COMDORA-SBN recommendations for patients with rare kidney diseases in relation to the Covid-19 pandemic

Recomendações do COMDORA-SBN a pacientes portadores de doenças renais raras em relação à pandemia de Covid-19

Authors

Vinícius Sardão Colares[1]
Silvana Maria Miranda[2]
Luis Gustavo Modelli de Andrade[3]
Lilian Monteiro Pereira Palma[4]
Maria Cristina Ribeiro de Castro[5]
Cassiano Augusto Braga Silva[6]
Maria Goretti Moreira Guimarães Penido[7]
Roberta Sobral[8]
Maria Helena Vaisbich[9]

[1]Santa Casa de Misericórdia de Juiz de Fora, Juiz de Fora, MG, Brazil.
[2]Santa Casa de Belo Horizonte, Belo Horizonte, MG, Brazil.
[3]Universidade Estadual Paulista, Faculdade de Medicina, Botucatu, SP, Brazil.
[4]Universidade Estadual de Campinas, Campinas, SP, Brazil.
[5]Universidade de São Paulo, Unidade de Transplante Renal, São Paulo, SP, Brazil.
[6]Grupo CSB, Departamento de Nefrologia, Feira de Santana, BA, Brazil.
[7]Santa Casa de Belo Horizonte, Unidade de Nefrologia Pediátrica, Belo Horizonte, MG, Brazil.
[8]Universidade Federal da Bahia, Nefrologia Pediátrica, Salvador, BA, Brazil.
[9]Universidade de São Paulo, Instituto da Criança, São Paulo, SP, Brazil.

Correspondence to:
Maria Helena Vaisbich
E-mail: vaisbich@terra.com.br / maria.vaisbich@hc.fm.usp.br

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Abstract

During the Covid-19 pandemic, the issue is how to maintain adequate care for people with other diseases. In this document, the SBN Rare Diseases Committee (COMDORA) gives some guidelines on the care of patients with rare kidney diseases. These patients should follow the recommendations for the general population, bearing in mind that, as they have chronic kidney disease, they are included in the risk group for more serious outcomes if they develop Covid-19. Non-essential decision-making procedures should be postponed. In stable cases under appropriate treatment, we must choose to contact our patients remotely, using teleconsultations and home exam collections (if possible). In the presence of a symptom or sign of decompensation of the underlying disease, or infection with Sars-cov-2, advise the patient to seek medical assistance. The patient should not be waiting to get worse. Changes to the prescription should only be made on a scientific basis. Dosage suspension or change is not recommended, even in cases in which the patient needs to go to a center to receive his medication; in this case, the infusion center must follow the recommendations of the Ministry of Health. If the patient develops Covid-19 and uses any drugs, check the need for dose adjustment of the routine medications. Avoid the use of antimetabolics and anti-CD20 in patients with Covid-19, as they reduce viral clearance and predispose to bacterial infections. Contact between the patient and the medical team is essential; changes are recommended only with specialized medical guidance.

Keywords: Chronic kidney disease, rare diseases, Covid-19, Sars-cov-2.

Resumo

Durante a pandemia da Covid-19, fica a questão de como manter o atendimento adequado aos portadores de outras doenças. O Comitê de Doenças Raras (COMDORA) da SBN neste documento dá algumas orientações ao atendimento de pacientes com doenças renais raras. Estes pacientes devem seguir as recomendações destinadas à população geral tendo em mente que, por serem portadores de doença renal crônica, estão incluídos no grupo de risco para desfechos mais graves, caso venham a desenvolver a Covid-19. Procedimentos não essenciais para tomada de decisão devem ser adiados. Deve-se optar por contatos a distância, como teleconsultas, e coletas de exames domiciliares (se possível) nos casos estáveis sob tratamento adequado. Na presença de sintoma ou sinal de descompensação da doença de base ou infecção pelo Sars-cov-2, orientar o paciente a procurar a equipe médica. O paciente não deve ficar esperando o quadro agravar-se. Alterações na prescrição só devem ser feitas com embasamento científico. Não se recomenda a suspensão ou alteração posológica, mesmo nos casos em que o paciente necessita ir a um centro para receber sua medicação; neste caso o centro de infusão deve seguir as recomendações do Ministério da Saúde. Caso o paciente desenvolva a Covid-19 e faça uso de alguma droga, verificar a necessidade de ajuste nas doses dos medicamentos rotineiros. Evitar o uso de antimetabólicos e antiCD20 nos pacientes com a Covid-9, por reduzirem o clareamento viral e predisporem a infecções bacterianas. O contato entre paciente e equipe médica é essencial; alterações são recomendadas apenas com orientação médica especializada.

Palavras-chave: Doença Renal Crônica; Doenças Raras; Covid-19; Sars-cov-2.

1. General recommendations

- Social isolation.
- Thoroughly sanitize hands with water and soap (liquid or foam), or alcohol gel with a final concentration of 70%.
- Wear a protective mask in public environments in general. Look for guidelines as to the type of fabric used to make the mask, its durability and the possibility of being properly reused or discarded.
- If you need to cough or sneeze the moment you are without the mask, cover your nose and mouth with your flexed elbow or tissue (and discard it immediately after use).
- Use disposable tissue for nasal hygiene (dispose of it immediately after use and perform hand hygiene).
- Avoid touching mucous membranes of the eyes, nose and mouth - if necessary, perform hand hygiene previously.
- Keep the rooms ventilated.
- Keep clean those surfaces that can be touched frequently (cell phones, computers, door handles, etc.).

2. How to handle cases of patients with rare kidney diseases during the pandemic

- The most important thing is not to lose contact with the patient and have a channel available for the patient or family to make contact with the medical team. Therefore, keep the patient's contact updated in the medical record.
- Postpone, if possible, in-person medical consultations and collection of non-essential tests. Use telemedicine and, if possible, blood collection at home[1].
- Instruct the patient to make contact with the medical team to receive the guidelines, or the professional himself can make contact with the patient to pass on the guidelines.
- Carry out face-to-face consultations and tests when there are doubts about the patient's evolution, or if new symptoms or signs arise.
- Instruct the patient to seek medical care if he has any symptoms related to decompensation of the underlying disease or any complication that may be related to the treatment of the underlying disease.
- Instruct the patient to contact the medical team if symptoms suggestive of SARS-CoV-2 infection occur, so that he/she can receive instructions regarding the need to go to a medical service for clinical, laboratory or imaging exam, or any intervention if necessary. THE PATIENT SHOULD NOT WAIT FOR THE SYMPTOMS TO WORSEN AND THEN LOOK FOR MEDICAL ASSISTANCE.

The symptoms seen in transplanted patients using immunosuppressants and who developed Covid-19 were similar to those in the general population, as per shown in Table 1[2,3,4].

Table 1 Symptoms and signs at the clinical presentation of patients with Covid-19 in the general population and in immunocompromised patients: reference data compilation[2,3,4]

Signs/ symptoms	General population	Immunosuppressed**
Fever	88 – 99 %	70 and 87 %
Dry cough	59 – 68 %	59 and 67 %
Fatigue	38 – 70 %	28 and 60 %
Anorexia	40 %	-----
Myalgia	15 – 35 %	13 %
Dyspnea	19 – 31 %	27 and 43 %
Diarrhea	-----	3 and 20 %

** Data taken from two case series of transplanted patients undergoing immunosuppression, with 90 and 15 patient, respectively.

- Assess, on a case-by-case basis, the possibility of initiating immunosuppression in the indicated cases and try to postpone it in patients in whom this is possible (stable renal function, oligosymptomatic patients, without risk of significant complications)[1].
- At this time of the Covid-19 pandemic, renal biopsy for diagnostic clarification should be performed only in critical cases for decision-making purposes. Protocol biopsies should be postponed[1].
- Patients with glomerular diseases, in which the delay in immunosuppressive treatment may determine worsening of renal function, this should be promptly instituted, as, for example,

in patients with SLE classes III and IV, or in the case of rapidly progressive glomerulonephritis, as well as in patients with active nephrotic syndrome, symptomatic and at risk for thromboembolic phenomena[1].

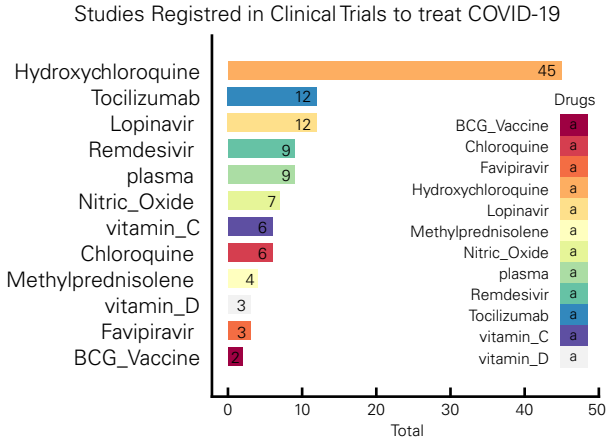
- Avoid the use of anti-CD20 therapy, such as rituximab, since there are but a handful of reports in the literature, and patients with low levels of immunoglobulin have a higher risk of secondary infection and less viral clearing[1].
- Patients compensated for glomerulopathy under immunosuppression should not have their medication suspended, due to the risk of recurrence. If possible, maintain the treatment with the same doses of immunosuppressants or reduce slowly, when indicated, monitoring side effects and clinical and laboratory evolution, in order to avoid decompensation and the need for hospitalization[1]. The home use of test tape or test with sulfosalicylic acid or trichloroacetic acid to assess proteinuria is very appropriate, as it can alert you early on the loss of proteins, before the patient clinically decompensates. In this case, the patient should be instructed to contact the medical team promptly.
- The attending physician must individually assess the possibility of early weaning and suspension of immunosuppression in cases of stable patients in complete remission of the underlying disease and without immediate risk of relapse. Do not abruptly suspend corticosteroids, due to the risk of adrenal insufficiency.
- In infected patients, when desired to reduce the dose of prednisone, a reduction of 0.2 mg/kg/day is indicated[1].
- In infected patients, watch the lymphocyte count and discontinue cytotoxic and antimetabolic medications[1].
- There is no evidence for suspending renin-angiotensin-aldosterone system (RAAS) inhibitors, such as ACEI or BRA. These drugs must be maintained[5], as withdrawal can lead to renal and/or cardiological decompensation, with increased levels of proteinuria and blood pressure, as well as worsening cardiac function in patients with insufficiency. Studies have shown no association between the use of SARS inhibitors and a higher likelihood of contracting SARS-CoV-2 or developing Covid-19; there is data showing that SARS inhibitors improve clinical outcomes in hypertensive patients with Covid-19[6].
- Patients taking specific medications at referral centers (such as Fabry's disease and atypical hemolytic-uremic syndrome [AHUS]) should continue treatment. Infusion centers must follow the protocols established by the Ministry of Health.
- According to new knowledge, severe and fatal cases may be more likely to develop thrombotic microangiopathy through pathogenic activation of the complement system[7]. Therefore, there is contraindication to change the dosage of eculizumab administration in patients using this medication, such as those with AHUS or paroxysmal nocturnal hemoglobinuria. A clinical study is even underway using complement inhibition as an alternative to treat Covid-19[8].
- In all rare kidney diseases in which the patient uses specific medications for his treatment, it must be maintained in the recommended dosage schedule, unless there is any interaction with drugs used to treat Covid-19.
- Non-hormonal anti-inflammatory drugs (ibuprofen, diclofenac, ketoprofen, among others) should not be used due to the risk of acute kidney injury, use only dipyrone or paracetamol.

3. Instructions on the interaction of medications used by the patient and medications that may be used in selected Covid-19 cases.

There are several treatments being tested to treat Covid-19 and its complications. The physician seeing patients with rare kidney diseases needs to assess a possible interaction between the drugs routinely used by the patient and the drugs/treatments used to treat Covid-19[9].

Figure 1 shows studies registered in the Clinical Trials for the treatment of Covid-19.

Figure 1. Studies registered in the Clinical Trials for the treatment of Covid-19. Reproduced with the permission of the author - L.G.M. de Andrade.



Source: <https://www.clinicaltrials.gov/ct2/results?cond=Covid>.

- **Remdesivir** is a pre-drug, analogous to the nucleotide that inhibits viral RNA polymerase. The remdesivir triphosphate metabolite is the active form of the drug. Its effect has already been demonstrated in vitro against SARS-CoV-2[10]. More recently, on May 1, 2020, the FDA approved the emergency use of remdesivir for treating severe cases of Covid-19 in adults and children, based on a review of key data from the study conducted by the National Institute of Health, with the compassionate use of remdesivir sponsored by Gilead, which analyzed different duration times of remdesivir[11]. In its clinical trial, remdesivir reduced the duration of symptoms from 15 to 11 days (p = 0.001), and reduced mortality from 12% to 8% (p = 0.06). Ongoing, randomized and open studies, using remdesivir, may provide more data on the true role of this drug in the treatment of Covid-19. Little is known about its interaction with immunosuppressive agents or other drugs; remdesivir is being used as a research drug, and there are still no pharmacokinetic studies in patients with impaired kidney or liver function.
- **Dexamethasone:** Dexamethasone was one of the treatment arms of the Recovery initiative of Great Britain, which evaluated 11,500 patients. In a preliminary analysis of the data before publication (press release), the researchers found a survival benefit in patients using dexamethasone. A total of 2,104 patients used dexamethasone 6 mg for 10 days, compared to 4,321 patients in the placebo group (usual treatment) in a randomized design. In patients on mechanical ventilation, there was a 35% reduction in mortality (RR 0.65 [95% CI: 0.48 - 0.88], p = 0.0003) and a 20% reduction in mortality in patients in need of oxygen (RR 0.8 [95% CI: 0.67 - 0.96], p = 0.0021). No benefit was found in patients without the need for oxygen or ventilatory support (RR 1.2 (95% CI: 0.86 - 1.75), p = 0.14). So far, although results are not yet available in a peer-reviewed publication, the results show a survival benefit with the prevention of one death for every 8 patients and one death in 25 of the patients who needed oxygen supplementation[12].
- The immunosuppressants used by the patient must have their dosage readjusted when combined with medications for Covid-19, according to the following recommendations[13].
  - » **In medications used routinely by the patient and subject to blood dosage**, such as, for example, tacrolimus, new measurements should be taken 3 to 5 days after the start of therapy for Covid-19 to adjust the serum level if necessary.
  - » **Cyclosporine:** An increase in blood level may occur with the combined use of lopinavir/ritonavir and an increase in blood level with the combined use of chloroquine and hydroxychloroquine.
  - » **Tacrolimus:** Increased blood level may occur with the combined use of lopinavir/ritonavir and increased blood level with the combined use of chloroquine and hydroxychloroquine.
  - » **Sirolimus:** A marked increase in blood level may occur with the combined use of lopinavir/ritonavir and an increase in blood level with the combined use of chloroquine and hydroxychloroquine.
  - » **Everolimus:** To date, there is no data on interactions with everolimus; we recommend serum dosing, and should be performed for possible adjustments.
- **For medications in which no dosage is made,** adjust according to interaction.[12]
  - » **Azathioprine:** Increased blood level with associated use of ribavirin.
  - » **Mycophenolate:** There are reports of increased and decreased blood levels with the associated use of lopinavir/ritonavir.

» **Remdesivir:** Little is known about the interaction of this drug with immunosuppressive agents or other medications. Thus, it is important to remember that remdesivir is being used as a research drug. There are still no pharmacokinetic studies in patients with impaired renal or liver function. The recommendation, when used, is to monitor the glomerular filtration rate and liver function tests, remembering that urinary excretion is approximately 74%, 49% as remdesivir triphosphate metabolite, and 18% in feces[14].

4. Differential diagnosis

Do not forget about other flu-like syndromes that can potentially also be involved in the complement system activation, as in the case of the H1N1 influenza virus[15].

5. Vaccination schedule

It is recommended that patients keep the vaccination schedule up to date and receive the influenza vaccine.

Collaborators

Lucimary Sylvestre, Fellype Barreto, Maria Izabel de Holanda, David José Machado, Valéria S P Veloso, Patrícia Pontes and Gilson Bianchini.

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