after kidney transplantation, given that the post-vaccination antibody response is lower in this population and is achieved in 38-54% of cases after completion of mRNA vaccines.[35-37] Optimally, the indication should be supported by negative anti-SARS-CoV-2 IgG after vaccination.

3. Immunomodulatory treatment

3.1 Dexamethasone

- We recommend treatment with intravenous or oral dexamethasone at a dose of 6mg daily for up to 10 days in patients requiring oxygen therapy including mechanical ventilation.
- We do not recommend routine use of dexamethasone in patients without a need for oxygen therapy.

Excessive systemic inflation in patients with severe COVID-19 can lead to lung injury and fatal consequences. Therefore, the potent anti-inflammatory effect of corticosteroids has the potential to influence the adverse course of COVID-19. A pooled analysis of randomized trials demonstrates a reduction in mortality with dexamethasone treatment in patients with severe and critical COVID-19; in patients requiring oxygen therapy without mechanical ventilation, the

composite endpoint of need for mechanical ventilation and death is reduced, in addition to significantly reducing the length of hospital stay.[7] The greater benefit of corticosteroid therapy is in patients requiring higher doses of oxygen. In contrast, patients with moderate COVID-19 without the need for oxygen therapy tend to have increased mortality. When indications are met, concurrent treatment with remdesivir is assumed. The main evidence comes from the multicenter RECOVERY trial with a relative reduction in 28-day mortality of 17%; in the artificial lung ventilation group, the reduction was 36%.[38]

Consistent with the mechanism of action of corticosteroids, the beneficial effect appears to be only in patients at least 7 days after the onset of symptoms.[39] During corticosteroid treatment, potential side effects (hyperglycemia, secondary infections, avascular necrosis, etc.) should be monitored and treated. Although most of the positive results are based on studies using dexamethasone, equivalent doses of other corticosteroids (prednisone, hydrocortisone, methylprednisolone) may be used as an alternative.[6,7]

3.2 Tocilizumab

- We recommend considering tocilizumab (in combination with dexamethasone) in a defined group of hospitalized patients with rapidly progressive respiratory decompensation.

Tocilizumab is a monoclonal antibody inhibiting the IL-6 receptor and is administered intravenously in a single dose (8mg/kg, maximum 800mg). In the general population, a beneficial effect was observed in patients with a short (≤ 3 days) hospitalization before admission to the intensive care unit for mechanical ventilation, non-invasive ventilation or high-flow nasal oxygen therapy and with evidence of significant systemic inflation (elevation of CRP, IL-6). In 2 randomized trials (RECOVERY and RAMAP-CAP), a modest mortality benefit and lower risk of needing mechanical ventilation were demonstrated in the above population.[40,41]

It is not clear whether this treatment is beneficial in patients who have had a kidney transplant. However, limited data show a decrease in inflammatory parameters after tocilizumab treatment.[42] Tocilizumab is not associated with a higher risk of infectious complications.[43]

Currently, there is insufficient evidence in the general population to recommend treatment with other immunomodulatory drugs such as JAK inhibitors (baricitinib), IL-1 inhibitors (anakinra), and a number of others.[6,7] The safety of such treatment in post-transplant patients is unproven.

4. Prophylaxis of venous thromboembolic disease

- We recommend treatment with prophylactic doses of anticoagulation (preferably low molecular weight heparin) in patients with moderate, severe and critical COVID-19.
- There is insufficient evidence for the routine use of prophylactic anticoagulation in mild COVID-19.

COVID-19 is associated with inflammation and a prothrombotic state with an increase in a number of laboratory markers (fibrin, fibrin degradation products, fibrinogen, D-dimers).[44] The incidence of venous thromboembolic disease is very high, especially in hospitalized patients.[45] Therefore, prophylactic anticoagulation is recommended for all patients with moderate, severe, or critical COVID-19, except for individuals at high risk of bleeding.[6,7,46] Increasing the dose from prophylactic to intermediate or full therapeutic does not lead to improved clinical outcomes even in patients with critical disease.[7]

Although thromboembolic complications may occur at a lower rate even with mild outpatient COVID-19 treatment, there is no evidence for the routine use of pharmacological prophylaxis. Nevertheless, bleeding risk should be considered and prophylactic anticoagulation may be used in patients at high risk of thromboembolic disease.[47] This includes renal transplant patients who have a significantly increased risk of thromboembolic disease compared with the general population, especially in the first year after transplantation.[48]

5. Monitoring and adjustment of immunosuppressive therapy

- We recommend monitoring calcineurin inhibitor levels in hospitalized patients.
- Drugs with strong interactions with immunosuppressive agents (e.g. macrolide antibiotics except azithromycin, azole antifungals) are not recommended unless there is no other alternative and frequent monitoring of immunosuppressive levels is possible at the same time.
- We suggest to reduce immunosuppressive therapy in patients with moderate, severe, and critical COVID-19 with a preference for withdrawal or reduction of antimetabolite.
- There is insufficient evidence for or against recommending a change in immunosuppressive therapy in asymptomatic patients or mild COVID-19.

Despite the absence of interacting medication, a significant proportion of patients hospitalized for COVID-19 had documented rising tacrolimus levels, and significantly elevated levels were associated with a risk of death.[49] Data on the effect of COVID-19 on cyclosporine or mTOR inhibitor levels have not yet been published. Reasons for the increase in tacrolimus levels are speculative and include gastrointestinal symptoms with COVID-19 and a pro-inflammatory state with elevation of IL-6, which inhibits cytochrome P450 3A4 activity.[50] Overexposure to tacrolimus can lead to secondary infections and direct toxic effects (e.g., nephrotoxicity, gastrointestinal adverse events, and neurotoxicity). Patients should be treated at a transplant centre or other healthcare facilities with the capacity to determine immunosuppressant levels and staff experienced in treating immunocompromised patients.

Commonly used antibiotics in the treatment of presumed concomitant bacterial pneumonia, such as macrolides (e.g. clarithromycin) or prophylactic or therapeutic use of azole antifungals in the later phase of the disease, interact strongly with the metabolism of tacrolimus, cyclosporine and mTOR inhibitors.[51] These drugs should only be used in the absence of an effective alternative under conditions of frequent monitoring of immunosuppression levels. In patients with a severe course, monitoring for the development of secondary opportunistic infections, especially reactivation of herpes viruses and mycotic superinfection, is necessary.

It is unclear how to optimally tailor immunosuppressive therapy in patients with COVID-19 after kidney transplantation.[1,39,52] Unlike other viral diseases with a severe course (e.g., cytomegalovirus, influenza), where reduction of immunosuppression (antimetabolite interruption, reduction of calcineurin inhibitor levels) to restore antiviral immunity is a generally accepted approach, COVID-19, with its biphasic course, poses a more complex problem.[1,52] After an initial phase with viral symptoms, a proportion of patients with a severe course progress to a phase characterized by intense inflammasome with immune response imbalance with reduced interferon expression and, conversely, high production of proinflammatory cytokines.[1,52] Immunosuppressive therapy with cellular immunity inhibition may theoretically be beneficial and dampen the inflammatory response. The course of COVID-19 and mortality does not correlate with the intensity of immunosuppression at the time of diagnosis.[3,53,54]

Registries and cohort studies show that antimetabolite therapy (mycophenolate mofetil, mycophenolate sodium) is most often reduced or

discontinued, as lymphopenia induced by it may predict an adverse course of COVID-19.[52,55] Conversely, complete withdrawal of immunosuppression is not recommended, and calcineurin inhibitors (often with reduced target levels) are given during COVID-19.[39,52,55-57] Analyses from the European Registry of Liver Transplant Patients suggest a lower risk of death in patients treated with tacrolimus.[57] However, further studies are needed to demonstrate the benefit of tacrolimus. Discontinuation of calcineurin inhibitors should be approached on an individual basis, e.g. in the situation of critical COVID-19 with proven severe bacterial, fungal or viral superinfections.

6. Supplements and associated medication

- There is not enough data for or against the use of vitamin D, vitamin C or zinc to treat COVID-19.
- We recommend not to interrupt chronically administered medication with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) except when the clinical condition requires their discontinuation.

Vitamin or mineral supplements are not currently recommended for routine use in the treatment of COVID-19.[6] Vitamin D is most commonly discussed, given its receptor expression on immune cells and its potential to modulate both natural and specific immune responses.[58] In COVID-19, vitamin D treatment was tested in a double-blind randomized trial in patients with moderate or severe course with no evidence of difference in mortality and a number of other parameters.[59]

Since ACE2 is the surface receptor for SARS-CoV-2, there has been speculation about the possible effect of ACEi or ARB treatment on viral replication.[60] However, later studies have not demonstrated an effect of ACEi/ARB on the course of COVID-19.[61] Similarly, the benefit of discontinuing chronic ACEi/ARB treatment in patients with mild or moderate COVID-19 was not demonstrated in a randomized trial; on the contrary, in the group of patients requiring oxygen therapy, it was preferable not to discontinue treatment.[62] For these reasons, it is not recommended to routinely discontinue ACEi/ARB therapy.[6,63] The same recommendation applies to other drugs commonly used after kidney transplantation, such as statins, proton pump inhibitors, or inhaled steroids.[6]

Appendix

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