Pan-American Guidelines for the Treatment of SARS-CoV-2/COVID-19: A Joint Evidence-Based Guideline of the Brazilian Society of Infectious Diseases (SBI) and the Pan-American Association of Infectious Diseases (API)

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Abstract

Background

Since the beginning of the COVID-19 pandemic, therapeutic options for treating COVID-19 have been investigated at different stages of clinical manifestations. Considering the particular impact of COVID-19 in the Americas, this document aims to present recommendations for the pharmacological treatment of COVID-19 specific to this population.

Method

Fifteen experts, members of the Brazilian Society of Infectious Diseases (SBI) and the Pan-American Association of Infectious Diseases (API) make up the panel responsible for developing this guideline. Questions were formulated regarding prophylaxis and treatment of COVID-19 in outpatient and inpatient settings. The outcomes considered in decision-making were mortality, hospitalisation, need for mechanical ventilation, symptomatic COVID-19 episodes, and adverse events. In addition, a systematic review of randomised controlled trials was conducted. The quality of evidence assessment and guideline development process followed the GRADE system.

Results

Nine technologies were evaluated, and ten recommendations were made, including the use of tixagevimab + cilgavimab in the prophylaxis of COVID-19, tixagevimab + cilgavimab, molnupiravir, nirmatrelvir + ritonavir, and remdesivir in the treatment of outpatients, and remdesivir, baricitinib, and tocilizumab in the treatment of hospitalised patients with severe COVID-19. The use of hydroxychloroquine or chloroquine and ivermectin was discouraged.

Conclusion

This guideline provides recommendations for treating patients in the Americas following the principles of evidence-based medicine. The recommendations present a set of drugs that have proven effective in the prophylaxis and treatment of COVID-19, emphasising the strong recommendation for the use of nirmatrelvir/ritonavir in outpatients as the lack of benefit from the use of hydroxychloroquine and ivermectin.

Background

The increased number of severe cases of viral pneumonia caused by SARS-CoV-2 in China in 2019 and its worldwide spread led the World Health Organization (WHO) to declare COVID-19 a pandemic on March 11, 2020 [1]. As of February 2023, more than 673.9 million confirmed cases and more than 6.86 million

deaths from COVID-19 have been reported worldwide [2]. According to the WHO, more than 188.4 million cases have been recorded in the Americas, and the continent has the highest COVID-19 death rate in the world with 2, 909,286 death records [3]. These figures are due to the high incidence of cases and deaths in the largest countries in the Americas. The United States of America (USA) has recorded more than 102.3 million cases and 1.1 million deaths, followed by Brazil with more than 36.8 million cases and 696,892 deaths, which is then followed by Argentina with more than 10.0 million cases and 130,421 deaths, and Mexico with more than 7.4 million cases and 332,190 deaths, among others [2]. These rates have made COVID-19 a severe public health threat worldwide and in Latin America.

Since the beginning of the COVID-19 pandemic, the global scale of SARS-CoV-2 infection has risen considerably over time and with regional variation [4]. Numerous drugs related to the pathogenesis of SARS-CoV-2, such as those with antiviral and immunomodulatory effects and inhibitors of the inflammatory cascade, have been proposed to minimise damage in patients with suspected or some degree of infection, with promising results, particularly in high-risk populations. This group includes individuals older than 65, individuals with obesity, cardiovascular or metabolic disease, or immunocompromising conditions, and individuals who are unvaccinated or under-vaccinated [5]. In addition, the overall increase in vaccination coverage has led to a substantial drop in the risk of hospitalisation and death [5]. However, increased transmissibility of new variants of concern would still result in a rise in cases leading to excessive hospitalisations associated with COVID-19 and its complications [6].

In light of new evidence, changes in the pandemic scenario and heterogeneity in clinical practice, it is necessary to evaluate the existing evidence and formulate recommendations so that health professionals can provide adequate treatment.

Methods

The guideline development group consisted of a group of coordinators, including one specialist in the proposed topic (ANB) and two methodologists (JCF, ST), and an expert committee (panel members), including experts from Brazil, Colombia, Ecuador, Peru, and the Dominican Republic who represent the Brazilian Society of Infectious Diseases (SBI) and the Pan-American Association of Infectious Diseases (API). Videoconferencing and face-to-face recommendation meetings, including asynchronous written communication (i.e., e-mail), were held from May 27, 2022, to July 6, 2022. The guideline development process followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system for assessing evidence and developing recommendations [7, 8].

The expert committee formulated ten questions related to the pharmacological treatment of COVID-19 according to the PICO framework (patients, intervention, comparator, and outcome). The outcomes of interest were defined *a priori* and classified as critical, important, or unimportant. Only critical and important outcomes were used for making the recommendations (Table 1).

Table 1
Guideline questions and outcomes of importance.

Question	Critical Outcomes	Important Outcomes
1. Should tixagevimab + cilgavimab be recommended for pre-exposure prophylaxis in people at high risk of developing severe COVID-19?	Symptomatic COVID-19 Adverse event with death	Serious adverse event
2. Should monoclonal antibodies be recommended for outpatients with mild COVID-19?[a]	Death	Hospitalisation Serious adverse event
3. Should molnupiravir be recommended for outpatients with mild COVID-19?	Hospitalisation Death	Serious adverse event
4. Should nirmatrelvir/ritonavir be recommended for outpatients with mild COVID-19?	Hospitalisation Death	Serious adverse event
5. Should remdesivir be recommended for outpatients with mild COVID-19?	Hospitalisation Death	Serious adverse event
6. Should hydroxychloroquine or chloroquine be recommended for outpatients with mild COVID-19?	Hospitalisation Death	Serious adverse event
7. Should ivermectin be recommended for outpatients with mild COVID-19?	Hospitalisation Death	Serious adverse event
8. Should remdesivir be recommended for hospitalised patients with severe COVID-19?	Mechanical ventilation Death	Serious adverse event
9. Should baricitinib be recommended for hospitalised patients with severe COVID-19?	Death	Serious adverse event
10. Should tocilizumab be recommended for hospitalised patients with severe COVID-19?	Mechanical ventilation Death	Serious adverse event

[a] In this question, the following monoclonal antibodies were considered: bamlanivimab + etesevimab, casirivimab + imdevimab, sotrovimab, bebtelovimab, and tixagevimab + cilgavimab. During the panel, members decided not to make recommendations for bamlanivimab, casirivimab, etesevimab, imdevimab, regdanvimab, and sotrovimab due to a lack of evidence of effectiveness in the scenario of omicron variant circulation and for bebtelovimab due to lack of evidence of effectiveness.

Evidence Search And Synthesis

A team of experienced methodologists searched and synthesised evidence independent of the expert committee.

Searches were performed on MEDLINE, Embase, ClinicalTrials.gov and Google Scholar databases. The search strategy was restricted to phase III randomised controlled trials (RCTs), with keywords pre-established by the specialist coordinators, without limitations on language or publication date (Additional Table 1).

Two researchers independently screened titles and abstracts. If an abstract was considered relevant, the paper was included for full-text review to confirm eligibility. The reasons for inclusion or exclusion were recorded and presented according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplemental Figs. 1–10). Then, two reviewers independently abstracted the data from selected studies and performed meta-analyses whenever possible. The risk of bias was assessed using an adapted version of the Cochrane Risk of Bias Tool 2.0. Finally, the quality of evidence was assessed using GRADE (Table 2).

Table 2
Levels of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Level	Definition	Implications
High ( )	We are very confident that the true effect lies close to that of the estimate of the effect.	Future research is unlikely to change confidence in the estimated effect.
Moderate (O)	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Future research will likely have a major impact on confidence in the estimated effect and may change this estimate.
Low (OO)	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	Future research will likely have a major impact on confidence in the estimated effect and will likely change this estimate.
Very low (OOO)	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.	Any estimate of an effect is very uncertain.

Adapted from: Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. Available from: https://gdt.gradepro.org/app/handbook/handbook.html [9].

Development Of Recommendations

On May 27, 2022, a recommendation meeting was held in São Paulo, Brazil, in a hybrid format (in person and remote). In the meeting, each question with the underlying evidence was presented to the panel of experts to develop recommendations. Before starting the meeting, all experts and methodologists declared and signed their relevant conflicts of interest pertinent to each of the 10 guideline questions. A second virtual meeting was required to finalise the process, held on July 6, 2022.

The GRADE Evidence to Decision (EtD) framework was used to evaluate the priority of the problem, the magnitude of undesirable effects, evidence of benefits and risks, quality of evidence, costs and use of resources, feasibility, and aspects related to equity, patient values and preferences, and acceptability. Finally, the panel made a recommendation, where the direction of the course of action was discussed (whether to recommend or not to recommend the use of the intervention), and the strength of recommendation was defined as strong or conditional according to the GRADE system (Table 3). The terminology "we recommend" and "we suggest" denote different degrees of emphasis on the strength of recommendation, as follows: "We recommend" represents a strong recommendation, which should be incorporated as a routine practice, either for or against the use of a given intervention; "We suggest" represents a conditional recommendation, which applies to most situations, but due either to the lack of robust evidence or to the expected variation in treatment effectiveness, other approaches may be justifiable.

Table 3
Implications of the strength of recommendation for clinicians, patients, and policymakers.

Target audience	Strong	Conditional
Policymakers	The recommendation should be adopted as a health care policy in most situations.	Substantial debate is required, with the involvement of stakeholders.
Clinicians	Most patients should receive the recommended intervention.	The health professional should acknowledge that different choices may be appropriate for individual patients and should help them make decisions consistent with their values and preferences.
Patients	Most individuals would want the intervention to be recommended, and only a small number would not accept this recommendation.	Most individuals would want the intervention to be recommended, although a considerable number would not accept this recommendation.

Source: Adapted from Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. Available from: https://gdt.gradepro.org/app/handbook/handbook.html.[9]

Members with a direct financial conflict of interest related to a given intervention did not vote for the related questions. The list of participants, their role in the guideline, and statement of conflicts of interest are provided in additional material (Additional Table 2).

Results

Ten recommendations were made. The guideline panel recommendations are summarised in Table 4 and Figure 1. Each recommendation with a summary of the underlying evidence is presented below. In addition, detailed information regarding the evidence supporting each recommendation is shown in additional material.

Table 4. Summary of recommendations.

Recommendation 1:	We suggest using tixagevimab + cilgavimab for prophylaxis in people at high risk of developing severe COVID-19 (conditional recommendation, very low certainty in evidence).
Recommendation 2:	We suggest using tixagevimab + cilgavimab in outpatients with mild COVID-19 (conditional recommendation, moderate certainty in evidence).
Recommendation 3.1:	We suggest against using molnupiravir in outpatients with mild COVID-19 and no risk factors for severe disease (conditional recommendation, very low certainty in evidence).
Recommendation 3.2:	We suggest using molnupiravir in outpatients with mild COVID-19 and risk factors for severe disease (conditional recommendation, very low certainty in evidence).
Recommendation 4:	We recommend using nirmatrelvir/ritonavir in outpatients with mild COVID-19 (strong recommendation, moderate certainty in evidence).
Recommendation 5:	We suggest using remdesivir in outpatients with mild COVID-19 (conditional recommendation, low certainty in evidence).
Recommendation 6:	We recommend against using hydroxychloroquine or chloroquine in outpatients with mild COVID-19 (strong recommendation, moderate certainty in evidence).
Recommendation 7:	We recommend against using ivermectin in outpatients with mild COVID-19 (strong recommendation, moderate certainty in evidence).
Recommendation 8:	We suggest using remdesivir in hospitalised patients with severe COVID-19 (conditional recommendation, low certainty in evidence).
Recommendation 9:	We suggest using baricitinib in hospitalised patients with severe COVID-19 (conditional recommendation, moderate certainty in evidence).
Recommendation 10:	We suggest using tocilizumab in hospitalised patients with severe COVID-19 (conditional recommendation, moderate certainty in evidence).

COVID-19 prophylaxis

Recommendation 1: We suggest using tixagevimab + cilgavimab for prophylaxis in people at high risk of developing severe COVID-19 (conditional recommendation, very low certainty in evidence).

Summary of evidence: The review identified 13 references, and one RCT (Levin et al., 2022) evaluating the effectiveness of tixagevimab + cilgavimab in the population of interest was included [10]. The trial tested a monoclonal-antibody combination of tixagevimab and cilgavimab (AZD7442). A single 300 mg dose of AZD7442 (two consecutive 1.5 mL intramuscular injections, one containing tixagevimab and the other containing cilgavimab) was administered on day 1. Compared with placebo, tixagevimab + cilgavimab reduced the occurrence of symptomatic COVID-19 by 2% (one RCT, n = 5197, absolute risk difference of 2.0%; 95% CI, -2.7% to -1.1%; very low certainty in evidence). No significant difference was observed for adverse events.

Treatment of outpatients with COVID-19

Recommendation 2: We suggest using tixagevimab + cilgavimab in outpatients with mild COVID-19 (conditional recommendation, moderate certainty in evidence).

Summary of evidence: The review identified 53 references, and one RCT (Montgomery et al., 2022) evaluating the effectiveness of tixagevimab + cilgavimab in the population of interest was included [11]. The trial tested the intramuscular administration of a single tixagevimab-cilgavimab 600 mg dose (two consecutive 3 mL intramuscular injections, one containing tixagevimab and the other containing cilgavimab) on day 1. Compared with placebo, tixagevimab + cilgavimab reduced hospitalisation by 5.1% (one RCT, n = 903, absolute risk difference of -5.1%; 95% CI, -8.2% to -1.9%; moderate certainty in evidence). No significant difference was observed for mortality or adverse events.

Recommendation 3.1: We suggest against using molnupiravir in outpatients with mild COVID-19 and no risk factors for severe disease (conditional recommendation, very low certainty in evidence).

Recommendation 3.2. We suggest using molnupiravir in outpatients with mild COVID-19 and risk factors for severe disease (conditional recommendation, very low certainty in evidence).

Summary of evidence: The review identified 26 references and one RCT (MOVe-OUT study) evaluating the effectiveness of molnupiravir in outpatients with mild COVID-19 and no risk factors for severe disease and one RCT (Tippabhotla et al., 2022) assessing the effectiveness of molnupiravir in the population of interest were included [12, 13]. Both trials tested the oral administration of 800 mg of molnupiravir twice daily for five days in addition to standard-of-care treatment. In patients without risk factors for severe disease, no significant difference was observed for molnupiravir as compared with placebo in hospitalisation (one RCT, n = 1220, absolute risk difference of -1.0%; 95% CI, -2.0% to 0.0%; moderate certainty in evidence), mortality (absolute risk difference of 0.0%; 95% CI, -0.0% to 0.0%; very moderate certainty in evidence), or serious adverse events (absolute risk difference of -0.0%; 95% CI, -4.0% to 3.0%; moderate certainty in evidence) [12]. In patients with risk factors for severe disease, molnupiravir, as compared with placebo, reduced mortality (one RCT, n = 1433, absolute risk difference of -1.0%; 95% CI,

-2.0% to -0.0%; high certainty in evidence) but did not reach statistical significance for hospitalisation (one RCT, n = 1433, absolute risk difference of -2.0%; 95% CI, -4.0% to 1.0%; high certainty in evidence). Molnupiravir did not increase serious adverse events (one RCT, n = 1433, absolute risk difference of -3.0%; 95% CI, -5.0% to 0.0%; high certainty in evidence) [13].

Recommendation 4: We recommend using nirmatrelvir/ritonavir in outpatients with mild COVID-19 (strong recommendation, moderate certainty in evidence)

Summary of evidence: The review identified 19 references, and one RCT (EPIC-HR study) evaluating the effectiveness of nirmatrelvir/ritonavir in the population of interest was included [14]. The trial assessed the administration of nirmatrelvir (300 mg) plus ritonavir (100 mg) twice daily for five days. As compared with placebo, nirmatrelvir/ritonavir reduced mortality (one RCT, n = 2246, absolute risk difference of -1.0%; 95% CI, -1.6% to -0.4%; moderate certainty in evidence) and hospitalisation (one RCT, n = 2246, absolute risk difference of -5.0%; 95% CI, -6.5% to -3.6%; high certainty in evidence). Patients who received nirmatrelvir/ritonavir had fewer serious adverse events than placebo recipients (one RCT, n = 2246, absolute risk difference of -4.9%; 95% CI, -6.5% to -3.3%; high certainty in evidence).

Recommendation 5: We suggest using remdesivir in outpatients with mild COVID-19 (conditional recommendation, low certainty in evidence).

Summary of evidence: The review identified 430 references, and one RCT (PINETREE study) evaluating the effectiveness of remdesivir in the population of interest was included [15]. The trial tested intravenous remdesivir, 200 mg administered on day one, followed by 100 mg on days 2 and 3. Compared with placebo, remdesivir reduced hospitalisation (one RCT, n = 562, absolute risk difference of -4.4%; 95% CI, -7.5% to -1.3%; moderate certainty in evidence). Serious adverse events were more frequently observed in the remdesivir group (one RCT, n = 562, absolute risk difference of -4.8%; 95% CI, -8.0% to -1.5%; moderate certainty in evidence). No deaths occurred during the study follow-up.

Recommendation 6: We recommend against using hydroxychloroquine or chloroquine in outpatients with mild COVID-19 (strong recommendation, moderate certainty in evidence).

Summary of evidence: The review identified 783 references and six RCTs (ALBERTA HOPE COVID-19 study, COPE – COALITION COVID-19 Brazil V study, Mitjà et al., 2021, Omrani et al., 2020, Skipper et al., 2020, and TOGETHER study) evaluating the effectiveness of hydroxychloroquine or chloroquine in the population of interest were included [16-21]. The largest trial (COPE – COALITION COVID-19 Brazil V study) tested the administration of 400 mg of hydroxychloroquine twice daily on day 1, followed by 400 mg once daily after that, for seven days [16]. As compared with placebo, hydroxychloroquine or chloroquine did not significantly reduce mortality (six RCTs, n = 2981, absolute risk difference of 0.0%; 95% CI, -1.0% to 0.0%; moderate certainty in evidence) or hospitalisation (six RCTs, n = 2981, absolute risk difference of -2.0%; 95% CI, -3.0% to 0.0%; moderate certainty in evidence). No impact was observed on severe adverse events (five RCTs, n = 2558, absolute risk difference of 0.0%; 95% CI, -2.0% to 1.0%; moderate certainty in evidence).

Recommendation 7: We recommend against using ivermectin in outpatients with mild COVID-19 (strong recommendation, low certainty in evidence).

Summary of evidence: The review identified 168 references, and three RCTs (ACTIV-6 study, López-Medina et al., 2021, and TOGETHER study) evaluating the effectiveness of ivermectin in the population of interest were included [22-24]. All trials assessed efficacy (death and hospitalisation) and safety outcomes (adverse events).

Two trials tested ivermectin 400 µg/kg of body weight administered once daily for three days [23, 24], and one trial tested ivermectin 300 µg/kg administered once daily for five days [22]. As compared with placebo, ivermectin did not reduce mortality (three RCTs, n = 3425, absolute risk difference of 0.0%; 95% CI, -1.0% to 1.0%; moderate certainty in evidence) or hospitalisation (three RCTs, n = 3425, absolute risk difference of -2.0%; 95% CI, -3.0% to 0.0%; moderate certainty in evidence). Ivermectin did not increase the incidence of serious adverse events (three RCTs, n = 3425, absolute risk difference of 0.0%; 95% CI, -2.0% to 1.0%; moderate certainty in evidence).

Hospitalised patients with COVID-19

Recommendation 8: We suggest using remdesivir in hospitalised patients with severe COVID-19 (conditional recommendation, low certainty in evidence).

Summary of evidence: The review identified 430 references and eight RCTs (Abd-Elsalam et al., 2021, ACTT-1 study, CATCO study, DISCOVERY study, Mahajan et al., 2021, SIMPLE-Moderate study, Wuhan-Hubei study, and WHO Solidarity study) evaluating the effectiveness of remdesivir in the population of interest were included [25-32]. A 200 mg dose of remdesivir was administered on day 1, followed by 100 mg once daily for 4 to 9 days. As compared with the standard of care, remdesivir significantly reduced progression to invasive mechanical ventilation (eight RCTs, n = 11857, absolute risk difference of -3%; 95% CI, -5% to -1%; low certainty in evidence) and showed a non-significant reduction in mortality (eight RCTs, n = 12608, absolute risk difference of -1%; 95% CI, -3% to 0%; moderate certainty in evidence). In addition, Remdesivir did not increase the incidence of serious adverse events (five RCTs, n = 2715, absolute risk difference of -3%; 95% CI, -8% to 2%; very low certainty in evidence).

Recommendation 9: We suggest using baricitinib in hospitalised patients with severe COVID-19 (conditional recommendation, moderate certainty in evidence).

Summary of evidence: The review identified 75 references, and one RCT (COV-BARRIER study) evaluating the effectiveness of baricitinib in the population of interest was included [33, 34]. The COV-BARRIER study assessed the administration of baricitinib 4 mg once daily (oral or nasogastric tube) for 14 days or until hospital discharge. As compared with the standard of care, baricitinib significantly reduced mortality (one RCT, n = 1525, absolute risk difference of -5.0%; 95% CI, -8.1% to -1.9%; moderate certainty in evidence). In addition, Baricitinib did not increase the incidence of serious adverse events (one RCT, n = 1525, absolute risk difference of -2.5%; 95% CI, -6.2% to 1.1%; low certainty in evidence).

Recommendation 10: We suggest using tocilizumab in hospitalised patients with severe COVID-19 (conditional recommendation, moderate certainty in evidence).

Summary of evidence: The review identified 358 references, and 14 RCTs evaluating the effectiveness of tocilizumab in the population of interest were included [35-47]. The intervention used in the most prominent trial (RECOVERY) consisted of the intravenous infusion of a single tocilizumab dose of 800 mg if weight > 90 kg, 600 mg if weight > 65 and ≤ 90 kg, 400 mg if weight > 40 and ≤ 65 kg, or 8 mg/kg if weight ≤ 40 kg, and a second dose could be administered 12 to 24 hours later if, in the opinion of the clinician, the patient's condition had not improved [35]. As compared with the standard of care, tocilizumab significantly reduced mortality (14 RCTs, n = 7866, absolute risk difference of -3.0%; 95% CI, -5.0% to -1.0%; moderate certainty in evidence) and progression to mechanical ventilation (seven RCTs, n = 6866, absolute risk difference of -2.0%; 95% CI, -4.% to -1.0%; moderate certainty in evidence). Tocilizumab did not increase the incidence of serious adverse events (11 RCTs, n = 2489, absolute risk difference of -1.0%; 95% CI, -5.0% to 2.0%; moderate certainty in evidence).

Discussion

This joint SBI-API evidence-based guideline was developed by a panel of experts based on a comprehensive systematic review with meta-analysis of RCTs focused on ascertaining the efficacy of therapies in the prevention and treatment of COVID-19. The guideline provides ten recommendations that include tixagevimab + cilgavimab in the prophylaxis of COVID-19, tixagevimab + cilgavimab, molnupiravir, nirmatrelvir + ritonavir, and remdesivir in the treatment of outpatients, and remdesivir, baricitinib, and tocilizumab in the treatment of hospitalised patients with severe COVID-19. In addition, the use of hydroxychloroquine or chloroquine and ivermectin was discouraged.

Some clinical treatments have been recommended in previous guidelines. Monoclonal antibodies (e.g., tixagevimab + cilgavimab), direct-acting antiviral agents (e.g., remdesivir), corticosteroids (e.g., dexamethasone), interleukin-6 antagonists (e.g., tocilizumab) and Janus kinase inhibitors (e.g., baricitinib) have been evaluated in guidelines for the treatment of patients with COVID-19 after RCT results became available indicating their benefit in specific populations [48, 49]. In Brazil, two guidelines were published for pharmacological treatment in outpatients and hospitalised patients. The Brazilian guidelines for the treatment of outpatients with suspected or confirmed COVID-19 provide ten recommendations, most of which advice against the use of the candidate technologies, contraindicating the clinical treatment of COVID-19 with anticoagulants, azithromycin, budesonide, colchicine, corticosteroids, hydroxychloroquine/chloroquine alone or combined with azithromycin, ivermectin, nitazoxanide, or convalescent plasma [50]. Using monoclonal antibodies in outpatients was impossible because of their uncertain benefits and high costs, with availability and implementation limitations [50]. The Brazilian guidelines for the pharmacological treatment of hospitalised patients with COVID-19 provide 16 recommendations that include treatment with corticosteroids in patients receiving supplemental oxygen and the use of prophylactic doses of anticoagulants for venous thromboembolism. In contrast, several medications were not recommended for this population [51].

Close to the scope of the current guideline, the renowned Infectious Diseases Society of America (IDSA) published guidelines on treating and managing patients with COVID-19 with 32 recommendations for prophylaxis in both outpatient and inpatient settings [52]. The IDSA guidelines apply to all patients with COVID-19, but some recommendations may differ based on disease severity [52]. The WHO definitions of disease severity for COVID-19 are as follows: (a) critical COVID-19 – defined by the criteria for acute respiratory distress syndrome, sepsis, septic shock, or other conditions that would generally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or noninvasive) or vasopressor therapy; (b) severe COVID-19 – defined by oxygen saturation < 90% on room air, severe pneumonia, or signs of severe respiratory distress; and (c) non-severe COVID-19 – defined as an absence of any criteria for severe or critical COVID-19 [52].

Although substantial progress has been made in COVID-19 treatment, some gaps remain. These include recommendations for treatment given the new SARS-CoV-2 variants of concern [53], as recruitment preceded the emergence of the omicron variant in most trials. The Pan-American Health Organization (PAHO) published an update on the emergence of omicron sublineages from SARS-CoV-2 recombination events [54]. In 2021, the omicron variant was introduced in the Americas and rapidly replaced delta and other lineages across the region and globally, becoming prevalent in all countries in the Americas since early 2022 [55–57]. The new emerging omicron sublineages carry additional S protein mutations, including BA.4.6 (with increasing incidence worldwide), BA.2.75.2 (with a growing incidence in India), BJ.1 (with increasing incidence mainly in India and Bangladesh), and BQ.1.1 (with a growing incidence in the USA and Europe) [53, 58]. On January 2023, the XBB.1.5 will be responsible for 61.3% of cases in the USA, following BQ.1.1 for 21.8% [59].

Emerging omicron sublineages resist some clinically used monoclonal antibodies, but preliminary data indicate complete resistance to XBB.1.5, BA.1.1 and BQ.1.1 to all monoclonal antibodies [53, 58, 60]. Therefore, in regions where this sublineage is spreading, patients may not respond well to clinical treatment with monoclonal antibodies alone, suggesting additional treatment options (e.g., nirmatrelvir/ritonavir or molnupiravir) should be considered for patients at high risk [58].

According to the FDA, over 90% of circulating variants are unlikely to be susceptible to tixagevimab-cilgavimab [60]. In this context, some organisations and societies remarked on neutralising antibodies. For example, on January 13, the IDSA added a remark to the neutralising antibodies for pre-exposure prophylaxis with tixagevimab/cilgavimab (Evusheld) recommendation due to resistance in the USA [52]. Also, the recommendation of neutralising antibodies for post-exposure prophylaxis with casirivimab/imdevimab was removed and replaced with a statement mentioning in vitro resistance to circulating strains in the USA [52].

Omicron sublineages BQ.1.1 and XBB1.5 can lead to a high volume of hospitalisations, which can strain healthcare systems and maintain a substantial number of deaths. That underscores the importance of preparing care units, specifically, hospital surge capacity and the ability to adequately staff health care systems and equip the health professionals who will care for these patients. In addition to vaccination,

following recommended prevention strategies is essential to prevent poor outcomes such as infections, severe illness, and death from COVID-19 [6].

Deciding on the best practice has been challenging, given the rapid generation of large amounts of data and sometimes conflicting clinical results [49]. Nevertheless, despite limited evidence, this guideline recommends using agents in the prophylaxis and treatment of outpatients and hospitalised patients, considering an application context encompassing the Americas. Thus, the scope of this guideline proved to be comprehensive by answering the main clinical questions based on a robust method such as GRADE.

The current guideline addresses pharmacological treatment in three different COVID-19 management scenarios contextualised in clinical practice in countries in the Americas. Further RCTs will be needed to update current recommendations as the pandemic still progresses in 2023.

Conclusions

Since the beginning of the COVID-19 pandemic, studies have been conducted to provide the evidence necessary to formulate recommendations. This guideline presents a set of drugs that have proven effective in the prophylaxis and treatment of COVID-19 following the principles of evidence-based medicine, emphasising the strong recommendation for the use of nirmatrelvir/ritonavir in outpatients. Evidence has shown the lack of benefit of hydroxychloroquine and ivermectin, contraindicating their use in both outpatient and inpatient settings. It is strongly advised that these recommendations be adopted in the Americas to optimise the use of health resources and reduce the heterogeneity of procedures.

Abbreviations

API	Pan-American Association of Infectious Diseases
CI	confidence interval
COVID-19	coronavirus disease 2019
EtD	Evidence to Decision
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IDSA	Infectious Diseases Society of America
PAHO	Pan-American Health Organization
PICO	patients, intervention, comparator, and outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomised controlled trial
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBI	Brazilian Society of Infectious Diseases
WHO	World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is within the manuscript and its additional file.

Competing interests

MF received consulting fees related to COVID-19 from Pfizer and MSD outside the context of the present study. AJRM, CP, DL, GZ, JCF, MT, SMP, ST, and WMB have no direct financial interests.

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Authors' contributions

SMP, ST, and WMB were involved in the evidence search and synthesis. ANB, AC, SC and AJRM made up the guideline coordination. AC, AJRM, ANB, CAC, CP, CS, DL, EPN, GZ, JC, JCF, MMGS, MT, SC, and ST were panel members. ANB, MF and SMP were involved to manuscript writing. All authors read and approved the final manuscript.

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Figures

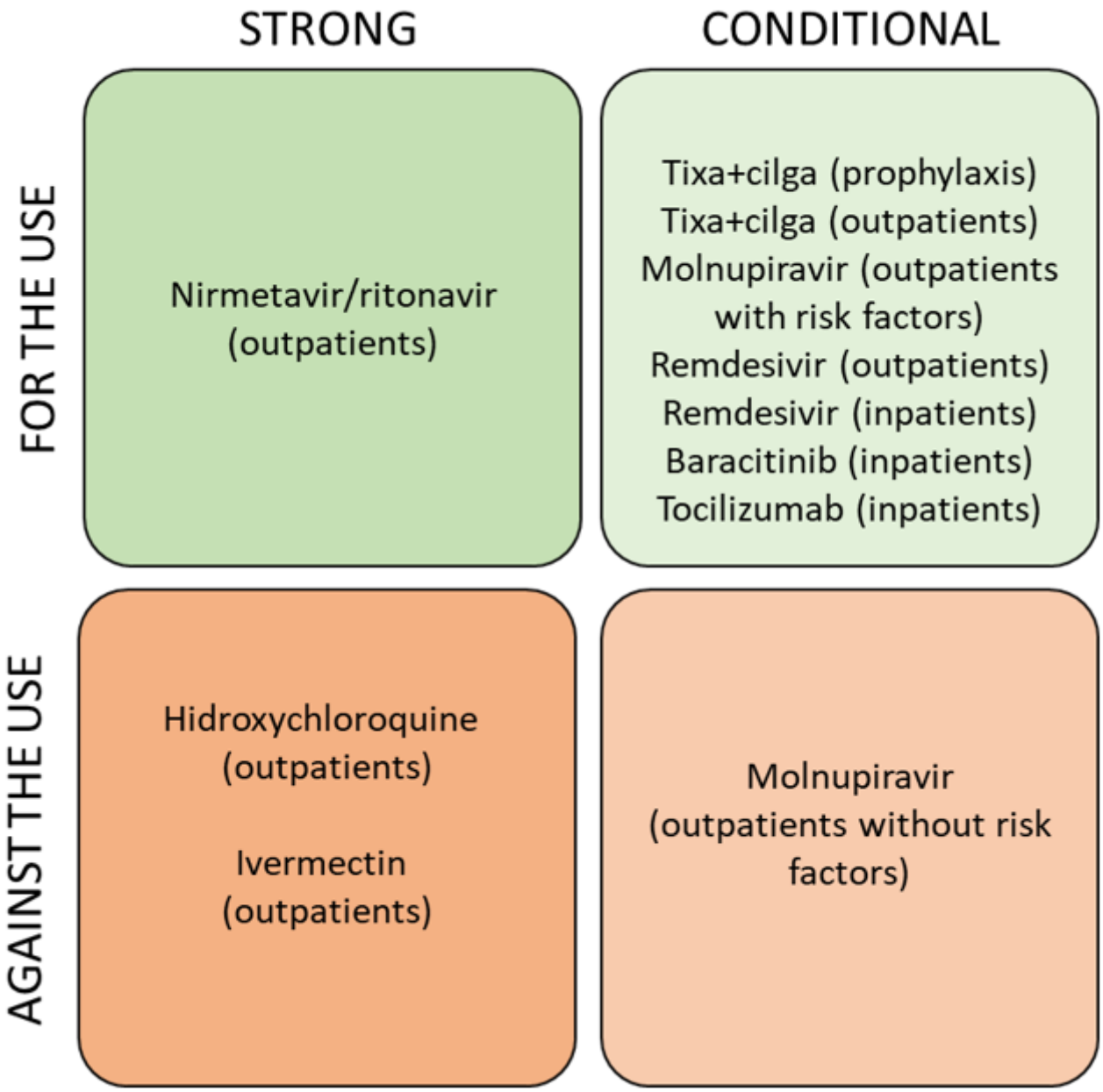

Figure 1

Summary of recommendations for the pharmacological treatment of COVID-19.

Tixa+cilga stands for tixagevimab + cilgavimab

Source: manuscript' authors.

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