NATIONAL INSTITUTE OF HEALTH (USA)

COVID-19 Treatment Guidelines

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ENFERMEDAD POR CORONAVIRUS 2019 (COVID-19) GUÍAS DE TRATAMIENTO

NATIONAL INSTITUTE OF HEALTH
Campus Bethesda
MARYLAND (EEUU).

Composición del Panel

Los miembros del Panel ***Guías de tratamiento COVID-19*** (Panel) fueron elegidos en base a su experiencia clínica y experiencia en manejo de pacientes , ciencias clínicas y medicina translacional; por experiencia previa en el desarrollo de guías de tratamiento. Entre los miembros del Panel se incluye a representantes de agencias federales, organizaciones de salud y académicas y sociedades profesionales. Las agencias federales y sociedades profesionales representados en el Panel son las siguientes:

- American College of Chest Physicians
- American College of Emergency Physicians
- American Society of Hematology
- American Thoracic Society
- Biomedical Advanced Research and Development Authority
- Centers for Disease Control and Prevention
- Department of Defense
- Department of Veterans Affairs
- Food and Drug Administration
- Infectious Diseases Society of America
- National Institutes of Health
- Pediatric Infectious Diseases Society
- Society of Critical Care Medicine
- Society of Infectious Diseases Pharmacists.

Método de sintesis de datos y formulación de recomendaciones

Los grupos de trabajo revisan críticamente los antecedentes y datos disponibles y los sintetizan para desarrollar las recomendaciones.
Los aspectos de los datos que son considerados incluyen , pero no son limitados a tipos de estudios, (ej. Series de casos, cohorte prospectiva, ensayo controlado randomizado) la calidad y adecuado del los métodos, número de participantes , y la magnitud de los efectos observados. A cada recomendación se le asignan dos categorías de acuerdo al esquema presentado en la Tabla 1.

Tabla 1. Esquema de Puntuación de la Recomendación

POTENCIA DE RECOMENDACIÓN	CALIDAD DE EVIDENCIA DE LA RECOMENDACIÓN
A: Fuerte recomendación para la indicación. B: Moderada recomendación para la indicación. C : Optativa recomendación para la indicación	I: Uno o más ensayos randomizados con resultados clínicos y/o endpoints validados en laboratorio. II: Uno o más ensayos no randomizados, bien diseñados o estudios observacionales de cohortes. III: Opinión de expertos

Tabla 2a Potenciales agentes virales bajo evaluación para el tratamiento de COVID-19: Datos clínicos a la fecha

Última actualización 12 de mayo, 2020.

La información presentada en esta tabla puede incluír datos obtenidos de artículos pre-impresos o de artículos no revisados por pares.
Esta Tabla será actualizada tan pronto haya nueva información.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Azithromycin **Note:** Studies on COVID-19 use AZM with HCQ.	• Mycobacterial (nontuberculous) infection • STIs and various bacterial infections[1]	**Proposed Antiviral Effects:** • Induction of IFN-stimulated genes, attenuating viral replication[2] **Immunomodulatory Effect:** • Enhanced neutrophil activation[3] **Anti-Inflammatory Effects:** • Attenuation of inflammatory cytokines (IL-6 and IL-8) in epithelial cells and inhibition of fibroblast growth factor in airway smooth muscle cells[2]	• AZM is studied for treatment of COVID-19 only in combination with HCQ. • Please see the description of study results in the Hydroxychloroquine plus Azithromycin section below and in Therapeutic Options for COVID-19 Currently Under Investigation.

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)

Chloroquine	• Malaria
	• Extra-intestinal amebiasis
		• *In vitro* antiviral activity by increasing the pH of intracellular vacuoles and altering protein degradation pathways, thereby interfering with the virus/cell fusion and glycosylation of cellular receptors[4,5]
		• Inhibits glycosylation of the cellular ACE2 receptor, which may interfere with the binding of the virus to the cell receptor[6]
		• Immunomodulatory effects may lead to a reduction in pro-inflammatory cytokines[5]
			High-Dose vs. Low-Dose CQ[7]
			• A randomized, double-blind, Phase 2b study compared two different CQ regimens, CQ 600 mg twice daily for 10 days (high dose) versus CQ 450 mg twice daily for 1 day followed by 450 mg for 4 days (low dose), in hospitalized adults with suspected severe COVID-19 (respiratory rate >24, heart rate >125, oxygen saturation <90%, and/or shock). All patients received ceftriaxone plus AZM; 89.6% of patients received oseltamivir. Of note, both AZM and oseltamivir can increase the QTc interval.
			• The primary outcome for this analysis was mortality at 13 days after treatment initiation. The planned study sample size was 440 participants, which was sufficient to show a reduction in mortality by 50% with high-dose CQ. The study was stopped by the study's DSMB after 81 patients were enrolled into the study.
			• *Results:*
			  • 41 and 40 patients were randomized into the high-dose and low-dose CQ arms, respectively.
			  • The overall fatality rate was 27.2%.
			  • Mortality by Day 13 was higher in the high-dose arm than in the low-dose arm (death in 16 of 41 patients [39%] vs. in 6 of 40 patients [15%], respectively; $P = 0.03$). This difference was no longer significant when controlled by age (OR 2.8: 95% CI, 0.9–8.5).
			  • Overall, QTcF >500 ms occurred more frequently among patients in the high-dose arm (18.9% of patients) than in the low-dose arm (11.1% of patients). Among those with confirmed COVID-19, QTcF >500 ms was also more frequent in the high-dose arm (24.1% of patients) than in the low-dose arm (3.6% of patients).
			  • Two patients in the high-dose arm experienced ventricular tachycardia before death.
			• *Limitations:* More older patients and more patients with history of heart disease were randomized to the high-dose arm than to the low-dose arm.
			• *Interpretation:* Despite the small number of patients enrolled, this study raises concern for increased mortality with high-dose CQ (600 mg twice daily) in combination with AZM and oseltamivir.
			CQ vs. LPV/r[8]
			• In a small randomized controlled trial in China, 22 hospitalized patients with COVID-19 (none critically ill) were randomized to CQ 500 mg twice daily or LPV/r 400 mg/100 mg twice daily for 10 days. Patients with a history of heart disease (chronic disease and history of arrhythmia), or kidney, liver, or hematologic diseases were excluded from participation. Primary study outcome was SARS-CoV-2 PCR negativity at Days 10 and 14. Secondary outcomes included improvement of lung CT scan at Days 10 and 14, discharge at Day 14, and clinical recovery at Day 10, as well as safety determined by evaluation of study drug-related AEs.

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Chloroquine, continued			• *Results*: • Ten patients received CQ and 12 patients received LPV/r. At baseline, patients had good SpO_2 levels (97% to 98%). • Compared to the LPV/r-treated patients, the CQ-treated patients had a shorter duration from symptom onset to initiation of treatment (2.5 days on CQ vs. 6.5 days on LPV/r, P < 0.001). • Though not statistically significant, patients in the chloroquine arm were younger (median age 41.5 years vs. 53.0 years for CQ and LPV/r arms, respectively; *P* = 0.09). Few patients had comorbidities. • At Day 10, 90% of the CQ-treated patients and 75% of the LPV/r-treated patients had negative SARS-CoV-2 PCR. At Day 14, the percentages for the CQ-treated patients and the LPV/r-treated patients were 100% and 91.2%, respectively. • At Day 10, 20% of the CQ-treated patients and 8.3% of the LPV/r-treated patients had CT scan improvement. At Day 14, the percentages for the CQ-treated patients and the LPV/r-treated patients were 100% and 75%, respectively. • At Day 14, 100% of the CQ-treated patients and 50% of the LPV/r-treated patients were discharged from the hospital. • The risk ratios of these outcome data cross 1, and the results were not statistically significant. • Both drugs were generally well-tolerated. • *Limitations:* • The trial sample size was very small, and the participants were fairly young. • The CQ-treated patients were younger and had fewer symptoms prior to treatment initiation, which are variables that could have affected the study protocol-defined outcomes. • Patients with chronic comorbidities and critically ill patients were excluded from the study. • *Interpretation:* No significant benefit of CQ, but the study was too small to draw conclusions.
Hydroxychloroquine	• Lupus erythematosus • Malaria • Rheumatoid arthritis[9]	• *In vitro* antiviral activity by increasing the pH of intracellular vacuoles and altering protein degradation pathways, thereby interfering with the virus/cell fusion and glycosylation of cellular receptors[4,5] • Immunomodulatory effects may lead to a reduction in pro-inflammatory cytokines.[5]	**Retrospective Observational Cohort from the United States Veterans Health Administration** (*This study has not been peer reviewed.*)[10] • An observational, retrospective cohort study analyzed data from patients hospitalized at the United States Veterans Health Administration medical centers between March 9, 2020, and April 11, 2020, with confirmed COVID-19. Patients were categorized as having received either HCQ, HCQ plus AZM, or no HCQ. Doses and duration of use of HCQ or AZM were not specified. All patients also received standard supportive management for COVID-19. The primary endpoints were death and the need for mechanical ventilation. Associations between treatment and outcomes were determined using propensity score adjustment including demographic, comorbid, and clinical data (including predictors of COVID-19 disease severity). Patients were included in the analysis if body mass index, vital signs, and discharge disposition were noted in their medical records.

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine, continued	• Lupus erythematosus • Malaria • Rheumatoid arthritis[9]	• *In vitro* antiviral activity by increasing the pH of intracellular vacuoles and altering protein degradation pathways, thereby interfering with the virus/cell fusion and glycosylation of cellular receptors[4,5] • Immunomodulatory effects may lead to a reduction in pro-inflammatory cytokines.[5]	• *Results:* • 368 patients were eligible for analysis; they were treated with HCQ (n=97), HCQ plus AZM (n=113), or no HCQ (n=158). The median age for the patients in each group was 70, 68, and 69 years, respectively. All patients were male. • 70 patients died; 35 of those who died (50%) were not receiving mechanical ventilation . • No difference was observed between the groups in the risk of mechanical ventilation. • Compared to the no HCQ group, the risk of death from any cause was higher in the HCQ group (adjusted HR: 2.61; 95% CI, 1.10–6.17; $P = 0.03$), but not in the HCQ plus AZM group (adjusted HR: 1.14; 95% CI, 0.56–2.32, $P = 0.72$). • There was no between-group difference in the risk of death after ventilation. • *Limitations:* • All male patient population. • The dose and duration of administration of HCQ and AZM are not clarified. Patients were included if they received a single dose of either or both drugs. • Propensity score adjustment was used to account for differences between the groups, but the possibility of residual confounding cannot be excluded as patients who were more ill may have been more likely to receive HCQ. • No imaging data were presented; severity of chest X-ray findings could predict worse outcomes. • Use of other antiviral or immune modulatory agents were not reported. • The reason for the high mortality in patients who did not receive mechanical ventilation is not clear, especially as most of these patients appear to have had mild/moderate disease on admission. • *Interpretation:* This study showed no beneficial effect of HCQ plus AZM and a possible association of HCQ with increased mortality; however, residual confounding may have affected the study results. **Randomized, Controlled Trial of HCQ vs. SOC** (*This study has not been peer reviewed.*)[11] • This multicenter, randomized, open-label trial compared HCQ 1,200 mg once daily for 3 days followed by HCQ 800 mg once daily for the rest of the treatment duration (2 weeks for patients with mild/moderate COVID-19 [99%] and 3 weeks for one patient with severe disease) versus SOC. • The primary outcome was negative PCR within 28 days. Secondary outcomes were alleviation of symptoms (resolution of fever, $SpO_2 > 94\%$ on room air, resolution of respiratory symptoms) and improvement of markers of inflammation (including CRP) and chest X-ray within 28 days. Secondary outcomes for severe cases included all-cause mortality, clinical status, days of mechanical ventilation, ECMO, supplemental oxygenation, and hospital stay.

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine, continued			• *Results:* • 75 patients were enrolled in each study arm. Patients were randomized at a mean of 16.6 days after symptom onset. • No difference was found between the HCQ and SOC arms in negative PCR conversion rate within 28 days (85.4% vs.81.3% of participants, respectively) or in time to negative conversion (median 8 vs. 7 days, respectively). • There was no difference in negative conversion rate by age, body mass index, comorbid conditions, days between symptom onset and randomization, or other conditions analyzed. • There was no between-group difference in rate of symptom alleviation in the intention-to-treat analysis. • There was more rapid normalization of CRP and lymphocytopenia in the HCQ group. • AEs: 30% of participants in the HCQ arm (most commonly diarrhea) versus 8.8% of participants in the SOC arm. • *Limitations:* • The definition of SOC and use of concomitant medications (two patients received AZM) were not clearly stated. • It is unclear how the overall rate of symptom alleviation was calculated. • The duration of HCQ use (2 weeks) was longer than in most other observational cohort or clinical trials for the treatment of COVID-19. • The authors note that HCQ was associated with increased alleviation of symptoms (HR 8.83; 95% CI, 1.09-71.3), but this was only in post-hoc subgroup analysis excluding patients on other antivirals. • *Interpretation:* This study demonstrated no difference in viral clearance between HCQ and SOC. **Observational Cohort of HCQ vs. No HCQ** (*This study has not been peer reviewed.*)[12] • This observational, retrospective cohort study analyzed data for adult patients hospitalized for COVID-19 pneumonia at four French tertiary care centers over a 2-week period (March 17–31, 2020). Patients were eligible if they required oxygen by mask or nasal cannula. Patients were excluded if they were immediately admitted to the ICU or admitted with ARDS (requiring non-invasive ventilation or mechanical ventilation). The treatment arms compared were initiation of HCQ at a daily dose of 600 mg within 48 hours of admission and the absence of HCQ during the same period. The primary outcome was a composite of transfer to the ICU within 7 days of enrollment and/or death from any cause. An inverse probability of treatment weighting approach was used to "emulate" randomization.

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine, continued			• *Results:* • 181 patients were eligible for the analysis: 84 patients received HCQ and 97 did not. • Comorbidities were less common in the HCQ group; overall initial COVID-19 severity was well balanced across the treatment arms. • In the HCQ group, 20% of the patients received concomitant AZM and 76% received amoxicillin/clavulanic acid. • In the inverse probability of treatment weighting analysis there was no difference in the composite outcome between the HCQ group (20.5%) and the non-HCQ group (22.1%). Similarly, there was no difference in the secondary outcomes of all-cause mortality and development of ARDS. • Among the 84 patients receiving HCQ, eight patients (9.5%) experienced ECG changes requiring treatment discontinuation at a median of 4 days from start of dosing, including seven patients with a QTc that prolonged >60 ms and one patient with new onset first-degree AV block. • *Limitations:* • This was a retrospective, non-randomized study. • The number of patients with QTc prolongation who received HCQ versus HCQ plus AZM (20% of all patients) was not reported. • *Interpretation:* In this retrospective study, there was no difference in clinically important outcomes between patients who received HCQ within 48 hours of hospital admission and those who did not. **Randomized Controlled Trial of HCQ Plus Standard Treatment vs. Standard Treatment Alone** (*This study has not been peer reviewed.*)[13] • In a randomized controlled trial in China, 62 hospitalized patients with mild (SaO_2/SpO_2 ratio > 93% or PaO_2/FIO_2 ratio >300 mm Hg) CT-confirmed COVID-19 pneumonia were randomized to HCQ 200 mg twice daily for 5 days plus standard treatment or to standard treatment only. Standard treatment included oxygen therapy, antiviral and antibacterial therapy, and immunoglobin, with or without corticosteroids. • *Results:* • Compared to the control patients, the HCQ-treated patients had a 1 day-shorter mean duration of fever (2.2 days vs. 3.2 days) and cough (2.0 days vs. 3.1 days). • 13% of the control patients and none of the HCQ-treated patients experienced progression of illness. • 80.6% of HCQ-treated patients and 54.8% of control patients experienced either moderate or significant improvement in chest CT scan. • AEs (1 rash, 1 headache) occurred among two of the HCQ-treated patients (6.4%); none occurred among the control patients.

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)

Hydroxychloroquine, continued			• *Limitations:*
			  • The trial had a small sample size and short follow-up.
			  • Standard treatment is complex and not well defined.
			  • The presence and distribution of associated comorbidities (e.g., HTN, DM, lung disease) was not reported.
			  • There was no indication that radiologists were blinded to the treatment status of the patients, which could have biased determination of the chest CT outcome.
			• *Interpretation:* The methodological limitations of this study preclude determination of efficacy for HCQ.
			A Case Series of HCQ vs. Control[14]
			• In a case series from France, 26 hospitalized adults with SARS-CoV-2 infection categorized as asymptomatic or with upper or lower respiratory tract infection who received HCQ 200 mg three times daily for 10 days were compared to 16 control individuals (i.e., who refused treatment, did not meet eligibility criteria, or were from a different clinic).
			• *Results:*
			  • Six patients in the HCQ group were excluded from the analysis for the following reasons:
			  • One died.
			  • Three were transferred to the ICU.
			  • One stopped the study drug due to nausea.
			  • One withdrew from the study.
			  • Six patients also received AZM.
			  • By Day 6, NP PCRs were negative in 14 of 20 HCQ-treated patients (70%) and two of 16 controls (12.5%).
			  • Among the HCQ patients, eight of 14 (57.1%) who received only HCQ and six of six (100%) who received HCQ and AZM had negative NP PCRs by Day 6.
			  • Clinical outcomes for all patients were not reported.
			• *Limitations:* There are several methodologic concerns with this case series:
			  • The small sample size of the series.
			  • The criteria for enrollment of cases and controls is unclear.
			  • Asymptomatic individuals were enrolled.
			  • Exclusion of six HCQ-treated patients includes one death and three ICU transfers.
			  • No clinical outcomes were reported; thus, the clinical significance of a negative PCR is unknown.

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine, continued			• The reason for the addition of AZM for some patients is unclear. • *Interpretation:* Methodologic problems with this case series limit the ability to draw conclusions regarding the efficacy of HCQ with or without AZM.
Hydroxychloroquine plus Azithromycin	See the Azithromycin plus Hydroxychloroquine section above.	See the Azithromycin plus Hydroxychloroquine section above.	**Case Series of HCQ Plus AZM**[15] • In a case series of 80 hospitalized patients with COVID-19 (including six patients from a previous study),[16] patients were treated with HCQ 200 mg three times daily for 10 days plus AZM 500 mg for 1 day followed by 250 mg once daily for 4 days. Mean time from symptom onset to treatment was about 5 days. Outcomes evaluated included the need for oxygen therapy or ICU transfer after ≥3 days of therapy, SARS-CoV-2 level by PCR, SARS-CoV-2 culture (in a subset of patients; a convenience sample), and length of stay in the infectious diseases ward. • *Clinical Results:* • One patient died (1.2%), three required ICU transfer (3.8%), and 12 required oxygen therapy (15%). • 65 patients (81.2%) were discharged to home or transferred to other units for continuing treatment; 14 patients (17.4%) remained hospitalized at the time the study results were published. • *Laboratory Results:* • NP SARS-CoV-2 PCR was negative in 83% of patients by Day 7 and in 93% of patients by Day 8. • In the subset of patients who had respiratory sample viral cultures performed at Day 5, results were negative for 97.5% of the samples. • *Limitations:* • The trial's lack of a control group, which is particularly important because many people with mild disease improve in the absence of treatment. • The definition of "discharge" varied. • The lack of complete or longer-term follow-up. • *Interpretation:* The multiple issues with trial design and lack of a comparison group limit the usefulness of this study to inform recommendations. **Small Prospective Case Series of HCQ Plus AZM**[17] • A prospective case series from France assessed eleven consecutive hospitalized patients with COVID-19. • *Results:* • Eight of the 11 patients had significant co-morbid conditions: obesity (2), solid cancer (3), hematological cancer (2), and HIV infection (1).

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine plus Azithromycin, continued			• Ten of 11 patients were receiving supplemental oxygen upon treatment initiation. • All patients were treated with HCQ 600 mg once daily for 10 days and AZM 500 mg once daily for 1 day followed by 250 mg once daily for 4 days. • Within 5 days, the condition of three patients worsened, including one patient who died and two patients who were transferred to the ICU. • AEs: HCQ was discontinued in one patient due to QTc prolongation. • Qualitative NP PCR remained positive at Days 5 and 6 after treatment initiation in eight of 10 patients. • *Limitations:* This is a case series that included few patients. • *Interpretation:* In this small case series, most patients who received HCQ plus AZM did not have rapid viral clearance. **Case Series of Changes in QTc Interval in Patients Who Received HCQ Plus AZM**[18] • A case series in the United States reported changes in QTc interval in 84 patients with COVID-19 who received the combination of HCQ (400 mg twice daily for 1 day, followed by 200 mg twice daily for 4 days) and AZM (500 mg once daily for 5 days). • *Results:* • 84 patients, 74% male, mean age 63 ± 15 years, 65% had HTN, mean serum creatinine 1.4 mg/dL at baseline, 13% required vasopressors, 11% had CAD. • Concomitant drugs that may prolong QTc interval: 11% of participants on neuropsychiatric drugs and 8% of participants received levofloxacin, lopinavir/ritonavir or tacrolimus. • Four patients died, without arrhythmia. • Mean baseline QTc was 435 ± 24 ms, mean maximum QTc was 463 ± 32 ms. • Mean time to maximum QTc was 3.6 ± 1.6 days, ECG follow-up was done for a mean of 4.3 days. • Nine patients (11%) developed QTc >500 ms; the QTc increased by 40 to 60 ms and >60 ms in 18% and 12% of patients, respectively. • *Limitations:* • Case series, descriptive • *Interpretation:* This case series demonstrates that HCQ and AZM in combination can prolong QTc and that use of the combination warrants careful monitoring.

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)

HIV Protease Inhibitors
Note: LPV/r and DRV/c have been studied in patients with COVID-19.
	• HIV Infection	• No data on *in vitro* activity of LPV/r against SARS-CoV-2
		• Possible inhibition of SARS-CoV-2 protease 3CLpro[19]
		• *In vitro* data does not support the use of DRV/c for the treatment of COVID-19.[20]
			Randomized Controlled Trial of LPV/r vs. SOC
			In a clinical trial that randomized 199 patients to LPV/r 400 mg/100 mg PO twice daily for 14 days or to SOC, patients randomized to the LPV/r arm did not have a shorter time to clinical improvement.
			• *Results:*
			  • There was a lower, but not statistically significant, mortality rate for those on LPV/r (19.2%) versus on SOC (25.0%) and shorter ICU stay for those given LPV/r compared to those given SOC (6 days vs. 11 days; difference = -5 days; 95% CI, -9 to 0).
			  • The duration of hospital stays and time to clearance of viral RNA from respiratory tract samples did not differ between the LPV/r and SOC arms.
			  • Nausea, vomiting, and diarrhea were all more frequent in the LPV/r-treated group.
			  • The study was powered only to show a fairly large effect.
			• *Limitations:*
			  • The study was not blinded, which may have affected the assessments of clinical improvement.
			  • The study was underpowered to show small effects.
			• *Interpretation:* A moderate-sized randomized trial failed to find a virologic or clinical benefit of LPV/r over SOC.
			LPV/r vs. Arbidol vs. SOC[21] (*This study has not been peer reviewed.*)
			• In a trial of 86 hospitalized patients with mild-to-moderate COVID-19, 34 patients were randomized to LPV/r, 35 patients to the broad-spectrum antiviral Arbidol (available in Russia), and 17 patients to SOC.
			• *Results* (comparison of LPV/r to SOC):
			  • The time to a negative SARS-CoV-2 nucleic acid pharyngeal swab was similar for patients receiving LPV/r (mean 9 days [SD 5.0]) and for those receiving SOC (mean 9.3 days [SD 5.2]).
			  • Progression to severe/critical status occurred among eight (24%) patients receiving LPV/r and two patients (12%) on SOC.
			• *Limitations:*
			  • Small sample size.
			  • The effectiveness of Arbidol in treating COVID-19 is unknown.
			• *Interpretation:* The small sample size limits the usefulness of this trial.
			LPV/r vs. CQ
			A small randomized study in China compared LPV/r to CQ. Please refer to the CQ section for the study description.

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)

Remdesivir (GS-5734)	• Not approved by FDA
	• Investigational antiviral agent
		• Adenosine nucleotide analog prodrug that undergoes hydrolysis to its active form, which inhibits viral RNA-dependent RNA polymerase[22]
		• Potent *in vitro* activity demonstrated in SARS-CoV-2-infected Vero E6 cells[23]
		• In a rhesus macaque model of SARS-CoV-2 infection, animals who were started on RDV soon after inoculation had lower lung virus levels and less lung damage than control animals.[24]
			Multinational Randomized Controlled Trial of RDV vs. Placebo in Hospitalized Patients (*These data have not been peer reviewed.*)
			• The Adaptive COVID-19 Treatment Trial (ACTT) is an NIH-sponsored international, randomized, double-blind trial of RDV versus placebo (1:1 randomization ratio) in hospitalized adult patients (aged ≥18 years) with laboratory confirmed COVID-19 who have at least one of the following clinical manifestations: pulmonary infiltrates by radiographic imaging, $SpO_2 \leq 94\%$ on ambient air, or require supplemental oxygen or mechanical ventilation. The study excluded people with ALT or AST level >5 times ULN or eGFR <30 ml/min, and people who were pregnant or breastfeeding. The primary study endpoint was time to recovery. Preliminary data were released on April 29, 2020, after an interim review by the study's DSMB. 1,063 participants enrolled into the study. Participants who received RDV had a 31% faster time to recovery than those who received placebo (median recovery time of 11 days vs 15 days, respectively; HR 1.31; 95% CI, 1.12 to 1.54, $P < 0.001$).[25] The results also showed a mortality rate of 8.0% versus 11.6% for the RDV and placebo groups, respectively ($P = 0.059$). Additional results (including analyses of important patient subgroups) are expected soon.[26]
			• *Limitations:* Only the preliminary analysis is available after the DSMB review. A full report of study results is still forthcoming.
			• *Interpretation:* First randomized, double-blinded, fully powered study to demonstrate the clinical benefit of a pharmacological treatment for COVID-19.
			Randomized Controlled Trial of RDV vs. Placebo for Severe COVID-19 in China[27]
			• Multicenter, double-blind, randomized, placebo-controlled trial in patients with severe COVID-19 in China. Patients were randomized 2:1 to IV RDV or normal saline placebo for 10 days. Concomitant use of LPV/r, corticosteroids, and interferons were allowed. The primary study endpoint was time to clinical improvement, defined as improvement on an ordinal scale or discharged alive from the hospital, whichever came first. The planned sample size was 453 patients.
			• Participant population: Hospitalized adults with laboratory confirmed COVID-19, symptom onset to randomization <12 days, O_2 saturation ≤ 94% on room air, or PaO_2/FiO_2 <300 mmHg, with radiographically confirmed pneumonia.
			• *Results:* Between February 6, 2020, and March 12, 2020, 237 hospitalized patients were enrolled and randomized to RDV (n = 158) or placebo (n = 79). The study was stopped before target enrollment was reached due to control of the COVID-19 outbreak in China.
			  • The participants' median age was 65 years, and 56% of the participants in the RDV arm and 65% in the placebo arm were male.
			  • There were more patients with HTN, DM, or CAD in the RDV arm than in the placebo arm.

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Remdesivir, continued (GS-5734)			• At Day 1, 83% of the patients required supplemental oxygen by nasal cannula or mask; only one patient required mechanical ventilation or ECMO. • Median time from symptom onset to randomization was 9 days in the RDV group and 10 days in the placebo group. • 65% of the patients in the RDV group and 68% of patients in the placebo group received corticosteroids. • 28% to 29% of participants in each arm received LPV/r. • 29% of participants in the RDV arm, and 38% of participants in the placebo arm received interferon alfa 2b. • *Study endpoints:* • There was no difference in the time to clinical improvement: a median of 21 days in RDV group versus 23 days in placebo group (HR 1.23; 95% CI, 0.87-1.75). • Though not statistically significant, for patients who started RDV or placebo within 10 days of symptom onset, faster time to clinical improvement was seen in the RDV arm than in the placebo arm (median of 18 days vs. 23 days, respectively [HR 1.52; 95% CI, 0.95-2.43]). • 28-day mortality was similar in the two arms: 14% of participants in RDV arm versus 13% in placebo arm. • There was no difference in SARS-CoV-2 viral load at baseline; the rate of decline over time was similar between the two groups. • The number of participants who had AEs was similar between the two groups (66% in RDV arm and 64% in placebo arm). • More participants in the RDV arm discontinued therapy due to AEs (12% in RDV group vs. 5% in placebo group). • *Limitations:* • The study was terminated early; as a result, the sample size did not have sufficient power to detect differences in clinical outcomes. • Use of concomitant medications (corticosteroids, LPV/r, interferon) may have obscured effects of RDV. • *Interpretation:* There was no difference in time to clinical improvement, 28-day mortality, or rate of viral clearance between RDV-treated and placebo-treated patients. The study was terminated early; consequently, the study sample size was too small to detect differences in clinical outcomes. **Uncontrolled Case Series from RDV Compassionate Use Program** • In an uncontrolled case series of 53 hospitalized patients with COVID-19, most patients needed less oxygen support after receiving compassionate use RDV. There was no comparison group, however, so it is not possible to assess whether the use of RDV led to the improvement.[28]

CLAVES:
ACE2 = angiotensin-converting enzyme 2; AE = adverse effect; ALT = alanine transaminase; ARDS = acute respiratory distress syndrome; AST = aspartate transaminase; AV = atrioventricular; AZM = azithromycin; CAD = coronary artery disease; CI = confidence interval; COVID-19 = coronavirus disease 2019; CQ = chloroquine; CRP = C-reactive protein; CT = computerized tomography; DM = diabetes; DRV/c = darunavir/cobicistat; DSMB = data safety monitoring board; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; eGFR = glomerular filtration rate; FDA = Food and Drug Administration; HR = hazard ratio; HTN = hypertension; ICU = intensive care unit; IFN = interferon; IL = interleukin; IV = intravenous; HCQ = hydroxychloroquine; LPV/r = lopinavir/ritonavir; NIH = National Institutes of Health; NP = nasopharyngeal; OR = odds ratio; PCR = polymerase chain reaction; PO = orally; RDV = remdesivir; QTcF = corrected QT interval by Fredericia; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; SOC = standard of care; STI = sexually transmitted infection; ULN = upper limit of normal

Tabla 2b Características de potenciales agentes virales bajo evaluación para el tratamiento de COVID-19

Última actualización 12 de mayo, 2020.

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Azithromycin (When Used with Hydroxychloroquine)	500 mg PO once on Day 1, then 250 mg PO daily on Days 2–5	Gastrointestinal effects (e.g., diarrhea, nausea, vomiting) Hepatotoxicity	Baseline/follow- up ECG Hepatic panel, SCr, potassium, magnesium	Additive effect with other drugs that prolong the QTc interval (including HCQ and CQ	The Panel **recommends against** the use of HCQ plus AZM for the treatment of COVID-19 except in a clinical trial setting **(AIII)**. Half-life of up to 72 hours A list of clinical trials is available here: Azithromycin

Recomendación: El Panel se manifiesta en contra del uso de HCQ +AZM para el tratamiento del COVID-19, excepto en el desarrollo de ensayos clínicos (AIII) .
Vida media sobre 72 horas.
Una lista de ensayos clínicos está disponible en
https://clinicaltrials.gov/ct2/results?term=azithromycin%2C+covid-19

Tabla 2b Características de potenciales agentes virales bajo evaluación para el tratamiento de COVID-19

Última actualización 12 de mayo, 2020.

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Chloroquine	**Suggested Dose in EUA[a] for Adults/ Adolescents Weighing ≥50 kg:** • 1 gm PO once on Day 1, then 500 mg PO once daily for 4–7 days of total treatment based on clinical evaluation. **Per EUA:** • Some experts recommend a dose reduction of 50% for GFR <10 mL/min, hemodialysis, or peritoneal dialysis; no dose reduction is recommended for GFR >10 mL/min.	Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia Gastrointestinal effects (e.g., nausea, vomiting, diarrhea, hepatitis) Hypoglycemia Hemolysis (especially if G6PD deficient) Myopathy Rash Given the risk of heart rhythm problems, the FDA cautions against the use of CQ for COVID-19 outside the setting of a hospital or clinical trial.[1]	CBC, hepatic panel, blood glucose, SCr, potassium, magnesium Baseline/follow-up ECG if given with concomitant QTc-prolonging drugs or if underlying cardiac disease Perform G6PD testing; CQ **is not recommended** in patients with G6PD deficiency. Consider using HCQ instead of CQ while awaiting G6PD result.	Additive effect with other drugs that prolong the QTc interval (including AZM or cause hypoglycemia CYP2D6 inhibitor (moderate) P-gp inhibitor	There are insufficient data for the Panel to recommend for or against the use of CQ or the treatment of COVID-19 **(AIII)**. The Panel **recommends against** using high-dose CQ (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**. CQ is available through an EUA for hospitalized patients with COVID-19 who cannot access the drug via a clinical trial. Dose-dependent toxicity A list of clinical trials is available here: Chloroquine

El Panel manifiesta que los datos existentes son insuficientes para pronunciarse a favor o en contra del uso de Cloroquina (CQ) o Hidroxicloroquina (HCQ) en el tratamiento de COVID-19 (AIII). Se manifiesta en contra del uso de alta dosis de CQ, 600mg 2 veces /día para tratar COVID-19 (AI).

Tabla 2b Características de potenciales agentes virales bajo evaluación para el tratamiento de COVID-19

Última actualización 12 de mayo, 2020.

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Hydroxychloroquine	**Adults:** • Various loading and maintenance doses have been reported in studies or in clinical care. **Suggested Dose in EUA[a] for Hospitalized Adults/Adolescents Weighing ≥50 kg:** • 800 mg PO once on Day 1, then 400 mg PO once daily for 4–7 days of total treatment based on clinical evaluation. **Per EUA:** • Some experts recommend a dose reduction of 50% for GFR <10 mL/min, hemodialysis, or peritoneal dialysis; no dose reduction is recommended for GFR >10 mL/min **Infants, Children, and Adolescents** *Dose Options for Malaria Treatment:* • 13 mg/kg (maximum: 800 mg) PO followed by 6.5 mg/kg (maximum: 400 mg) PO at 6 hours, 24 hours, and 48 hours after initial dose; could extend for a total treatment duration of up to 5 days. • 6.5 mg/kg/dose (maximum: 400 mg/dose) PO BID on Day 1, followed by 3.25 mg/kg/dose (maximum: 200 mg/dose) PO BID for a total treatment duration of up to 5 days **Neonates:** • Dosing not established.	Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia Gastrointestinal effects (e.g., nausea, vomiting, diarrhea, hepatitis) Hypoglycemia Myopathy Anxiety, agitation, hallucinations, psychosis Allergic reaction/rash Given the risk of heart rhythm problems, the FDA cautions against the use of HCQ for COVID-19 outside the setting of a hospital or clinical trial.[1]	CBC, hepatic panel, blood glucose, SCr, potassium, magnesium Baseline ECG Follow-up ECG if given with concomitant QTc prolonging drugs (e.g., AZM) or if underlying cardiac diseases	Additive effect with other drugs that prolong the QTc interval (including AZM) or cause hypoglycemia CYP2D6 inhibitor (moderate) P-gp inhibitor	There are insufficient data for the Panel to recommend for or against the use of HCQ for the treatment of COVID-19 **(AIII)**. The Panel **recommends against** the use of HCQ plus AZM for the treatment of COVID-19 except in a clinical trial setting **(AIII)**. Available through EUA for hospitalized patients who cannot access HCQ via clinical trials. Long elimination; half-life is 40–55 days. Dose-dependent toxicity A list of clinical trials is available here: Hydroxychloroquine

El Panel manifiesta que los datos existentes son insuficientes para pronunciarse a favor o en contra del uso de Cloroquina (CQ) o Hidroxicloroquina (HCQ) en el tratamiento de COVID-19 (AIII). Se manifiesta en contra del uso de alta dosis de CQ, 600mg 2 veces /día para tratar COVID-19 (AI).

Tabla 2b Características de potenciales agentes virales bajo evaluación para el tratamiento de COVID-19

Última actualización 12 de mayo, 2020.

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Lopinavir/Ritonavir	**Adults:** • Lopinavir 400 mg/ritonavir 100 mg PO twice daily for 10–14 days **Neonates Aged ≥14 Days with a PMA ≥42 Weeks and Children Aged <18 Years:** • Lopinavir 300 mg/m² plus ritonavir 75 mg/m² (maximum: lopinavir 400 mg/ritonavir 100 mg per dose) PO twice daily for a total of 7 days	Nausea, vomiting, diarrhea Transaminase elevation QTc interval prolongation and Torsades de Pointes have been reported. PR interval prolongation	HIV antigen/antibody testing at baseline Serum transaminase levels Consider monitoring ECG when given with other QTc-prolonging medications.	**High Drug Interaction Potential** *Lopinavir:* • CYP3A4 inhibitor and substrate *Ritonavir:* • CYP3A4 > 2D6 substrate • Potent CYP3A4 and 2D6 inhibitor • Inducer of UGT1A1 and CYPs 1A2, 2C8, 2C9, and 2C19	The Panel **recommends against** the use of lopinavir/ritonavir and other HIV PIs for the treatment of COVID-19 except in a clinical trial setting **(AI)**. Liquid formulation commercially available. Crushing lopinavir/ritonavir tablets may result in significantly decreased drug exposure (AUC↓ 45%).[2] Use with caution in patients with hepatic impairment. A list of clinical trials is available here: Lopinavir/Ritonavir

El Panel se manifiesta en contra del uso de Lopinavir/Ritonavir y otras Fosfolipasas HIV para el tratamiento del COVID-19, excepto en estudios clínicos (AI).

Tabla 3a Terapia inmunológica bajo evaluación para el tratamiento del COVID-19. Datos clínicos a la fecha

Última actualización, 12 de mayo, 2020.
La información presentada en esta Tabla puede incluir datos de artículos antes de impresión, no revisados por pares. Esta Tabla será actualizada cuando esté disponible nueva información

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/ Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood Products			
COVID-19 Convalescent Plasma and SARS-CoV-2 Immune Globulins	Not approved by the FDA	Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2.[1] Similarly, SARS-CoV-2 immune globulin is a concentrated antibody preparation derived from the plasma of people who have recovered from COVID-19. Both products may help suppress the virus and modify the inflammatory response.	**For COVID-19:** • Data supporting the use of convalescent plasma for COVID-19 are limited to a small retrospective cohort study, small case series, and case reports. • There are no clinical data on the use of SARS-CoV-2 immune globulin or hyperimmune globulin in COVID-19. **For Other Viruses:** • The use of convalescent plasma has been evaluated in other respiratory virus outbreaks, including H1N1 influenza, SARS, andviral diseases (e.g., SARS), with some suggestion of potential benefit.[2-9] No convalescent blood products are currently licensed by the FDA. • There are no clinical data on the use of specific immune globulin or hyperimmune globulin in patients with SARS or MERS.
Non-SARS-CoV-2 Specific Intravenous Immune Globulin	Primary immune disorders Thrombocytopenic purpura Kawasaki disease Motor neuropathy Prophylaxis of various bacterial and viral diseases	Passive immunity; human immunoglobulin is derived from pooled plasma of blood donors and contains antibodies against a broad spectrum of pathogens. Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, products derived from the plasma of donors who were not confirmed to have had SARS-CoV-2 infection are not likely to contain SARS-CoV-2 antibodies.	**For COVID-19** • *Not Peer Reviewed:* A retrospective, nonrandomized cohort study of IVIG in eight treatment centers in China between December 2019 and March 2020 found no difference in 28-day or 60-day mortality between the 174 patients who were treated with IVIG and the 151 patients who were not treated with IVIG. Patients who received IVIG were hospitalized for longer (median of 24 days vs. 16 days) and experienced longer duration of disease (median of 31 days vs. 23 days). It should be noted that a higher proportion of IVIG-treated patients had severe disease at study entry (71 [41%] with critical status in the IVIG group vs. 32 [21%] in the non-IVIG group). A subgroup analysis that was

Los datos que soporten el uso de plasma convalecente para COVID-19 están limitados a un pequeño estudio retrospectivo de cohorte, pequeñas series de casos y reportes de casos. No hay datos clínicos para el uso de Inmunoglobulina de SARS-COV-2 o globulina hiperinmune en COVID-19.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/ Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood Products, continued			
Non-SARS-CoV-2 Specific Intravenous Immune Globulin, continued			limited to the critical patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days. The results are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive IVIG versus no IVIG, and the IVIG group was older, was more likely to have coronary heart disease, and had a higher proportion of patients with severe COVID-19 disease at study entry. Also, patients received numerous other concomitant therapies for COVID-19.[10]
Interferon Alfa and Interferon Beta			
Interferon Alfa	IFN alfa-2b: Leukemia, melanoma, lymphoma, condylomata acuminata, Kaposi sarcoma, hepatitis B, hepatitis C IFN alfa-1b is not available in the United States.	Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types[11-13]	No clinical data for COVID-19. **For MERS:**[14-17] • Retrospective studies with IFN alfa-2a, IFN alfa-2b, or IFN beta-1a in combination with ribavirin showed no clear benefit. • Ribavirin plus IFN alfa-2a survival rates: 30% to 100% in three small studies (n < 20)[18] • Ribavirin plus IFN alfa-2a or IFN alfa-2b: No significant improvement in clinical outcome or survival at 28 days.[19] • Ribavirin plus IFN beta-1a SQ: Retrospective analyses showed no significant effect on clinical outcome.[14] **Inhaled IFN beta-1a (SNG001):** • Phase 2 clinical trials showed improved lung function in asthma patients with respiratory infections.[20]
Interferon Beta	Multiple sclerosis (IFN beta-1a, IFN beta-1b)	Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types (T cell, B cell, and cytokine function)[11,21] Among IFN subtypes, IFN beta-1b shows greatest *in vitro* inhibition of MERS-CoV.[16,22] *In vitro* activity against MERS-CoV in lung cells.[20]	
Interleukin-1 Inhibitor			
Anakinra	Rheumatoid arthritis Cryopyrin-associated periodic syndromes[23]	Competitively inhibits IL-1 binding to the interleukin-1 type I receptor	No clinical data for COVID-19, SARS, or MERS

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/ Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Interleukin-6 Inhibitors Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in some patients with COVID-19; IL-6 inhibition may reduce these effects.			
Sarilumab	Rheumatoid arthritis[24]	Human recombinant monoclonal antibody IL-6 receptor antagonist[25]	**For COVID-19** • *Press Release:* A Phase 2/3 randomized clinical trial (NCT04315298) of hospitalized COVID-19 patients. Preliminary data were released after an independent DMC recommended discontinuing the 200-mg arm and restricting future enrollment to critical patients only. Of the first 457 participants enrolled, 145 were randomized to sarilumab 400 mg, 136 to sarilumab 200 mg, and 77 to placebo. At study entry, 28% had severe illness, 49% had critical illness, and 23% had multisystem organ dysfunction. Sarilumab decreased CRP, which changed by -79%, -77%, and -21% in the sarilumab 400 mg group, sarilumab 200 mg group, and placebo group, respectively (primary outcome of the Phase 2 trial). Of the 226 critical patients, 28% in the sarilumab 400 mg group had died or were on a ventilator at the time of data analysis, compared with 46% in the sarilumab 200 mg group and 55% in the placebo group. Comparing mortality alone, 23% of those in the sarilumab 400 mg group died, compared with 36% in the sarilumab 200 mg group and 27% in the placebo group. In contrast to positive outcomes among critical patients, the press release cited "negative trends" for most outcomes in severe patients.[26]
Siltuximab	Multicentric Castleman disease	Human-mouse chimeric monoclonal antibody IL-6 antagonist[27]	In a single-center observational study of 21 patients with COVID-19 who developed pneumonia/ARDS and received treatment with IV siltuximab, some patients experienced decreased CRP levels (16 of 21) and improved clinical condition following siltuximab (7 of 21). Other patients experienced no clinically relevant change in condition (9 of 21) or worsening condition (5 of 21). Of the five patients with worsening conditions, there was one death and one cerebrovascular event (median follow-up time of 8 days).

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/ Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on *ClinicalTrials.gov*)
Tocilizumab	Cytokine release syndrome (induced by CAR T-cell therapy) Rheumatoid arthritis Giant cell arteritis Polyarticular juvenile idiopathic arthritis Systemic juvenile idiopathic arthritis[28]	Recombinant humanized monoclonal antibody IL-6 receptor antagonist	**For COVID-19** • *Press Release:* Early results from the CORIMUNO-TOCI trial (NCT04331808); open-label randomized trial of hospitalized patients with COVID-19 (n = 129; seven sites in France) at moderate or severe disease stage, who were randomized to receive tocilizumab (n = 65) or standard of care alone (n = 64). The dosing strategy was tocilizumab 8 mg/kg on Day 1; if there was no response (i.e., no decrease of oxygen requirement), a second infusion was repeated on Day 3. In this preliminary report, the proportion of participants who died or needed ventilation (noninvasive or mechanical) was lower in the tocilizumab group compared with standard of care. Detailed results of the trial have not been reported. • An uncontrolled, retrospective cohort study of 21 hospitalized COVID-19 patients who received tocilizumab reported improvement in oxygenation, systemic inflammation, and hypoxic respiratory failure.[29] At study entry, 17 of the 21 patients had severe disease and four of the 21 patients had critical disease; mean age was 56 years (range 25–88), all patients were febrile, had abnormal chest CT findings, and required oxygen supplementation (two required mechanical ventilation). Mean CRP level was 75 mg/L, mean IL-6 expression level was 153 pg/mL, mean D-dimer level was 0.80 μg/mL, and mean lymphocyte percentage was 15.5%. Eighteen patients were given tocilizumab IV infusion once, and three were dosed a second time for indication of fever within 12 hours. Following tocilizumab administration, fever normalized, lymphocyte percentage improved, and CRP level declined. Oxygen requirements were reduced by Day 5 in 15 of 20 participants (75%). There were no serious AEs attributed to tocilizumab, and no concurrent infections (bacterial, fungal, or viral) were observed during the treatment. The interpretability of this retrospective case series is limited due to its small sample size and lack of control group.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/ Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Janus Kinase Inhibitor			
Baricitinib	Rheumatoid arthritis[30]	JAK inhibitor Inhibition of kinases that regulate endocytosis (AAK1 and GAK) Baricitinib is predicted to interfere with SARS-CoV-2 receptor-mediated endocytosis in lung AT2 alveolar epithelial cells.[31]	No clinical data for COVID-19, SARS, or MERS Baricitinib plasma concentrations are predicted to potentially be sufficient for AAK1 inhibition when administered at labeled dose (for the FDA-approved indication).[31]

Key: AAK1 = AP2-associated protein kinase 1; AE = adverse event; ARDS = acute respiratory distress syndrome; AT2 = alveolar type 2; CAR = chimeric antigen receptor; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; DMC = data monitoring committee; FDA = Food and Drug Administration; GAK = cyclin G-associated kinase; IL = interleukin; IV = intravenous; IVIG = intravenous immunoglobulin; JAK = Janus kinase inhibitor; MERS = Middle East respiratory syndrome; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Actualizaciones y Guías
Fármacos antivirales potenciales bajo evaluación para el tratamiento del COVID-19

REMDESIVIR:

• En base de datos de ensayos clínicos preliminares, el Panel recomienda el agente antiviral investigacional REMDESIVIR para el tratamiento de COVID-19 en pacientes hospitalizados con enfermedad severa, definida como SpO2 ≤94% en aire ambiental (a nivel del mar), requiriendo oxígeno suplementario, ventilación mecánica o oxigenación por membrana extracorpórea (BI).

• Remdesivir no está aprobado por la Food and Drug Administration (FDA); sin embargo, está disponible a través de una autorización de emergencia de la FDA para el tratamiento de adultos hospitalizados y niños con COVID-19. Remdesivir está también siendo investigado en ensayos clínicos, y está disponible a traves de programas de acceso de emergencia para niños y pacientes embarazadas.
• El Panel no recomienda Remdesivir para el tratamiento de COVID-19 suave a moderado fuera de lo que es el ámbito de un ensayo clínico (AIII).

Actualizaciones y Guías
Fármacos antivirales potenciales bajo evaluación para el tratamiento del COVID-19

Cloroquina/Hidroxicloroquina:

• El Panel se manifiesta en contra del uso de alta dosis de Cloroquina (600 mg dos veces al día durante 10 días) para el tratamiento de COVID-19 (AI), ya que la alta dosis conlleva un mayor riesgo de toxicidad que la dosis más baja.

• Se agrega a esta sección la alerta del FDA contra el uso de Cloroquina y de Hidroxicloroquina para el COVID-19 fuera del ámbito hospitalario o del desarrollo de ensayos clínicos.

Terapia Inmune bajo evaluación para el tratamiento del COVID-19

Los siguientes cambios claves fueron hechos en esta sección:

Plasma Convaleciente e Inmuno globulinas:

• Nueva información ha sido agregada a la sección de plasma convaleciente e Inmunoglobulinas específicas para el SARS-CoV-2.

• Se creó una nueva sección para inmuno globulinas intravenosas no-SARS-CoV-2 (IVIG), en las cuales el Panel se manifiesta en contra del uso de IVIG no específicas para SARS-CoV-2 para el tratamiento del COVID-19, excepto en el contexto de un ensayo clínico (AIII).
Esto no debería imposibilitar el uso de IVIG cuando sea de otro modo indicado para el tratamiento de complicaciones que surjan durante el curso de COVID-19.

Terapia Inmune bajo evaluación para el tratamiento del COVID-19

Los siguientes cambios claves fueron hechos en esta sección:

Inhibidores de Interleukina-6

• Se han incluido nuevos datos de una revision provisional de un ensayo clínico Fase 2/3 para Sarilumab.
• Se han adicionado nuevos resultados preliminaries de un ensayo clínico para Tocilizumab (CORIMUNO-TOCI).
• No hay cambios en las recomendaciones hechas por el Panel para inhibidores de IL-6. Hay datos insuficientes para manifestarse a favor o en contra del uso de inhibidores de IL-6 (Ej. sarilumab, siltuximab, tocilizumab) para el tratamiento de COVID-19 (AIII).

Consideraciones para ciertos medicamentos de uso concomitante en Pacientes con COVID-19

(Actualizado por última vez 21 de abril, 2020)

RESUMEN DE RECOMENDACIONES

Inhibidores de la Enzima Convertidora de Angiotensina* y Antagonistas del Receptor de Angiotensina**

- Las personas con COVID-19 bajo prescripción de IECAs o ARA II para enfermedad cardiovascular deberían continuar utilizando estos medicamentos (AIII).
- La Guía de tratamiento COVID-19 del Panel se manifiesta en contra del uso de IECAs o ARA II para el tratamiento de COVID-19 fuera del Desarrollo de un ensayo clínico (AIII).

***IECAs en español, ACE en inglés**
****** ARA II en español, ARBs en inglés**

RESUMEN DE RECOMENDACIONES

Corticosteroides

Para pacientes críticos III con COVID-19

• El Panel se manifiesta en contra del uso rutinario de corticoesteroides sistémicos para el tratamiento de pacientes con ventilación mecánica con COVID-19 sin sindrome de estrés respiratorio agudo (ARDS) (AIII).
• Para pacientes con ARDS ventilados mecánicamente, hay evidencia insuficiente para manifestarse (recomendar) a favor o en contra del uso sistémico de corticoesteroides (CI).
• Para adultos con COVID-19 y shock refractario , el Panel recomienda usar terapia de bajas dosis de corticoesteroides (ej. Reversión de shock) por sobre el no uso de corticoesteroides (BII).

RESUMEN DE RECOMENDACIONES

Para Pacientes hospitalizados No Críticos III con COVID-19

• El Panel se manifiesta en contra del uso de rutina de corticoesteroides sistémicos para el tratamiento de COVID-19 en pacientes hospitalizados a menos que estén en la Unidad de Cuidados Intensivos (AIII).

Para pacientes con tratamiento crónico con corticoesteroides:

• No debe discontinuarse la terapia oral con corticoesteroides usada antes del diagnóstico de COVID-19 para otras condiciones subyacentes (ej., Insuficiencia adrenal primaria o secundaria, enfermedades reumatológicas) (AIII). Sobre una base de caso a caso, pueden ser indicados esteroides suplementarios o bien dosis de estrés de esteroides (AIII).

• Corticoesteroides inhalados usados diariamente por los pacientes con asma y enfermedad pulmonar obstructiva crónica para el control de la inflamación de vías aéreas no debe ser discontinuado en pacientes con COVID-19 (AIII).

RESUMEN DE RECOMENDACIONES

Consideraciones en el embarazo:

• Se sabe que los corticoesteroides betametasona y dexametasona cruzan la placenta y entonces generalmente son reservados para administrarlos en circunstancias que favorecen el beneficio fetal (BIII). Otros corticoesteroides sistémicos no cruzan la placenta y el embarazo no es una razón para restringir su uso si fuera de otro modo indicado (CIII).
• El Colegio Americano de Obstetras y Ginecólogos se manifiesta en contra del ofrecimiento de corticoesteroides antenatales para beneficio fetal en el período de pretérmino tardío (34 0/7 semanas –36 6/7 semanas) porque los beneficios de corticoesteroides antenatales en el período de pretérmino tardío estan menos bien establecidos (CIII).
• Las modificaciones al cuidado de estas pacientes pueden ser individualizadas , sopesando los beneficios neonatales del uso antenatal de corticoesteroides con los riesgos de daño potencial a la pacientes embarazada (CIII).

RESUMEN DE RECOMENDACIONES

Inhibidores de la HMG-CoA Reductasa (Estatinas):

• Personas con COVID-19 a las que se les ha prescrito terapia con estatinas para el tratamiento o prevención de enfermedad cardiovascular debería continuar con estos medicamentos (AIII).

• El Panel se manifiesta en contra del uso de estatinas para el tratamiento de COVID-19 fuera del ámbito de realización de un ensayo clínico (AIII).

Fármacos Anti Inflamatorios no esteroidales* :

• Personas con COVID-19 que esten tomando AINEs para una condición co-mórbida deben continuar su terapia como haya sido indicado previamente por su medico tratante (AIII).

• El Panel manifiesta que no hay diferencia en el uso de diferentes estrategias antipiréticas (ej., con paracetamol o AINEs) entre pacientes con o sin COVID-19 (AIII).

*** (AINEs en español; NSAIDs en inglés)**