PAHO Pan American Health Organization

World Health Organization Regional Office for the Americas

CONSIDERATIONS ON THE USE OF ANTIVIRALS, MONOCLONAL ANTIBODIES, AND OTHER INTERVENTIONS FOR THE MANAGEMENT OF COVID-19 PATIENTS IN LATIN AMERICA AND THE CARIBBEAN

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Considerations on the Use of Antivirals, Monoclonal Antibodies, and Other Interventions for the Management of COVID-19 Patients in Latin America and the Caribbean

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OPS Organización Panamericana de la Salud Organización Mundial de la Salud Américas

Conócelo. Prepárate. Actúa.

INTRODUCTION

Since the onset of the COVID-19 pandemic, a large number of clinical trials have been planned and developed to assess the effectiveness and safety of various interventions that could prevent hospitalizations and progression to severe disease in people infected with SARS-CoV-2. Currently, the World Health Organization (WHO) and the Pan American Health Organization (PAHO) recommend the use of corticosteroids, tocilizumab, nirmatrelvir-ritonavir, baricitinib, and casirivimab e imdevimab (the latter in seronegative COVID-19 patients) and propose the use of sotrovimab, casirivimab/imdevimab, and molnupiravir in patients with non-severe illness who are at high risk for complications.[1],[2],[3] Other potential therapeutic interventions are currently undergoing study or evaluation by WHO and PAHO.

The interventions recommended at present and those that will be recommended at a later date pose challenges in terms of route of administration (e.g., oral or intravenous); efficacy, which depends on the viral variant; establishment of high-risk status (e.g., relative to vaccination status); cost; resources required to administer them; and other implementation-related aspects (e.g., distribution, drug safety monitoring, contraindications, interactions, etc.). To support decision-making for patient management, in this document PAHO presents considerations on the rational use of antivirals, monoclonal antibodies, and other interventions in light of the most current evidence, vaccination status, access, and the costs to countries of the Region of the Americas.

The guidelines for the management of COVID-19 developed by WHO/PAHO have been developed using the GRADE (The Grading of Recommendations Assessment, Development and Evaluation) methodology, which considers evidence, risk-benefit, costs, patient preference and implementation context. The certainty of the GRADE evidence is presented as high (new studies are very unlikely to change the confidence in the estimated outcome), moderate (new studies are likely to have a major impact on the confidence in the estimated outcome and may change the outcome), low (new studies are very likely to have a major impact on the confidence in the estimated outcome and may change the outcome) and very low (any estimated outcome is very uncertain). The strength of the recommendations presented in the guidelines is either strong (when the desirable effects of an intervention clearly outweigh the undesirable effects) or conditional (when the balance between the desirable and undesirable effects of the intervention is less clear either because of: low or very low quality of evidence, uncertainty or variability in values and preferences, concern that the intervention is resource intensive, or because the evidence suggests little or little difference between the desirable and undesirable effects of the intervention).

PAHOs' COVID-19 Treatment Guidelines Panel assessed the information presented above and emphasized that countries should direct their efforts toward increasing coverage of the full vaccination schedule in order to effectively and safely reduce viral transmission, severe cases, and SARS-CoV-2-associated mortality.

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[1]World Health Organization. Therapeutics and COVID-19: living guideline. Geneva: WHO; 2022. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1.

[2]Pan American Health Organization. Guidelines for prophylaxis and management of patients with mild and moderate COVID-19 in Latin America and the Caribbean. Washington, D.C.: PAHO; 2021. Available at: https://iris.paho.org/handle/10665.2/550999

[3]Pan American Health Organization. Guidelines for care of critically ill adult patients with COVID-19 in the Americas. Summary, version 3. Washington, D.C.: PAHO; 2021. Available at: https://iris.paho.org/handle/10665.2/53894

THERAPEUTIC MANAGEMENT OF PATIENTS WITH MILD OR MODERATE COVID-19

New evidence has recently been published for sotrovimab, molnupiravir, casirivimab e imdevimab, bamlanivimab, remdesivir, and fluvoxamine. PAHO publishes a monthly systematic review evaluating therapeutic interventions for patients with COVID-19. Table 1 below presents the most recent evidence on the impact of these interventions on hospitalizations and on their safety.

Table 1. Evidence on decreased hospitalizations and the safety of antivirals, monoclonal antibodies, and antidepressants of interest in the treatment of COVID-19 and considerations on their administration in patients with mild or moderate illness

Intervention		Impact on hospitalizations[3]			Safety*	Administration	Other considerations
		Unvaccinated high-risk patients (baseline risk of 4.8%)	Vaccinated patients (baseline risk of 0.5%)	Certainty of the evidence based on GRADE (grading of recommendations, assessment, development, and evaluation)			
Monoclonal	**Casirivimab e imdevimab** (5049 patients in 3 trials)	34 fewer per 1000	3 fewer per 1000	●●●○ Moderate[a]	No differences in side effects with respect to the control group have been reported. Theoretical risk of anaphylaxis and allergic infusion reactions.	Intravenous infusion. Single dose. *In vitro* data suggest that it is less effective against the Omicron variant of SARS-CoV-2.[c]	Limited access.
	Sotrovimab (1622 patients in 2 trials)	41 fewer per 1000	4 fewer per 1000	●●●○ Moderate[b]	No differences in side effects with respect to the control group have been reported. Theoretical risk of anaphylaxis and allergic infusion reactions.	Intravenous or subcutaneous infusion. Single dose. The Omicron BA.2 variant may substantially reduce clinical efficacy of sotrovimab.	Limited access.
	Bamlanivimab (1804 patients in three trials)	30 fewer per 1000	3 fewer per 1000	●●●○ Moderate[c]	No differences in side effects with respect to the control group have been reported. Theoretical risk of anaphylaxis and allergic infusion reactions.	Intravenous infusion. Single dose. *In vitro* data suggest that it is less effective against the Omicron variant of SARS-CoV-2.[c]	Limited access.

[4] See footnote 1.

Intervention		Impact on hospitalizations[3]			Safety*	Administration	Other considerations
		Unvaccinated high-risk patients (baseline risk of 4.8%)	Vaccinated patients (baseline risk of 0.5%)	Certainty of the evidence based on GRADE (grading of recommendations, assessment, development, and evaluation)			
Antivirals	**Remdesivir** (562 patients in one trial)	35 fewer per 1,000	3 fewer per 1,000	●●○○ Low[d]	Hepatotoxicity	Perfusión intravenosa Tres dosis	Limited access.
	Molnupiravir (1,610 patients in 2 trials)	14 fewer per 1,000	1 fewer per 1,000	●●●○ Moderate[e]	No differences in side effects with respect to the control group have been reported. Theoretical risk of mutagenicity, hepatotoxicity, hematologic risks, and carcinogenesis (over the long term).	Oral	Limited access.
	Nirmatrelvir/ ritonavir (2,940 patients in 2 trials)	11 fewer per 1,000	1 fewer per 1,000	●●●○ Moderate[f]	Interactions with other drugs.	Oral	Limited access
Antidepressants	**Fluvoxamina** (1,649 patients in 2 trials)	11 fewer per 1,000	1 fewer per 1,000	●●●○ Moderate[g]	No differences in side effects have been reported.	Oral	Limited access

* Safety information from clinical trials only.

a - Serious imprecision: small number of events (n=108).
b - Serious imprecision: small number of events (n=24)
c - Serious imprecision: small number of events (n=85)
d - Very serious imprecision: very small number of events (n=23)
e - Serious inaccuracy: small number of events (n=170)
f - Serious imprecision: small number of events (n=74)
g - Serious imprecision: small number of events (n=179)

CONSIDERATIONS REGARDING THE RATIONAL USE OF MEDICINES IN PATIENTS WITH MILD OR MODERATE COVID-19 IN LATIN AMERICA AND THE CARIBBEAN

WHO developed recommendations for the use of the following drugs in patients with non-severe COVID-19 (mild or moderate; and with a confirmatory diagnostic test)[1]

Recomendation
Conditional recommendation to use a combination of neutralizing monoclonal antibodies (casirivimab and imdevimab)
Conditional recommendation for the use of a combination of neutralizing monoclonal antibodies (casirivimab and imdevimab) in patients with non-severe COVID-19, at the highest risk of severe disease, where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e. excluding Omicron BA.1)
Conditional recommendation for the use of molnupiravir in patients with non-severe COVID-19, at highest risk of hospitalization (excluding pregnant or breastfeeding women, and children)
Strong recommendation for the use of nirmatrelvir-ritonavir in patients with non-severe illness at the highest risk of hospitalization.
Conditional recommendation against the use of nirmatrelvir-ritonavir in patients with non-severe illness at a low risk of hospitalization.
Conditional recommendation for the use of remdesivir in patients with non-severe COVID-19 at the highest risk of hospitalization.

The PAHO panel discussed and examined the context of Latin America and the Caribbean and suggested that each country evaluate its decision regarding use in light of available resources, feasibility of implementation, access, patient-specific factors (e.g., duration of symptoms, kidney function, drug interactions), vaccination coverage, and mode of administration. It is also important to determine the capacity of services to administer the drugs and to consider the most appropriate timing for their use. In countries where the Omicron variant of SARS-CoV-2 is more prevalent, consideration should be given to not administering casirivimab/imdevimab or sortrovimab, given its reduced efficacy against this variant, or using it only in patients infected with a different variant of SARS-CoV-2 and are not vaccinated.

The PAHO panel was of the opinion that the criteria presented in Table 2 can guide implementation of the aforementioned interventions in patients with non-severe (mild or moderate) COVID-19.

Table 2. Considerations on the administration and safety of antivirals and monoclonal antibodies for the management of patients with mild or moderate COVID-19

Medication	Considerations relative to dosage and administration	Side effects
Molnupiravir	800 mg orally, twice daily. Administer to adult patients (do not administer to children under 18 years of age) who cannot be treated with other medicines. Administer as soon as possible and within 5 days of onset of symptoms. Do not administer to prevent disease in patients who have been in contact with positive cases. Avoid in women who are pregnant or breast-feeding: It is strongly recommended to do a pregnancy test and practice abstinence, or use contraception during treatment and for at least 4 days after the most recent dose. Promote reporting of events to the national drug safety monitoring system.	Dizziness. Headache. Vomiting. Allergy. No drug interactions have been reported.
Sotrovimab	500 mg of sotrovimab by intravenous infusion over 30 minutes, one time only. Continuous patient monitoring. Administer as soon as possible and within 10 days of onset of symptoms. It is available as a concentrated solution and should be diluted prior to administration. Patients should be monitored during infusion and observed for at least one hour after infusion has been completed.	Allergic reactions associated with IV administration. It can weaken the immune response. It is associated with more side effects in individuals showing clinical decline.
Casirivimab e imdevimab	Intravenous dose of 1,200 mg to 2,400 mg (600 to 1,200 mg of each antibody). Intravenous administration with a 0.2 micron filter. Patients must be monitored during administration and afterwards due to risk of anaphylaxis.	Allergic reactions. Side effects associated with administration. Fever, increased respiratory distress, arrhythmia, fatigue, altered mental state.
Nirmatrelvir-Ritonavir	Nirmatrelvir: 150 mg / ritonavir: 100 mg Assess whether the patient is taking medications that interact with nirmatrelvirritonavir. Patient should see health care provider. Administer as soon as possible and within 10 days of symptom onset.	Ritonavir should not be administered with drugs such as amiodarone (and several other antiarrhythmic drugs). Ritonavir should not be administered with drugs such as amiodarone (and several other antiarrhythmic drugs), rifampicin or rivaroxaban. Other drugs, such as calcineurin inhibitors,may require dose reduction or close monitoring. The list of interactions can be found at this link:https://www.fda.gov/media/155050/download

Medication	Considerations relative to dosage and administration	Side effects
Remdesivir	The recommended dose of remdesivir is a daily dose for 3 consecutive days as an intravenous infusion. It is administered as 200 mg intravenously on the first day, followed by 100 mg intravenously on the second day, followed by 100 mg intravenously on the second day. Day 1, followed by 100 mg intravenously on days 2 and 3 possible in the course of the disease. In the included studies, remdesivir was administered within 7 days of disease onset the onset of the disease.	Allergic reactions. Risk of increased transaminase levels of transaminases.
Given the particularities involved in the administration of these medicines, it is advisable, for each one, to consult the information on dosage and administration provided by the national regulatory authority or the technical data sheet.		

Sources: Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Limits Use of Certain Monoclonal Antibodies to Treat COVID-19 Due to the Omicron Variant. Maryland: FDA; 2022. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-certain-monoclonal-antibodies-treat-covid-19-due-omicron.

Food and Drug Administration. Fact sheet for patients, parents, and caregivers. Emergency use authorization (EUA) of sotrovimab for the treatment of coronavirus disease 2019 (COVID-19). Philadelphia: 2021. Available at: https://www.fda.gov/media/149533/download#:~:text=The%20side%20effects%20of%20getting,possible%20side%20effects%20of%20sotrovimab.

European Medicines Agency. Conditions of use, distribution and patients targeted for Lagevrio (molnupiravir). Amsterdam: EMA; 2022. Available at: https://www.ema.europa.eu/en/documents/referral/lagevrio-also-known-molnupiravir-mk-4482-covid-19-article-53-procedure-conditions-use-conditions_en.pdf.

Food and Drug Administration. Highlights of prescribing remdesivir. Filadelfia: FDA; 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_ docs/label/2022/214787Orig1s010Lbl.pdf

Food and Drug Administration. Emergency use authorization for paxlovid. Filadelfia: FDA; 2021. Available at: https://www.fda.gov/media/155050/download

Selection of high-risk patients with mild or moderate COVID-19 for allocation of drug-based therapies

Given the likelihood that demand for the management of patients with mild or moderate COVID-19 will be high and the possibility that limitations in access to antivirals and monoclonal antibodies will arise, the panel suggests identifying those groups that would most benefit from the administration of these drugs. The National Institutes of Health (NIH) of the United States of America have identified four groups in terms of the following four key elements: age, vaccination status, immune status, and clinical risk factors.[5] Based on this classification, the panel proposes that the countries of the Region give first consideration to groups at risk for hospitalization, as described in Table 3, on the basis of immune response to infection and on the presence of certain risk factors.

The other risk groups consist of individuals who have been vaccinated with the complete schedule or with a single dose and who possess risk factors for progression to severe disease, as well as unvaccinated individuals with risk factors, regardless of age. Use of these medicines in these risk groups shall be established on the basis of clinical judgment.

Table 3. Groups of individuals at high risk for hospitalization due to COVID-19

Tier	Risk group
1	• Immunocompromised individuals,[a] who are not expected to mount an adequate immune response to the COVID-19 vaccine or to infection with SARS-CoV-2, regardless of vaccination status; or • Unvaccinated individuals at increased risk of developing severe illness (anyone aged 75 years or older or anyone aged 65 years or older with additional clinical risk factors[b])
2	• Personas no vacunadas que corran un mayor riesgo de desarrollar enfermedad grave no incluidas en el nivel 1 (toda persona de 65 años o más con factores de riesgo clínico[b])

[a] Immunocompromised individuals:

• Patients within one year of having received B-cell-depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
• Patients receiving Bruton's tyrosine kinase inhibitors
• Chimeric antigen receptor T-cell (CAR T-lymphocyte) recipients
• Hemocytoblast transplant recipients who have chronic graft-versus-host disease or who are taking immunosuppressants for another indication
• Patients with hematologic malignancies who are on active therapy
• Lung transplant recipients
• Patients within one year of having received a solid organ transplant (other than a lung transplant)
• Solid organ transplant recipients recently treated for acute rejection using T-cell or B-cell-depleting agents
• Patients with severe combined immunodeficiencies
• Patients with untreated HIV infection whose CD4-T-cell count is < 50 cells/mm^3

[b] Patients with clinical risk factors: age (risk increases with each decade starting at 50 years), presence of two or more comorbidities, hypertension, obesity (BMI > 30), diabetes, cardiovascular disease, chronic lung disease, chronic kidney disease, chronic liver disease, cerebrovascular disease, thrombocytopenia, active smoking, and cancer.

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[5]Food and Drug Administration. Emergency use authorization of REGEN-COV. Maryland: FDA; 2021. Available at: https://www.fda.gov/media/145611/download.
Sources: Food and Drug Administration. Emergency use authorization of REGEN-COV. Maryland: FDA; 2021. Available at: https://www.fda.gov/media/145611/download; and Pan American Health Organization. Guidelines for prophylaxis and management of patients with mild and moderate COVID-19 in Latin America and the Caribbean. Washington, D.C.: PAHO; 2021. Available at: https://iris.paho.org/handle/10665.2/55099.
Sources: Food and Drug Administration. Emergency use authorization of REGEN-COV. Maryland: FDA; 2021. Available at: https://www.fda.gov/media/145611/download; Pan American Health Organization. Guidelines for prophylaxis and management of patients with mild and moderate COVID-19 in Latin America and the Caribbean. Washington, D.C.: PAHO; 2021. Available at: https://iris.paho.org/handle/10665.2/55099; and World Health Organization. Therapeutics and COVID-19: living guideline. Geneva: WHO; 2022. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1

THERAPEUTIC MANAGEMENT OF SEVERELY OR CRITICALLY ILL PATIENTS

New data and recommendations have been published for baricitinib and casirivimab/imdevimab. Table 4 below presents the most recent evidence on the safety of these interventions and their impact on mortality.

Table 4. Evidence of reduced mortality and of the safety of antivirals, monoclonal antibodies, and antidepressants, and considerations surrounding their administration

Intervention	Impact on mortality*		Safety*	Administration	Other considerations
	Patients with severe disease (baseline risk of 16%)	Certainty of the evidence based on GRADE (grading of recommendations, assessment, development, and evaluation)			
Baricitinib (2,659 patients in 3 trials)	58 fewer per 1,000	●●●○ Moderate	No differences in side effects have been reported. Theoretical risk of infections, thrombi, and infusion reactions.	Oral	Limited access.
Casirivimab e imdevimab (16,667 patients in 4 trials)	32 fewer per 1,000	●●●○ Moderate	No differences in side effects have been reported. Theoretical risk of anaphylaxis and allergic infusion reactions.	Intravenous infusion. Single dose. *In vitro* data suggest that it is less effective against the Omicron variant of SARS-CoV-2.[c]	Limited access.
Corticosteroids (8,000 patients in 12 trials)	16 fewer per 1,000	●●●○ Moderate	High safety profile. Hyperglycemia, hypertension, and infections may occur.	Intravenous infusion in low doses.	
Tocilizumab (8,455 patients in 20 trials)	24 fewer per 1,000	●●●● High	No differences in side effects have been reported. Theoretical risk of infections, thrombi, and allergic infusion reactions.	Intravenous infusion.	

[a]Pan American Health Organization. Guidelines for care of critically ill adult patients with COVID-19 in the Americas. Summary, version 3. Washington, D.C.: PAHO; 2021 Available at: https://iris.paho.org/handle/10665.2/53894
[b]Evidence obtained from reported clinical trials.
[c]Pan American Health Organization. Ongoing Living Update of Potential COVID-19 Therapeutic Options: Summary of Evidence. Rapid Review. Washington, D.C.: PAHO; 2022. Available at: https://iris.paho.org/handle/10665.2/52719

CONSIDERATIONS ON THE RATIONAL USE OF MEDICINES RECOMMENDED FOR SEVERELY OR CRITICALLY ILL PATIENTS WITH COVID-19 IN LATIN AMERICA AND THE CARIBBEAN

WHO developed a new conditional recommendation for the use of baricitinib in critically ill patients, and of casirivimab e imdevimab in severely or critically ill patients with COVID-19, conditional to those who are seronegative.

The PAHO panel examined the context of Latin America and the Caribbean in view of the fact that currently WHO and PAHO evidence-based guidelines include recommendations for the use of corticosteroids and tocilizumab in severely and critically ill patients. It also indicated that each country should evaluate its decision on the use of baricitinib and casirivimab e imdevimab in light of available resources, feasibility of implementation, access, vaccination coverage, patient-specific factors (e.g., duration of symptoms, kidney function, drug interactions), mode of administration, and prevalence of the Omicron variant. In countries where the Omicron variant of SARS-CoV-2 is more prevalent, consideration should be given to not administering casirivimab/imdevimab, given its reduced efficacy against this variant, or using it only in patients infected with a different variant of SARS-CoV-2.

The PAHO panel was of the opinion that, should any of the aforementioned interventions in severely and critically ill patients be implemented, patients should be selected following the criteria presented in Table 5.

Table 5. Considerations on the administration and safety of antivirals and monoclonal antibodies for the management of patients with mild or moderate COVID-19.

Medication	Considerations relative to dosage and administration	Side effects
Baricitinib	A total of 4 mg daily in adults with eGFR ≥ 60 ml/min/1.73 m2 for 14 days or until hospital discharge. Can be given with corticosteroids.	Should not be given simultaneously with tocilizumab. Do not administer to patients with tuberculosis. Consider the benefit-risk ratio in patients with severe active infections. Should be used in patients on prophylactic anticoagulant therapy. Thrombosis, pulmonary embolism, and severe infections may occur.[a,b]
Casirivimab e imdevimab	1,200-mg dose, intravenously or subcutaneously.	Allergic reactions. Side effects associated with administration. Fever, increased respiratory distress, arrhythmia, fatigue, and altered mental state may occur. [a,b]

Medication	Considerations relative to dosage and administration	Side effects
Tocilizumab	Single intravenous doses (8 mg/kg body weight up to a maximum of 800 mg), usually over a one-hour period. A second dose may be administered 12 to 48 hours after the first dose, depending on clinical judgment. Ḅlood tests should be done before initiating treatment and should include neutrophil and platelet counts, transaminases, and total bilirubin. No specific time for initiating therapy is indicated.	All patients should be monitored for signs and symptoms of infection, given the increased risk from immunosuppression and systemic corticosteroids combined. Patients on long-term therapies are at risk for active tuberculosis, invasive fungal infections, and infections from opportunistic pathogens. Caution is advised when considering the use of tocilizumab in patients with a history of recurring or chronic infections or with underlying conditions that may predispose them to infections.
Corticosteroids	Dexamethasone (6 mg daily for no more than 10 days or until hospital discharge). Hydrocortisone (50 mg every 8 hours). Prednisone (40 mg every 6 hours or 16 mg every 12 hours) Methylprednisolone (8 mg every 6 hours or 16 mg every 12 hours) Treatment should be started within 7 days of onset of symptoms.	Possible hyperglycemia and hypernatremia. In general, corticosteroids have an adequate safety profile and most medical staff are experienced in using these medications.

[a]World Health Organization. Therapeutics and COVID-19: living guideline. Geneva: WHO; 2022. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1.

[b]Pan American Health Organization. Guidelines for prophylaxis and management of patients with mild and moderate COVID-19 in Latin America and the Caribbean. Washington, D.C.: PAHO; 2021. Available at: https://iris.paho.org/handle/10665.2/55099.

Sources: Food and Drug Administration. Emergency use authorization of sotrovimab for the treatment of coronavirus disease 2019. Philadelphia: FDA; 2021. Available at: https://www.fda.gov/media/149533/download#:~:text=The%20side%20effects%20of%20getting,possible%20side%20effects%20of%20sotrovimab.

National Institutes of Health of the United States of America. The COVID-19 Treatment Guidelines Panel's Interim Statement on Patient Prioritization for Outpatient Anti-SARS-CoV-2 Therapies or Preventive Strategies When There Are Logistical or Supply Constraints. Maryland: NIH; 2021. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/.

Food and Drug Administration. Emergency use authorization of REGEN-COV. Maryland: FDA; 2021. Available at: https://www.fda.gov/media/143823/download.