Stanford Medicine COVID-19 Pharmacotherapy Information

There are currently no FDA-approved therapies for the treatment of COVID-19. This document is designed to reflect information about therapies that have theoretical activity against SARS-CoV-2 and are not based on high quality evidence. The information in this document is not medical advice. Clinicians should consult with the appropriate healthcare professional when managing COVID-19.

Last Updated: April 6, 2020

Resources

LitCOVID (https://www-ncbi-nlm-nih-gov.laneproxy.stanford.edu/research/coronavirus/)

University of Liverpool COVID-19 Drug Interactions (http://www.covid19-druginteractions.org/)

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Pharmacotherapy Information

Remdesivir

Considerations for use

- Remdesivir clinical trials are ongoing at Stanford Health Care (SHC) and may be considered for patients with Coronavirus Disease 2019 (COVID-19)

Acquisition and Administration

- Not FDA approved. Available only through Expanded Access Program (EAP) or clinical trial.
- Dosage: 200 mg IV on day 1, followed by 100 mg IV once daily on days 2-5 or 2-10[1,2]
- Duration: 5-10 days
    - Of note, clinical trials are ongoing for 5- or 10-day durations of remdesivir for COVID-19. In advance of results of these trials the optimal duration of therapy is unknown.[1–3]
    - In a study of 3 patients who received remdesivir with symptom resolution, duration of therapy was 4, 5, and 10 days.[4]

Tolerability

- **Nausea and Transaminitis (common, mild):** Associated with nausea and transient mild transaminitis, which may be related to hepatic metabolism.[4] It should be noted that COVID-19 itself is also clinically associated with transaminitis.
    - In 2 of 3 patients receiving remdesivir, peak AST/ALT were: 129/219 on days 2-3 of therapy and47/75 after 4 days of therapy.[4]
- **Renal toxicity (theoretical, clinical relevance uncertain):** Drug is co-formulated sulfobutylether β-cyclodextrin (SBECD). There is a theoretical risk of accumulation in renal failure promoting further renal injury but the clinical relevance of this is uncertain.[5]
- **Hypotension (unclear):** Appears to be well tolerated from clinical trials in Ebola in which 175 patients received remdesivir 200 mg IV loading dose on day 1 followed by 100 mg IV daily for 9-13 days thereafter. One patient in the remdesivir group had hypotension that resulted in cessation of a loading dose of remdesivir and that was followed rapidly by cardiac arrest. However, even in this case, the death could not readily be distinguished from underlying fulminant Ebola virus disease itself.[6] Consult remdesivir prescribing information (included with shipment) regarding extension of infusion time for improved tolerability.

Drug interactions

- See: http://www.covid19-druginteractions.org/
- ~~Remdesivir is a prodrug requiring CYP3A4 for activation thus there is potential for reduced conversion in the presence of CYP3A4 inhibitors like lopinavir, ritonavir, darunavir, or cobicistat.~~[7]
    - ~~⊖~~ This statement was initially believed to be true based on NIH study protocol but has since been likely invalidated for the IV form of remdesivir. Activation of remdesivir (prodrug) is through hydrolysis by intracellular esterases and does not appear to be significantly dependent on CYP3A4.[8]

Supportive Data

- Non-FDA approved investigational nucleotide analog from Gilead Sciences[9]
- In vitro activity against novel coronavirus[10]
- Reports on clinical outcomes of remdesivir are limited, however, it was used in the first confirmed case of COVID-19 in the United States. The patient initially presented with mild symptoms but, after the first week of largely supportive care, had progression of disease to pneumonia requiring supplemental oxygenation, which

prompted the initiation of remdesivir through compassionate use and the patient's clinical condition subsequently improved. (Clinical outcomes copied below).[11]

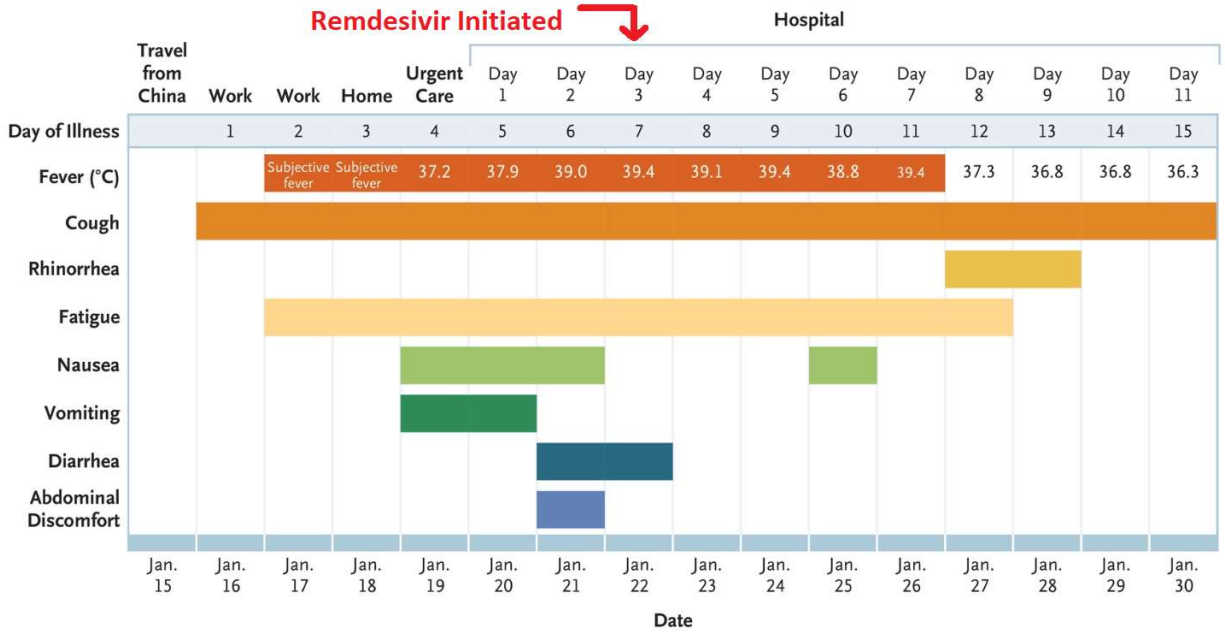


Table 1. Clinical Laboratory Results.*

Measure	Reference Range	Illness Day 6, Hospital Day 2†	Illness Day 7, Hospital Day 3	Illness Day 9, Hospital Day 5	Illness Day 11, Hospital Day 7	Illness Day 13, Hospital Day 9	Illness Day 14, Hospital Day 10
White-cell count (per μl)	3800–11,000	"Slight decrease"	3120‡	3300‡	5400	5600	6500
Red-cell count (per μl)	4,200,000–5,700,000	—	4,870,000	5,150,000	5,010,000	4,650,000	5,010,000
Absolute neutrophil count (per μl)	1900–7400	—	1750‡	1700‡	3700	3800	3200
Absolute lymphocyte count (per μl)	1000–3900	—	1070	1400	1400	1400	2100
Platelet count (per μl)	150,000–400,000	"Adequate"	122,000‡	132,000‡	151,000	150,000	239,000
Hemoglobin (g/dl)	13.2–17.0	12.2‡	14.2	14.8	14.8	13.5	14.2
Hematocrit (%)	39.0–50.0	36.0‡	42.0	43.0	43.0	39.3	42.0
Sodium (mmol/liter)	136–145	134‡	136	138	138	135‡	138
Potassium (mmol/liter)	3.5–5.1	3.3‡	3.6	3.4‡	3.6	4.1	3.9
Chloride (mmol/liter)	98–107	99	101	105	106	100	103
Calcium (mg/dl)	8.7–10.4	—	8.5‡	9.3	9.0	8.6‡	9.3
Carbon dioxide (mmol/liter)	20–31	—	26	24	25	23	36§
Anion gap (mmol/liter)	5–16	—	9	9	7	12	9
Glucose (mmol/liter)	65–140	104	103	120	96	148§	104
Blood urea nitrogen (mg/dl)	9–23	15	10	13	13	22§	18
Creatinine (mg/dl)	0.7–1.3	1.0	1.06	1.06	0.88	1.08	0.84
Total protein (g/dl)	5.7–8.2	—	6.9	7.1	6.8	6.9	6.8
Albumin (g/dl)	3.2–4.8	—	4.2	4.7	4.5	2.9‡	4.4
Total bilirubin (mg/dl)	0.3–1.2	—	1.0	1.1	1.5§	0.8	1.0
Procalcitonin (ng/ml)	<0.05	—	—	<0.05	<0.05	—	—
Alanine aminotransferase (U/liter)	10–49	—	68§	105§	119§	219§	203§
Aspartate aminotransferase (U/liter)	≤33	—	37§	77§	85§	129§	89§
Alkaline phosphatase (U/liter)	46–116	—	50	68§	88§	137§	163§
Fibrinogen (mg/dl)	150–450	—	477§	—	—	—	—
Lactate dehydrogenase (U/liter)	120–246	—	250§	465§	—	—	388§
Prothrombin time (sec)	12.2–14.6	—	11.9‡	11.9‡	—	—	12.7
International normalized ratio	0.9–1.1	—	0.9	0.9	—	—	1.0
Creatine kinase (U/liter)	62–325	—	353§	332§	—	—	—
Venous lactate (mmol/liter)	0.4–2.0	—	1.3	1.7	—	—	—

* To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for blood urea nitrogen to millimoles per liter of urea, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for total bilirubin to micromoles per liter, multiply by 17.1.
† Results are from point-of-care blood analyzer (iStat) testing.
‡ The value in the patient was below normal.
§ The value in the patient was above normal.

- In a study of the first 12 patients with COVID-19 in the U.S., remdesivir was administered to 3 patients, all male, 2 in their 30s, 1 in his 60s, all requiring supplemental oxygenation, 1 requiring ICU admission. Clinical outcomes are further described in the tables below.[4]

Red boxes notate patients (6, 8, and 9) who received remdesivir and durations of therapy.

Figure 1: Timeline of illness onset, SARS-CoV-2 RNA detection, hospitalization, oxygen requirement, and reported symptom resolution among the first 12 patients with COVID-19 in the United States, January–February 2020

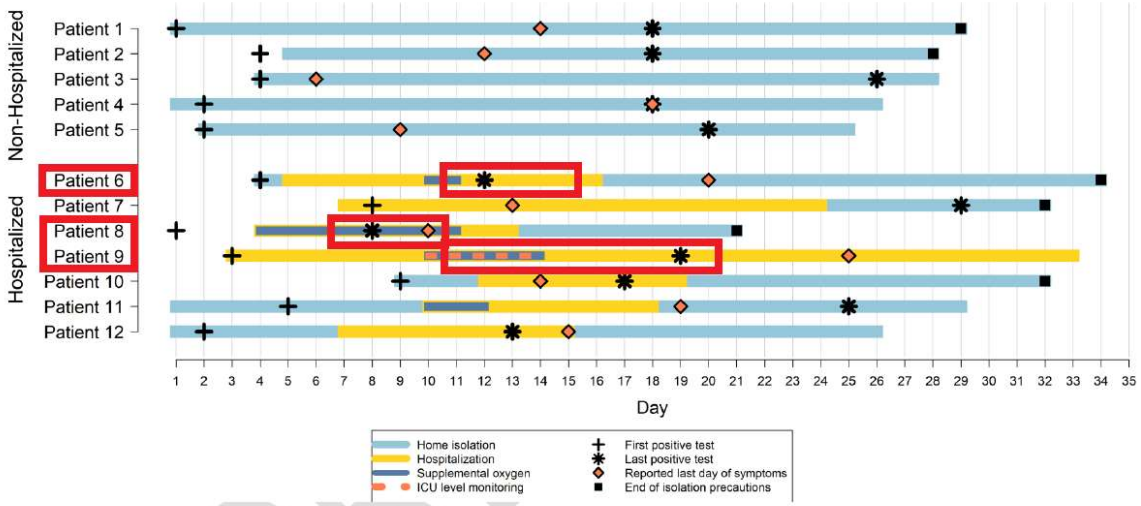
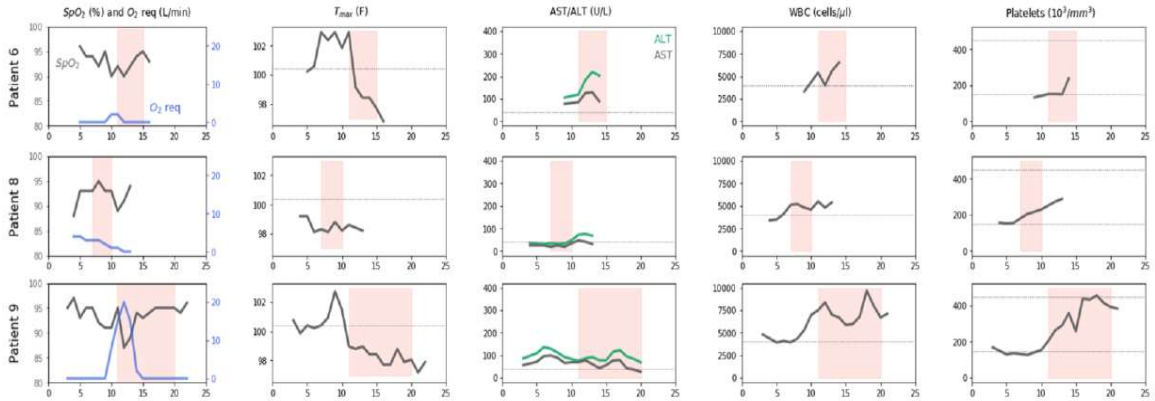


Figure 1 legend: Patients 1 – 5 were not hospitalized and Patients 6 – 12 were hospitalized. Days are sequential from day of symptom onset (Day 1). Light blue bars indicate time patients were under home isolation. Yellow bars indicate duration of hospitalization. Dark blue bars indicate duration of supplemental oxygen administration in hospital. The orange dashed bar indicates duration of intensive care-level monitoring for Patient 9. The black "+" indicates collection date of the earliest sample that tested positive for SARS-CoV-2 by rRT-PCR. The black asterisk indicates collection date of the latest sample to test positive for SARS-CoV-2 by rRT-PCR. The orange diamond indicates date of last report of COVID-19-related symptoms. The black square indicates the last day of isolation precautions; patients with no black square were still under isolation precautions as of February 22. The last date of specimen collection was February 21, and the last date of testing was February 22. Patient 1 reported a cough with initial onset in mid-December before the patient traveled to China. The patient reported no change in the cough

Laboratory parameters for patients (6, 8, and 9) who received remdesivir.

Abbreviations: SpO_2, oxygen saturation; O_2 req, supplemental oxygen requirement; T_{max}, maximum body temperature; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood cell count.

Pink shading: remdesivir administration. Dotted lines: 100.4 F (T_{max}), 40 U/L (AST/ALT), 4000 cells/µl (WBC), 150 and 250 $10^3/mm^3$ (platelets)



- There are a number of ongoing clinical trials for remdesivir in mild to severe COVID-19 in the US
    - NIAID Adaptive COVID-19 Treatment trial (NCT04280705) is a phase II, randomized, placebo-controlled trial in US of remdesivir for mild to severe COVID-19.[3]
    - Gilead randomized clinical trials of moderate and severe COVID-19 (NCT04292730 and NCT04292899).[1,2]
    - US Army Medical Research and Development Command Expanded Access Remdesivir Trial (NCT04302766).[12]
    - WHO Trial of Treatments for COVID-19 in Hospitalized Adults (NCT04315948).[13]
    - Two ongoing randomized, placebo-controlled clinical trials in China of mild/moderate and severe COVID-19 (NCT04252664 and NCT04257656).[14,15]

Hydroxychloroquine (or Chloroquine)

Considerations for use

- May be considered on a case-by-case basis if remdesivir is not accessible

Acquisition and Administration

- Hydroxychloroquine is available on SHC Formulary, no anticipated delay to administration assuming no drug shortage
    - Tablet should not be split or crushed but drug may be prepared into an oral suspension in patients who cannot take whole tablets (discuss with pharmacy)[7]
    - Administration should be separated from antacids by at least 4 hours[7]
- Chloroquine is not on SHC formulary and is currently in shortage with sporadic availability. Consult with pharmacy regarding availability of this agent if considering use.

Dosing/Administration

- **Hydroxychloroquine Dosage:** Multiple dosing regimens have been proposed
    - 400 mg PO BID on day 1 followed by 200 mg PO BID on days 2-5[16]
    - 400 mg PO daily x 5 days[17]
        - A once-daily dosing regimen may decrease use of personal protective equipment (PPE) but may increase risk of GI-related adverse events
    - 200 mg PO TID x 10 days[18]
    - Prophylaxis Dosing (University of Minnesota Clinical Trial)[19]:
        - 800 mg PO x 1 dose, followed in 6 to 8 hours by 600 mg PO x 1 dose, then 600mg PO daily for 6 consecutive days
    - Renal Dosage Adjustments:
        - CrCl 10-59: No dose change for short term use. Small PopPK study found mean ±SD HCQ serum concentrations in patients with CrCl 15-59 dosed HCQ 300mg PO daily (980±290 to 1030±360 ng/ml) similar to general population dosed 200mg PO BID. (1,024±519 ng/ml) It also showed a trend towards decreased clearance and increased half-life with worsening CrCl.[20–22]
        - CrCl < 10, IHD, peritoneal dialysis: No data. Some experts recommend 50% dose reduction.[22]
        - CRRT: No data
- **Chloroquine Dosage:**
    - Body weight ≥ 50kg: 500 mg PO BID x 7 days[23]
    - Bodyweight < 50kg: 500mg twice daily for day 1 and 2, 500mg once daily for day 3 through 7[23]

Tolerability

- General:
    - Dizziness, headache, dizziness, loss of appetite, nausea, vomiting, abdominal pain, diarrhea, tinnitus, irritability. Most are mild and remit upon drug discontinuation.[24]
- Cardiotoxicity (long term use, possibly also short term use):
    - Causes suppression of SA node, which can lead to arrhythmias.[24] In a 2018 systematic review of 127 patients of whom 58% received chloroquine and 39% hydroxychloroquine (both drugs in the remainder), conduction disorders most common (85% of patients). Median treatment duration was 7 years but minimum duration was 3 days.[25]
    - Risk cannot be quantified because of lack of controlled trials but mainly appears to be associated with long term use. That said, minimum duration was 3 days in this study, thus, toxicity with short term use is

not impossible and may be a more significant consideration in critically ill patients and those with underlying cardiac conditions.[25]
    - QTc prolongation is of concern with one reported case of TdP (associated with long term hydroxychloroquine use for SLE).[26] It is prudent to monitor QTc interval and electrolytes, and if possible avoiding other drugs that prolong QTc.
- Hematologic toxicity (rare)
    - Hemolysis, aplastic anemia, reversible agranulocytosis, thrombocytopenia are rare.[24]
    - G6PD Deficiency: It has been proposed that patients with G6PD deficiency may be at higher risk of hemolytic anemia with hydroxychloroquine. In a retrospective study of 275 patients on hydroxychloroquine for rheumatologic indications (i.e. long term therapy) and a total of 700 combined months of exposure, 4% (N=11) of patients G6PD deficient and zero reported episodes of hemolysis among them. There were two episodes of hemolysis but they did not occur on hydroxychloroquine therapy.[27]
- Hypoglycemia[7]
- Retinal toxicity (long term use):
    - Chloroquine secreted by lacrimal glands. Accumulation of chloroquine may be associated with retinopathy, macular degeneration. Observed in long term use for rheumatologic conditions.[24] Unlikely to be observed during shorter courses for COVID-19.
    - A safe daily dose of 5 mg/kg/day actual body weight or 6.5 mg/kg/day ideal body weight has been correlated with avoidance of retinopathy.[28]
    - Higher doses and longer hydroxychloroquine durations linked to retinal toxicity; thus cumulative dose suggested as most important risk factor for ophthalmologic toxicity.[29,30]
- Other toxicities
    - Other toxicities have been observed with unknown incidence rates. Dystonia, dyskinesia, tongue extension, torticollis, drug-induced psychosis, leukopenia, purple scar, rash, dermatitis, photosensitive dermatitis and even exfoliative dermatitis, psoriasis, whitening of hair, hair loss, neuromuscular pain, mild transient headache have been described.[24]

Drug Interactions

- See: http://www.covid19-druginteractions.org/

Supportive Data

- Hydroxychloroquine and chloroquine have in vitro activity against SARS-CoV-2.[10] Antiviral activity may be due to increase in endosomal pH and interference with glycosylation of cellular receptors of SARS-CoV-2.[31] Image credit below.[32]

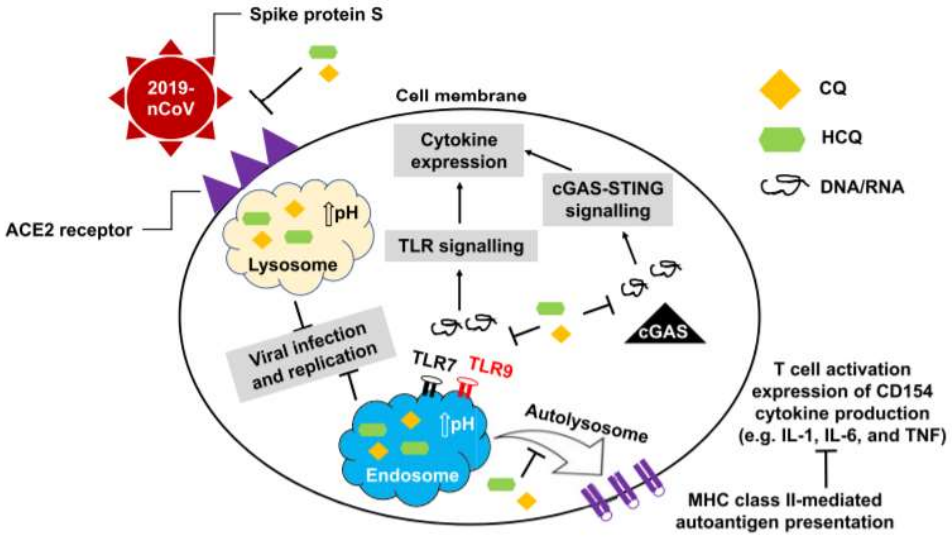


Figure 2. A graphical illustration of the antiviral mechanisms of CQ and HCQ. Both chemicals can interfere with the glycosylation of ACE2 and reduce the binding efficiency between ACE2 on the host cells and the spike protein on the surface of the coronavirus. They can also increase the pH of endosomes and lysosomes, through which the fusion process of the virus with host cells and subsequent replication are prevented. When HCQ enters APCs, it prevents antigen processing and MHC class II-mediated autoantigen presentation to T cells. The subsequent activation of T cells and expression of CD154 and other cytokines are repressed. In addition, HCQ disrupts the interaction of DNA/RNA with TLRs and the nucleic acid sensor cGAS and therefore the transcription of pro-inflammatory genes cannot be stimulated. As a result, administration of CQ or HCQ not only blocks the invasion and replication of coronavirus, but also attenuates the possibility of cytokine storm. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Yao et al[16]

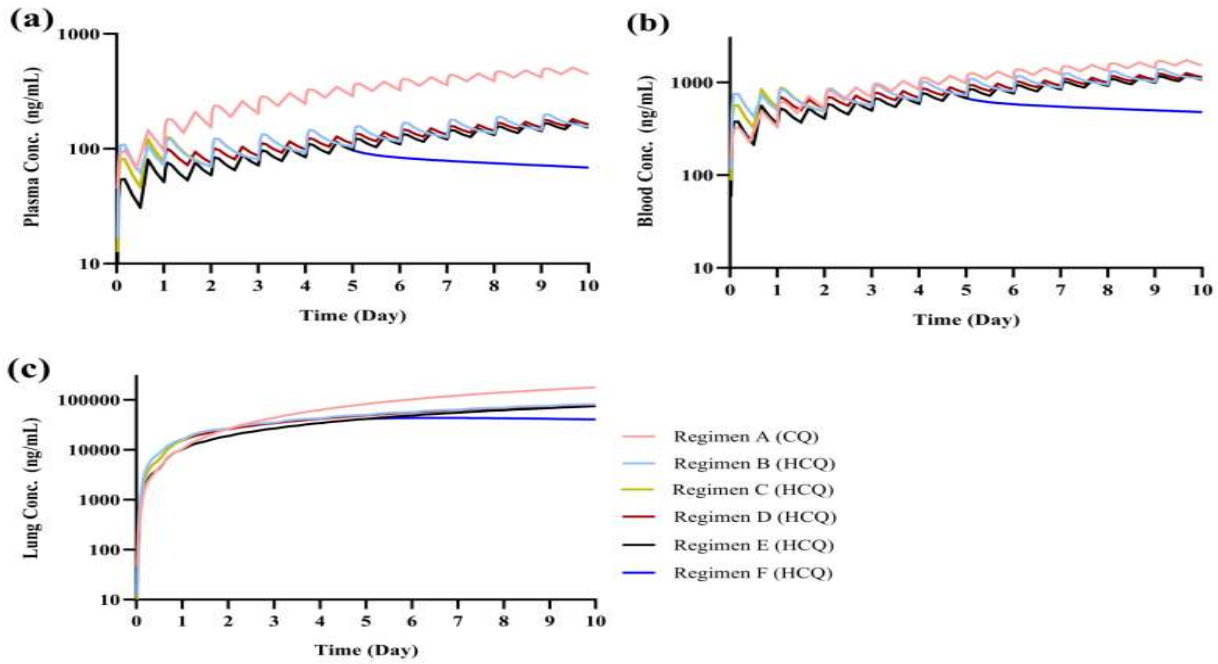
- In vitro data suggested that hydroxychloroquine (EC50=0.72 µM) is more potent than chloroquine (EC50=5.47 µM) against SARS-CoV-2. The ratio of free lung trough concentration to EC50 (RL_{TEC}) to determine the optimal dose of hydroxychloroquine was assessed using a goal chloroquine dosing regimen of 500 mg BID (Table 1 below) and simulated for plasma, blood, and lung concentrations (Figure 3 below).

Table 1: Ratios of free lung tissue trough concentration/EC_{50} (R_{LTEC}) under different dosage regimens

Drug	NO.	Dosing Regimen	R_{LTEC}			
			Day1	Day3	Day5	Day10
Chloroquine phosphate	A.	D1-D10 500 mg BID	2.38	5.92	18.9	40.7
Hydroxychloroquine sulfate	B.	D1 800 mg+400 mg; D2-D10 400 mg QD	33.3	55.1	103	168
	C.	D1 600 mg BID; D2-D10 400 mg QD	31.7	54.7	103	169
	D.	D1 600 mg BID; D2-D10 200 mg BID	31.7	53.1	101	167
	E.	D1 400 mg BID; D2-D10 200 mg BID	21.0	38.9	85.4	154
	F.	D1 400 mg BID; D2-D5 200 mg BID	21.0	38.9	85.4	83.3

R_{LTEC}: ratio of free lung tissue trough concentration/EC_{50}.

Figure 3



Gautret et al.[33]

- An open-label non-randomized clinical trial in France of 36 patients with COVID19 (20 of whom received hydroxychloroquine [200 mg PO TID] and 16 control patients) indicated that hydroxychloroquine decreases SARS-CoV-2 viral load in comparison to no therapy (6 days vs. 20 days). This effect was found to possibly be synergistic with Azithromycin (but given the QTc-prolongation interaction potential of hydroxychloroquine & azithromycin, risk benefit needs to be weighed).
    - The outcome data notwithstanding, a number of caveats should be noted in interpreting this study:[34]
    - Virologic clearance at 6 days was used as the primary outcome, no clinical efficacy nor safety outcomes were reported for the study patients.
    - Six patients were lost to follow up in the hydroxychloroquine arm and not included in the final results. Of these six patients, three were transferred to ICU (PCR positive), one died (PCR negative), one stopped therapy due to nausea (PCR positive), and one left the hospital (PCR negative). If the first five of these patients were included and considered failures, the primary outcome is substantially attenuated from 70% to 54%.
    - Virologic clearance was defined as a SARS-CoV-2 PCR cycle threshold of 35 despite being typically defined at 40
    - At higher baseline viral burden (day 0 cycle threshold < 24), hydroxychloroquine performed poorly (primary outcome 33% vs. placebo 12.5%). Notably, higher viral burden may be associated with more severe disease.[35]
    - Most patients (5/6, 83%) receiving hydroxychloroquine + azithromycin had lower viral burden (cycle threshold ≥ 24) compared with those receiving hydroxychloroquine alone (8/14, 57%) making the outcome comparison between the two difficult to interpret. When comparing patients with lower viral burden, a difference between hydroxychloroquine + azithromycin combination therapy and hydroxychloroquine monotherapy alone is not readily apparent (5/6, 83% vs. 6/8, 75%, respectively).

Table 1 Characteristics of the study population.

	Age (years)			Male gender		Clinical status				Time between onset of symptoms and inclusion (days)		
	Mean ± SD	t	p-value	n (%)	p-value	Asymptomatic	URTI	LRTI	p-value	Mean ± SD	t	p-value
Hydroxychloroquine treated patients (N=20)	51.2 ± 18.7	-1.95	0.06	9 (45.0)	0.65	2 (10.0)	12 (60.0)	6 (30.0)	0.30	4.1 ± 2.6	-0.15	0.88
Control patients (N=16)	37.3 ± 24.0			6 (37.5)		4 (25.0)	10 (62.5)	2 (12.5)		3.9 ± 2.8		
All patients (36)	45.1 ± 22.0			15 (41.7)		6 (16.7)	22 (61.1)	8 (22.2)		4.0 ± 2.6		

URTI: upper tract respiratory infection, LRTI: lower tract respiratory infection

Figure 1. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine and in COVID-19 control patients.

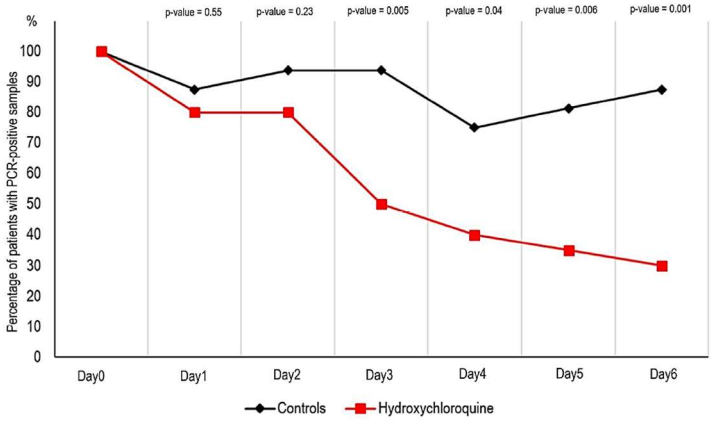
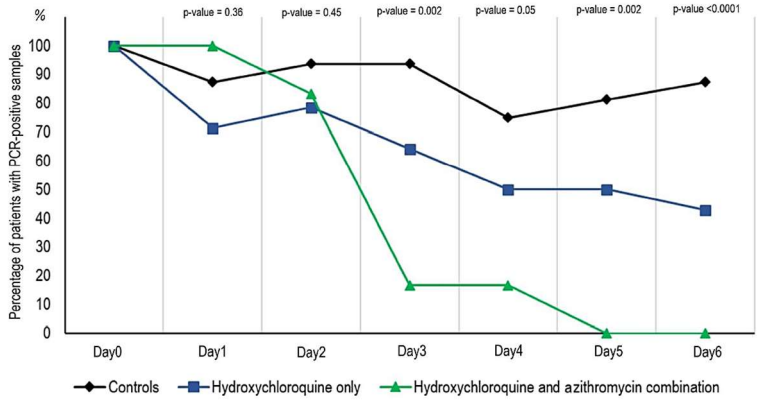


Figure 2. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine only, in COVID-19 patients treated with hydroxychloroquine and azithomycin combination, and in COVID-19 control patients.



Chen et al. (Pilot Hydroxychloroquine RCT)[36]

- Randomized, controlled trial of hydroxychloroquine vs. control in Shanghai for patients hospitalized with COVID-19. This study found no difference in virologic clearance between hydroxychloroquine and control. Of note, the study population was relatively healthy with mild-moderate disease and all patients were given concomitant treatments with inhaled α-interferon, many received arbidol, and some received lopinavir/ritonavir.

- 30 patients were randomized 1:1 to hydroxychloroquine 400 mg PO daily (N=15) or control. Both groups received "conventional treatment" (bed rest, oxygen, and symptomatic support). Primary efficacy endpoint = virus clearance from throat swabs, sputum, or lower respiratory tract secretions on day 7 or within 2 weeks.
- Demographic data is shown below:

Table 1 Demographic data and clinical characteristics of the two groups

[$x \pm s$ or M (Q_1, Q_3) or n (%)]

Group	*n*	Male *	average age	Mean course of disease (D)	test	Basic diseases *		
						hypertension	diabetes	Chronic obstructive pulmonary disease
test group	15	9 (60.0)	50.5 ± 3.8	6.6 ± 3.9	9 (60.0)	5 (33.3)	1 (6.7)	0 (0.0)
Control group	15	12 (80.0)	46.7 ± 3.6	5.9 ± 4.1	13 (86.7)	3 (20.0)	1 (6.7)	1 (6.7)
t / *U* value	—	—	0.72	0.45	—	—	—	—
P value	—	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Group	*n*	White blood cell count ($\times 10^9$ / L)	lymphocyte count ($\times 10^9$ / L)	ALT (U / L)	eGFR (ML · min $^{-1}$ · 1.73m $^{-2}$)	Lactic acid (mmol / L)	CD4 + cytometer Number (pcs / μL)	CT lesions of the chest (two Lung / Side Lung) *
test group	15	5.2 (3.9 ~ 6.7)	1.11 ± 0.43	18 (15 ~ 23)	117 ± 29	1.4 ± 0.4	415 (275 ~ 589)	12/3
Control group	15	4.9 (4.5 ~ 7.4)	1.18 ± 0.55	24 (14 ~ 47)	120 ± 29	1.4 ± 0.5	395 (272 ~ 710)	14/1
t / *U* value	—	101	0.39	87	0.30	0.19	110	—
P value	—	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

"—" No relevant data. * Fisher test. ALT: Alanine aminotransferase; eGFR: Estimate of glomerular filtration rate.

- On day 7, 13/15 patients (86.7%) in experimental vs. 14/15 (93.3%) patients in the control group had a negative throat swab.
- All patients had negative throat swabs at day 14.
- Time to negative conversion was 4 days (1-9) in the experimental group vs 2 days (1-4) in the control group.
- No patients died
- No difference was observed in rate of adverse drug events. Hydroxychloroquine arm: 4 cases – diarrhea, weakness, progression to severe disease, and AST/ALT elevations. Control arm: 3 cases – elevated AST/ALT, anemia, and elevation in serum creatinine.

Gautret et al. Hydroxychloroquine + Azithromycin Single Arm Study of 80 patients[37]

- Study Design
  - Single center, "observational," non-controlled study in France of 80 patients with COVID-19 treated with hydroxychloroquine + azithromycin +/- ceftriaxone
    - Dosing: HCQ 200 mg PO TID x 10 days combined with azithromycin 500 mg PO on day 1 followed by 250 mg PO daily on days 2-5
    - Patients with pneumonia and NEWS score >= 5 also received ceftriaxone
  - Details regarding how patients were included in the study are unclear and it is not mentioned if any patients were excluded. The authors note, they included 6 patients from a previously published study.[33] Patients with a QTc > 500 ms, EKG signs of channelopathy, and based on risk/benefit assessment were excluded.
  - Safety monitoring: EKG performed at baseline and 2 days after start of treatment

- Primary outcomes: “i) an aggressive clinical course requiring oxygen therapy or transfer to the ICU after at least three days of treatment, ii) contagiousness as assessed by PCR and culture, and iii) length of stay in the ID ward”

- Results: (see screenshots below)
  - Tables 1 and 2 show demographics and baseline clinical status.
    - Patients were younger (median age 52.5 [IQR 42-62] years), had a relatively low incidence of chronic comorbidities. 53.8% of patients had pneumonia on CT, however, 20% of patients did not have CT performed.
    - Patients had relatively mild disease with most (69 of 75 [92%], 5 with missing data) had a low NEWS score (0-4) and only 15% required oxygen therapy.
    - Mean time between the onset of symptoms and the initiation of treatment was 4.9 days (SD = 3.6 days), and most patients were treated on day 1 or 2 of hospitalization (93.7%).
    - 22.5% of patients received “other antibiotic,” possibly ceftriaxone based on stated methods
    - Treatment was stopped in one patient due to drug interaction.
  - Table 3 shows clinical outcomes.
    - At the time of writing, 65 (81.2%) patients were discharged, 13 (16.2%) and 1 (1.2%) were hospitalized on ID wards and ICU, respectively. One patient died.
      - Supplemental Table 1 shows characteristics of 4 patients who required ICU level care (N=3) or died (N=1)
    - Adverse events: 4 (5%) had diarrhea, 2 (2.5%) had nausea or vomiting, and 1 (1.2%) had blurred vision
  - Figures 1 and 2 show virologic outcomes.
    - Authors note “A rapid fall of nasopharyngeal viral load tested by qPCR was noted, with 83% negative at Day7, and 93% at Day8. The number of patients presumably contagious (with a PCR Ct value <34) steadily decreased overtime and reached zero on Day12”
    - It should be noted that only 80% of patients were tested at baseline and the total number of patients tested decreases over time. Also, given the absence of a control group, these results cannot be adequately assessed, however, these virologic dynamics mirror untreated patients[38], especially if correcting day of hospital admission to day of symptom onset.

Table 1: Sociodemographic characteristics and chronic conditions

	n	%
Age (years)		
Median	52.5	
Interquartile	42	62
Min - Max	20	88
[20-45[	24	30.0
[45-50)	12	15.0
[50-60)	21	26.2
[60-70)	13	16.2
[70-80)	5	6.3
≥80	5	6.3
Male	42	52.5
Chronic conditions		
Cancer	5	6.3
Diabetes	9	11.2
Coronary artery disease	6	7.5
Hypertension	13	16.3
Chronic respiratory diseases	8	10.0
Obesity	4	5.0
Immunosuppressive treatment	4	5.0
Non-steroid anti-inflammatory treatment	2	2.5

Table 2: Clinical status at admission

	n	%
Time between onset of symptoms and hospitalisation		
Mean ± SD	4.8 ± 5,6	
Min - Max	1	17
Clinical classification		
Asymptomatic	4	5.0
Upper respiratory tract infection symptoms	33	41.2
Lower respiratory tract infection symptoms	43	53.8
Fever	12	15.0
Temperature in febrile patients		
Mean ± SD	38.6 ± 0.12	
Min - Max	38.5	38.8
Cough	47	58.8
Rhinitis	13	16.3
NEWS score (N = 75, 5 missing data)		
0 – 4 (low)	69	92.0
5 – 6 (medium)	4	5.3
≥ 7 (high)	2	2.7
Pulmonary CT-scanner within 72 hours of admission		
Not performed	16	20.0
Not consistent with pneumonia	21	26.2
Consistent with pneumonia	43	53.8
Viral load at inclusion (Ct)		
Mean ± SD	23.6 ± 4.3	
Min - Max	14	33
Time between onset of symptoms and treatment		
Mean ± SD	4.9 ± 3.6	
Min - Max	1	17
Treatment started on Day0	49	61.2
Treatment started on Day1	26	32.5
Treatment started on Day2	3	3.8
Treatment started on Day3	2	2.5

Table 3: Treatment and outcome

	n	%
Oxygen therapy	12	15.0
Transfer to intensive care unit	3	3.8
Death	1	1.2
Discharged	65	81.2
Currently hospitalised		
ICU	1	1.2
Infectious disease ward	13	16.2
Other antibiotic intake	18	22.5
Possible adverse events		
Nausea or vomiting	2	2.5
Diarrhoea	4	5.0
Blurred vision*	1	1.2
Time from treatment initiation to discharge (n = 65)		
Mean ± SD	4.1 ± 2.2	
Min - Max	1	10
Length of stay in infectious diseases ward (n = 65)		
Mean ± SD	4.6 ± 2.1	
Min - Max	1	11
NEWS score in discharged patients (N = 65)		
0 – 4 (low)	61	93.8
5 – 6 (medium)	4	6.2
≥ 7 (high)	0	-

*after five days of treatment

Legends to figures

Figure 1. SARS-CoV-2 PCR from nasopharyngeal samples overtime. Black bars: number of patients with available results, grey bars: number of patients with PCR Ct value <34, solid line: percentage of patients with PCR Ct value <34, dashed line: polynomial regression curve.

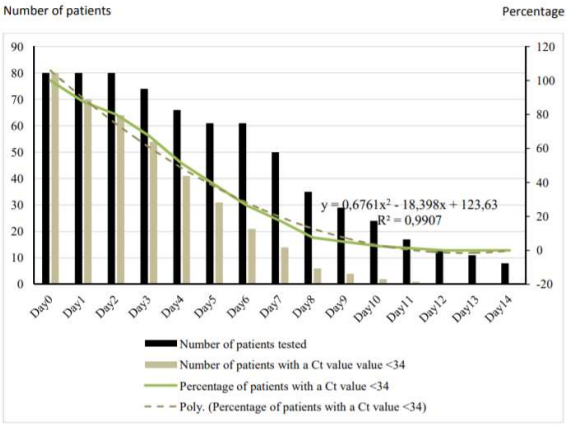
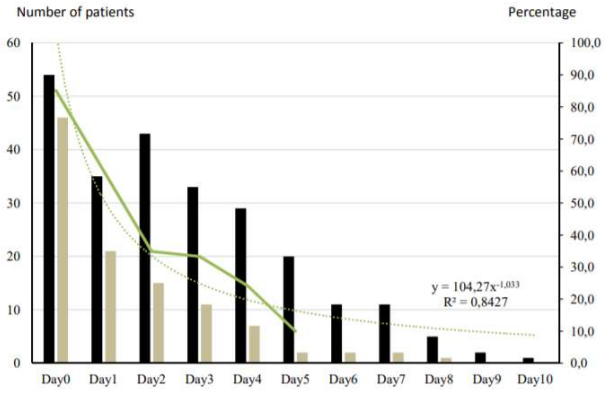


Figure 2. SARS-CoV-2 culture from nasopharyngeal samples overtime. Black bars: number of patients with available results, grey bars: number of patients with positive culture, solid line: percentage of patients with a positive culture, dashed line: polynomial regression curve.



Supplementary Table 1. Detail of patients who were transferred to the intensive care unit or who died

Age (years)	Sex	Comorbidities	Time between symptom onset and treatment (days)	Ct value at admission	Time between initiation of treatment and transfer to ICU (days)	Reason for ICU transfer	Time between initiation of treatment and PCR Ct value ≥34 (days)	Time in ICU (days)	Outcome
46	M	None	16	29	1	Polypnea 50 cycles/minutes	3	2	Return to infectious diseases ward
54	M	Hypertension, Diabetes	11	22	2	ARDS	Still < 34	8	Return to infectious diseases ward
75	F	None	3	25	8	Hypoxaemia (PaO_2 62mmHg_3 despite non-invasive oxygenation	8	1	Still hospitalised in ICU
86	M	Hypertension, Corticosteroid medication for five days before admission	5	19	7	No ICU transfer	Still < 34	0	Died in infectious diseases ward

Chen et al. Hydroxychloroquine vs. Standard of Care RCT of 62 Patients[39]

- Study Design
  - Randomized, parallel group, clinical trial of 62 patients with mild COVID-19 treated with hydroxychloroquine 200 mg PO BID + standard of care (N=31) vs. standard of care (N=31)
    - Of note, standard of care in this study was defined was "oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids"
    - The authors state "Neither the research performers nor the patients were aware of the treatment assignments." However, the definition of 'research performers' is not clear and there is no mention of use of placebo despite being mentioned (starch pill) in the registered methods in the Chinese RCT database.[40] Additionally, the registered methods also describe a three-arm study (i.e. 100 mg PO BID vs 200 mg PO BID vs placebo) that is not reflected in the manuscript.
  - Primary endpoint: Time to clinical recovery (TTCR) defined as normalization of body temperature and cough relief, maintained for more than 72 h assessed at day 5 after enrollment.
- Figure 1 below shows study enrollment.
  - Patients were included if they were 18 years and older, had RT-PCR positive for SARS-CoV-2, chest CT demonstrating pneumonia, SaO2/SPO2 ratio > 93% or PaO2/FIO2 ratio > 300 mmHg (mild illness)
  - Patients were excluded if they had severe/critical illness, retinopathy, conduction block/arrhythmias, severe liver disease, renal insufficiency (eGFR ≤ 30 ml/min/1.73m^2) or RRT, pregnant/breastfeeding, or received any treatment for COVID.
- Results
  - Patients were generally younger (mean age 44.7 [SD 15.3] years) with mild disease based on inclusion/exclusion criteria. Notably, comorbidities were not documented in any patient population. (Table 1)
  - For primary outcome, the authors state (for Table 1): For fever, 17 patients in the control group and 22 patients in the HCQ treatment group had a fever in day 0. Compared with the control group [3.2 (1.3)

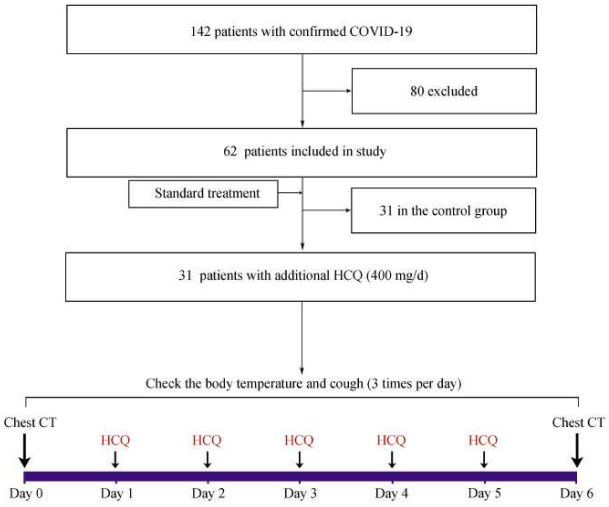
days], the body temperature recovery time was significantly shortened in the HCQ treatment group [2.2 (0.4) days]. For cough, 15 patients in the control group and 22 patients in the HCQ treatment group had a cough in day 0, The cough remission time was significantly reduced in the HCQ treatment group.

- Four of the 62 patients progressed to severe illness, all four were in the control group.
- Two patients experienced ADRs in HCQ group (one patient with rash, one patient with headache, both deemed not severe)
- Table 2 shows CT findings on day 0 vs. day 6 in both treatment groups. The authors note: "a larger proportion of patients with improved pneumonia in the HCQ treatment group (80.6%, 25 of 31) compared with the control group (54.8%, 17 of 31)"

Figures captions

Figure 1: Study flow diagram.

Abbreviations: COVID-19, severe acute respiratory syndrome coronavirus; HCQ, hydroxychloroquine; CT, computed tomography.



Characteristics	All	Control	HCQ	P value
Cases, n	62	31	31	
Age, mean (SD)	44.7 (15.3)	45.2 (14.7)	44.1 (16.1)	0.8809
Sex, n (%)				0.7991
Male	29 (46.8%)	15 (48.3%)	14 (45.2%)	
Female	33 (53.2%)	16 (51.7%)	17 (54.9%)	
Fever, day (SD)[a]	2.6 (1.0)	3.2 (1.3)	2.2 (0.4)	0.0008
Cough, day (SD)[b]	2.4 (1.1)	3.1 (1.5)	2.0 (0.2)	0.0016
Progressed to severe illness	4 (6.5 %)	4 (12.9 %)	0	
Adverse effects	2 (3.2 %)	0	2 (6.4 %)	

Table 1: Characteristics of patients in this trial.

[a]22 patients in the HCQ treatment group,17 patients in the control group with a fever one day before the intervention. [b]22 patients in the HCQ treatment group,15 patients in the control group with a cough one day before the intervention. Abbreviations: SD, standard deviation; HCQ, hydroxychloroquine; CT, computed tomography.

Group	All	Exacerbated	Unchanged	Improved		
				Moderate	Significant	Total
All	62	11 (17.7 %)	9 (14.5 %)	18 (29.0 %)	24 (38.7 %)	42 (67.7 %)
Control, n (%)	31	9 (29.0 %)	5 (16.1%)	12 (38.7 %)	5 (16.1%)	17 (54.8%)
HCQ, n (%)	31	2 (6.5 %)	4 (12.9 %)	6 (19.4%)	19 (61.3%)	25 (80.6%)
P value	0.0476					

Table 2: Absorption of pneumonia on chest CT.

Abbreviations: HCQ, hydroxychloroquine.

- Initial reports from more than 100 patients showed superiority of chloroquine to control treatment in inhibiting exacerbation of pneumonia, promoting negative conversion, and shortening the disease. This is per a news briefing in China. No clinical details of these patients have yet been published.[31]

- A multicenter collaborative Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia recommended chloroquine phosphate for mild, moderate, and severe cases of novel coronavirus pneumonia and without contraindications to chloroquine.[24]
- Some concern expressed regarding lack of correlation between in vitro and in vivo effects with treatment or prophylaxis with hydroxychloroquine in other viral diseases.[41]
- In vitro data has also suggested that immunomodulatory activity of hydroxychloroquine may inhibit cytokine storm late in COVID-19 disease process.[16]

Molina et al. Hydroxychloroquine + Azithromycin No Rapid Virologic Clearance in 11 Patients[42]

- Prospective, observational, non-controlled, single cohort study of virologic and clinical outcomes of 11 patients with COVID-19
- Demographics: 11 patients (7 male, 4 female). Mean age of 58.7 years (range: 20-77). Eight of 11 had significant comorbidities associated with poor outcomes (obesity: 2; solid cancer: 3; hematological cancer: 2; HIV-infection: 1)
- Clinical Results (Reported in 11 of 11)
    - At the time of treatment initiation, 10/11 had fever and received nasal oxygen therapy.
    - Within 5 days, one patient died, two were transferred to the ICU. In one patient, hydroxychloroquine and azithromycin were discontinued after 4 days because of a prolongation of the QT interval from 405 ms before treatment to 460 and 470 ms under the combination.
    - Mean through blood concentration of hydroxychloroquine was 678 ng/mL (range: 381-891) at days 3-7 after treatment initiation.
- Virologic Results (Reported in 10 of 11)
    - Repeated nasopharyngeal swabs in 10 patients (not done in the patient who died) using a *qualitative* PCR assay (nucleic acid extraction using Nuclisens Easy Mag®, Biomerieux and amplification with RealStar SARS CoV-2®, Altona), were still positive for SARS-CoV2 RNA in 8/10 patients (80%, 95% confidence interval: 49-94) at days 5 to 6 after treatment initiation.

Nitazoxanide

Considerations for use

- Data not specific to COVID-19, was mainly in influenza; await further data

Acquisition and Administration

- Dosing/Administration
  - 500mg PO BID x5 days
  - Studies in influenza and other respiratory viral infections: 600mg PO BID x5 days[43,44]
  - Available as 500mg tablet or suspension 20mg/ml (60ml)
    - AWP $1739 vs $2610 for 500mg PO BID 5 d course

Tolerability

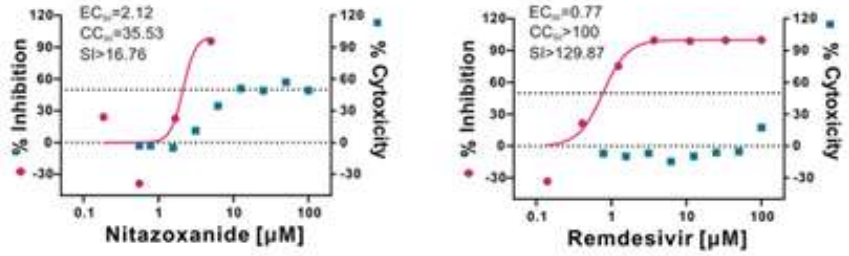
- General: headache, GI upset, urine discoloration (> 2%)

Drug Interactions

- None known

Supportive Data

- Nitazoxanide is an antiprotozoal agent used to treat infectious diarrhea caused by Cryptosporidium parvum or Giardia lamblia. It has shown antiviral activity against a broad range of viruses including human and animal coronaviruses, inhibited SARS-CoV-2at a low-micromolar concentration (EC50 = 2.12 µM; CC50 > 35.53 µM; SI > 16.76).[10]
  - Structurally similar to niclosamide



- Haffizulla et al[43], Lancet ID 2014 "Effect of nitazoxanide in adults and adolescents with acute uncomplicated influenza: a double-blind, randomised, placebo-controlled, phase 2b/3 trial."
  - Age 12+, enrolled within 48h of influenza symptom onset
  - 12/624 (1.9%) participants had coronavirus; 257/624 (41%) had Influenza A or B
  - Tx arms: nitazoxanide 600mg vs 300mg vs placebo BID x 5 days, 28d follow-up
  - Findings: **In those with confirmed Influenza A or B, nitazoxanide 600mg BID arm reduced duration of symptoms from 116.7h to 95.5h compared to placebo (p=0·0084), i.e. ~21 hours shorter sx.**
- Gamiño-Arroyo et al[44], CID 2019. "Efficacy and Safety of Nitazoxanide in Addition to Standard of Care for the Treatment of Severe Acute Respiratory Illness"
  - double-blind, placebo-controlled trial, 260 adults and children, ≥50% with pneumonia at presentation
  - Tx arms: NTZ (age ≥12 years, 600 mg twice daily; age 4–11 years and 1–3 years, 200 or 100 mg twice daily, respectively) or placebo for 5 days in addition to standard of care
  - **No difference in median duration of hospitalization** in NTZ group vs placebo (6.5 IQR 4-9 vs 7.0 IQR 4-9 days), P=0.56

- Influenza A or B: 50/257 (19.5%); coronavirus 17/257 (6.6%); RSV 30/257 11.7%; rhinovirus 59/257 23%

Lopinavir/Ritonavir (+/- Ribavirin)

Clinical considerations

- Evidence for efficacy of lopinavir/ritonavir (with or without ribavirin) for COVID-19 is unclear. Recommendations for use are primarily based on positive outcomes in SARS.
- ~~Of note, lopinavir/ritonavir may have a significant drug interaction with remdesivir (see remdesivir section). Will need to be discontinued prior to initiating remdesivir.~~[7]
    - ~~This statement was initially believed to be true based on NIH study protocol but has since been likely invalidated for the IV form of remdesivir. Activation of remdesivir (prodrug) is through hydrolysis by intracellular esterases and does not appear to be significantly dependent on CYP3A4.~~[8]

Acquisition and Administration

- Lopinavir/ritonavir is not on SHC formulary but an emergency stock is being maintained for COVID-19
- Dosage: 400/100 mg PO BID for up to 10 days[23] (in SARS studies[45,46] given with Ribavirin 2.4 gram or 4 gram PO loading dose followed by 1.2 grams PO every 8 hours)
    - If administering via feeding tube, liquid formulation available but may be in shortage. Crushed tablets administered via feeding tube decreased AUC by 45 and 47% for lopinavir and ritonavir, respectively.[47] If liquid unavailable and must use crushed tablets via feeding tube, consider doubling dose either 800/200 mg PO BID or 400/100 mg PO 4x daily. The latter may have better GI tolerance.

Drug Interactions

- See: http://www.covid19-druginteractions.org/

Supporting evidence

- Lopinavir is an HIV protease inhibitor that has been reported to have activity against SARS-CoV-2. It is unclear whether inhibitors of HIV protease (in the aspartic protease family) can effectively inhibit that of SARS-CoV-2 (in the cysteine protease family).[48] It has been shown to have modest ability to inhibit MERS-CoV in vitro, but was less potent than remdesivir.[49]

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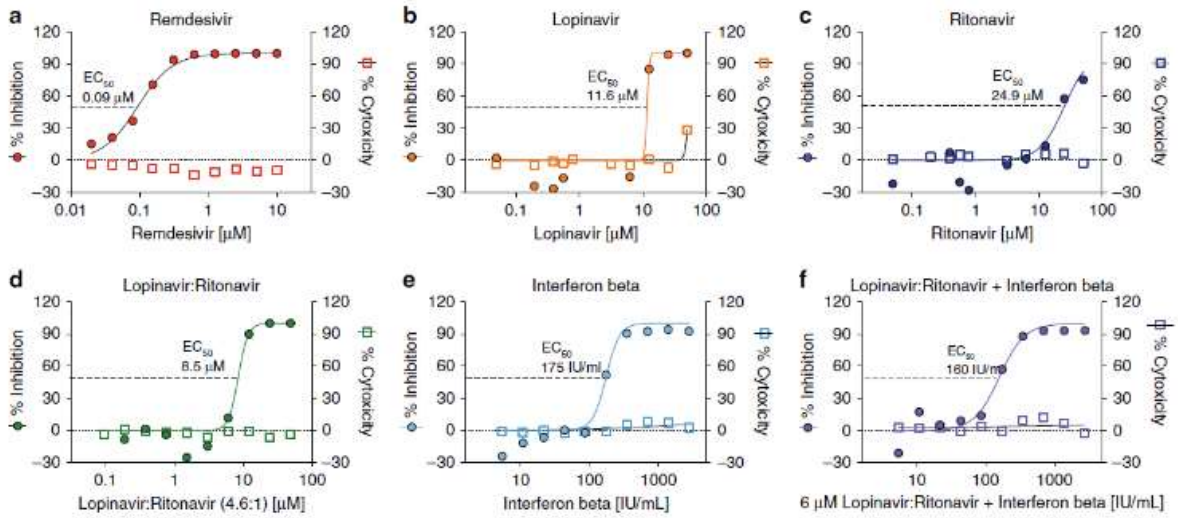


Fig. 1 RDV and IFNb have superior antiviral activity to LPV and RTV. Graphs depict mean % inhibition of MERS-CoV replication (left Y-axis) and % cytotoxicity (right Y-axis) of antivirals. Calu-3 cells were infected in sextuplicate with MERS-CoV nanoluciferase (nLUC) at a multiplicity of infection (MOI) of 0.08 in the presence of a dose response of drug for 48 h, after which replication was measured through quantitation of MERS-CoV-expressed nLUC. Cytotoxicity was measured in similarly treated but uninfected cultures via Cell-Titer-Glo assay. Representative data are shown from four independent experiments.

LOTUS China Study[50]

- An open label, randomized, controlled trial of 199 patients with COVID-19 in Wuhan.
- Assignment/Intervention: 99 were assigned to the LPV/r (400/100 mg PO BID x 14 days) + Standard of Care (SOC), and 100 to the SOC only group (SOC was comprised, as necessary, supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and ECMO)
- Demographics described in table below

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Total (N=199)	Lopinavir–Ritonavir (N=99)	Standard Care (N=100)
Age, median (IQR) — yr	58.0 (49.0–68.0)	58.0 (50.0–68.0)	58.0 (48.0–68.0)
Male sex — no. (%)	120 (60.3)	61 (61.6)	59 (59.0)
Coexisting conditions — no. (%)			
Diabetes	23 (11.6)	10 (10.1)	13 (13.0)
Cerebrovascular disease	13 (6.5)	5 (5.1)	8 (8.0)
Cancer	6 (3.0)	5 (5.1)	1 (1.0)
Body temperature, median (IQR) — °C	36.5 (36.4–36.8)	36.5 (36.4–37.0)	36.5 (36.5–36.8)
Fever — no. (%)	182 (91.5)	89 (89.9)	93 (93.0)
Respiratory rate >24/min — no. (%)	37 (18.8)	21 (21.6)	16 (16.0)
Systolic blood pressure <90 mm Hg — no. (%)	2 (1.0)	2 (2.0)	0
White-cell count ($\times 10^{-9}$/liter) — median (IQR)	7.0 (5.1–9.4)	7.3 (5.3–9.6)	6.9 (4.9–9.1)
4–10 $\times 10^{-9}$/liter — no. (%)	137 (70.3)	64 (67.4)	73 (73.0)
<4 $\times 10^{-9}$/liter — no. (%)	20 (10.3)	12 (12.6)	8 (8.0)
>10 $\times 10^{-9}$/liter — no. (%)	38 (19.5)	19 (20.0)	19 (19.0)
Lymphocyte count ($\times 10^{-9}$/liter) — median (IQR)	0.9 (0.6–1.2)	0.8 (0.6–1.4)	0.9 (0.5–1.2)
≥1.0 $\times 10^{-9}$/liter — no. (%)	73 (37.4)	37 (38.9)	36 (36.0)
<1.0 $\times 10^{-9}$/liter — no. (%)	122 (62.6)	58 (61.1)	64 (64.0)
Platelet count ($\times 10^{-9}$/liter) — median (IQR)	207.0 (158.0–284.0)	201.0 (155.0–287.0)	210.0 (163.0–269.5)
≥100 $\times 10^{-9}$/liter — no. (%)	186 (95.4)	91 (95.8)	95 (95.0)
<100 $\times 10^{-9}$/liter — no. (%)	9 (4.6)	4 (4.2)	5 (5.0)
Serum creatinine (μmol/liter) — median (IQR)	69.5 (57.2–82.5)	70.7 (56.4–82.7)	67.4 (58.4–82.5)
≤133 μmol/liter — no. (%)	189 (96.9)	93 (96.9)	96 (97.0)
>133 μmol/liter — no. (%)	6 (3.1)	3 (3.1)	3 (3.0)
Aspartate aminotransferase (U/liter) — median (IQR)	34.0 (26.0–45.0)	33.0 (25.0–42.0)	34.0 (27.0–45.0)
≤40 U/liter — no. (%)	155 (79.5)	78 (81.3)	77 (77.8)
>40 U/liter — no. (%)	40 (20.5)	18 (18.8)	22 (22.2)
Alanine aminotransferase (U/liter) — median (IQR)	33.0 (22.0–55.0)	33.0 (22.0–53.5)	34.0 (22.0–59.0)
≤50 U/liter — no. (%)	115 (59.0)	61 (63.5)	54 (54.5)
>50 U/liter — no. (%)	80 (41.0)	35 (36.5)	45 (45.5)
Lactate dehydrogenase (U/liter) — median (IQR)	325.0 (245.0–433.0)	322.0 (243.0–409.0)	327.0 (245.0–470.0)
≤245 U/liter — no. (%)	50 (25.8)	24 (25.3)	26 (26.3)
>245 U/liter — no. (%)	144 (74.2)	71 (74.7)	73 (73.7)
Creatine kinase (U/liter) — median (IQR)	69.0 (44.0–115.0)	57.0 (42.0–126.0)	72.0 (45.0–110.0)
≤185 U/liter — no. (%)	168 (86.6)	81 (85.3)	87 (87.9)
> 185 U/liter — no. (%)	26 (13.4)	14 (14.7)	12 (12.1)

* The values shown are based on available data. Laboratory values for white-cell count, lymphocyte count, platelet count, lactate dehydrogenase, and creatine kinase were available for 95 patients in the lopinavir–ritonavir group; and values for serum creatinine, aspartate aminotransferase, and alanine aminotransferase were available for 96 patients in that group. Laboratory values for serum creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and creatine kinase were available for 99 patients in the standard-care group. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. IQR denotes interquartile range.

- The primary end-point was the time to clinical improvement, defined as the time from randomization to an improvement of two points (from the status at randomization) on a seven-category ordinal scale or live discharge from the hospital, whichever came first.
- Patients assigned to LPV/r did not have a time to clinical improvement different from that of patients assigned to standard care alone in the intention-to-treat population (median, 16 day vs. 16 days; hazard ratio for clinical improvement, 1.31; 95% CI, 0.95 to 1.85; P=0.09). In the modified intention-to-treat population, the median time to clinical improvement was 15 days in the LPV/r group, as compared with 16 days in the standard-care group (hazard ratio, 1.39; 95% CI, 1.00 to 1.91).
- In the intention-to-treat population, lopinavir–ritonavir treatment within 12 days after the onset of symptoms was not found to be associated with a shorter time to clinical improvement (hazard ratio, 1.25; 95% CI, 0.77 to

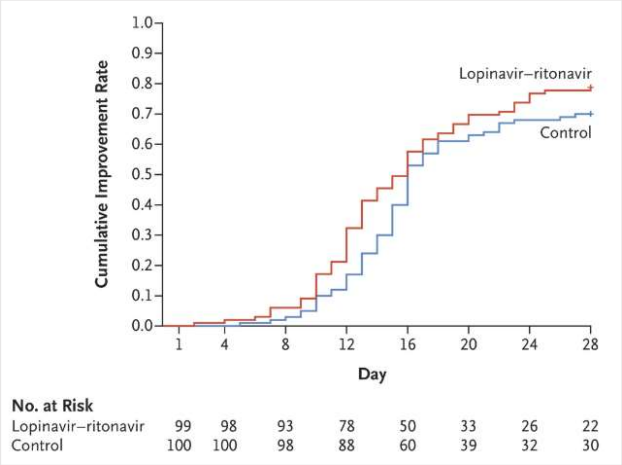
2.05); similar results were found regarding later treatment with lopinavir–ritonavir (hazard ratio, 1.30; 95% CI, 0.84 to 1.99)

- The 28-day mortality was numerically (but not significantly) lower in the lopinavir–ritonavir group than in the standard-care group for either the intention-to-treat population (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7) or the modified intention-to treat population (16.7% vs. 25.0%; difference, −8.3 percentage points; 95% CI, −19.6 to 3.0)
- The viral RNA loads of 69 patients (35% of total N) over time did not differ between the lopinavir–ritonavir recipients and those receiving standard care
- A total of 46 patients (48.4%) in the lopinavir–ritonavir group and 49 (49.5%) in the standard-care group reported adverse events between randomization and day 28. Gastrointestinal adverse events including nausea, vomiting, and diarrhea were more common in lopinavir–ritonavir group than in the standard-care group. The percentages of patients with laboratory abnormalities were similar in the two groups. There were 4 serious gastrointestinal adverse events in the lopinavir–ritonavir group but none in the standard-care group. Nearly 14% of lopinavir–ritonavir recipients were unable to complete the full 14-day course of administration. This was due primarily to gastrointestinal adverse events, including anorexia, nausea, abdominal discomfort, or diarrhea, as well as two serious adverse events, both acute gastritis.

Table 2. Patients' Status and Treatments Received at or after Enrollment.*

Characteristic	Total (N=199)	Lopinavir–Ritonavir (N=99)	Standard Care (N=100)
NEWS2 score at day 1 — median (IQR)	5.0 (4.0–6.0)	5.0 (4.0–6.0)	5.0 (4.0–7.0)
Seven-category scale at day 1			
3: Hospitalization, not requiring supplemental oxygen — no. (%)	28 (14.1)	11 (11.1)	17 (17.0)
4: Hospitalization, requiring supplemental oxygen — no. (%)	139 (69.8)	72 (72.7)	67 (67.0)
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation — no. (%)	31 (15.6)	15 (15.2)	16 (16.0)
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both — no. (%)	1 (0.5)	1 (1.0)	0
Days from illness onset to randomization — median (IQR)	13 (11–16)	13 (11–17)	13 (10–16)
Earlier (≤12 days of symptom onset) — no. (%)	90 (45.2)	42 (42.4)	48 (48.0)
Later (>12 days of symptom onset) — no. (%)	109 (54.8)	57 (57.6)	52 (52.0)
Mean viral load — $\log_{10}$ copies per ml at day 1	4.0±2.1	4.4±2.0	3.7±2.1
Using interferon at enrollment — no. (%)	22 (11.1)	9 (9.1)	13 (13.0)
Treatments during study period — no. (%)			
Vasopressors	44 (22.1)	17 (17.2)	27 (27.0)
Renal-replacement therapy	9 (4.5)	3 (3.0)	6 (6.0)
Noninvasive mechanical ventilation	29 (14.6)	10 (10.1)	19 (19.0)
Invasive mechanical ventilation	32 (16.1)	14 (14.1)	18 (18.0)
ECMO	4 (2.0)	2 (2.0)	2 (2.0)
Antibiotic agent	189 (95.0)	94 (94.9)	95 (95.0)
Glucocorticoid therapy	67 (33.7)	32 (32.3)	35 (35.0)
Days from illness onset to glucocorticoid therapy — median (IQR)	13 (11–17)	13 (12–19)	13 (9–17)
Days of glucocorticoid therapy — median (IQR)	6 (3–11)	7 (3–11)	6 (2–12)

* Plus–minus values are means ±SD. ECMO denotes extracorporeal membrane oxygenation, HFNC high-flow nasal cannula for oxygen therapy, and NEWS2 National Early Warning Score 2.



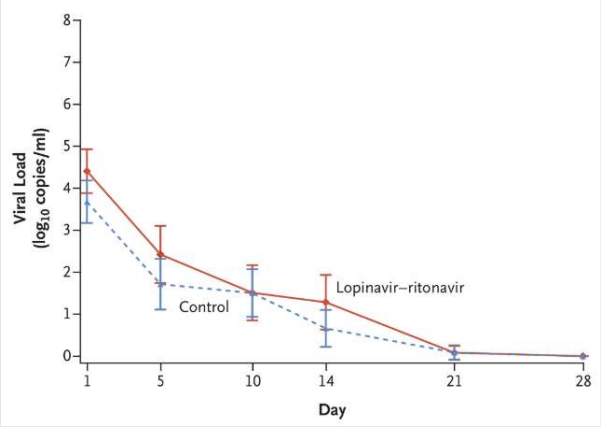


Table 3. Outcomes in the Intention-to-Treat Population.*

Characteristic	Total (N=199)	Lopinavir–Ritonavir (N=99)	Standard Care (N=100)	Difference†
Time to clinical improvement — median no. of days (IQR)	16.0 (15.0 to 17.0)	16.0 (13.0 to 17.0)	16.0 (15.0 to 18.0)	1.31 (0.95 to 1.80)‡
Day 28 mortality — no. (%)	44 (22.1)	19 (19.2)§	25 (25.0)	−5.8 (−17.3 to 5.7)
Earlier (≤12 days after onset of symptoms)	21 (23.3)	8 (19.0)	13 (27.1)	−8.0 (−25.3 to 9.3)
Later (>12 days after onset of symptoms)	23 (21.1)	11 (19.3)	12 (23.1)	−3.8 (−19.1 to 11.6)
Clinical improvement — no. (%)				
Day 7	8 (4.0)	6 (6.1)	2 (2.0)	4.1 (−1.4 to 9.5)
Day 14	75 (37.7)	45 (45.5)	30 (30.0)	15.5 (2.2 to 28.8)
Day 28	148 (74.4)	78 (78.8)	70 (70.0)	8.8 (−3.3 to 20.9)
ICU length of stay — median no. of days (IQR)	10 (5 to 14)	6 (2 to 11)	11 (7 to 17)	−5 (−9 to 0)
Of survivors	10 (8 to 17)	9 (5 to 44)	11 (9 to 14)	−1 (−16 to 38)
Of nonsurvivors	10 (4 to 14)	6 (2 to 11)	12 (7 to 17)	−6 (−11 to 0)
Duration of invasive mechanical ventilation — median no. of days (IQR)	5 (3 to 9)	4 (3 to 7)	5 (3 to 9)	−1 (−4 to 2)
Oxygen support — days (IQR)	13 (8 to 16)	12 (9 to 16)	13 (6 to 16)	0 (−2 to 2)
Hospital stay — median no. of days (IQR)	15 (12 to 17)	14 (12 to 17)	16 (13 to 18)	1 (0 to 2)
Time from randomization to discharge — median no. of days (IQR)	13 (10 to 16)	12 (10 to 16)	14 (11 to 16)	1 (0 to 3)
Time from randomization to death — median no. of days (IQR)	10 (6 to 15)	9 (6 to 13)	12 (6 to 15)	−3 (−6 to 2)
Score on seven-category scale at day 7 — no. of patients (%)				
2: Not hospitalized, but unable to resume normal activities	4 (2.0)	4 (4.0)	0	
3: Hospitalization, not requiring supplemental oxygen	29 (14.6)	12 (12.1)	17 (17.0)	
4: Hospitalization, requiring supplemental oxygen	109 (54.8)	58 (58.6)	51 (51.0)	
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation	35 (17.6)	14 (14.1)	21 (21.0)	
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both	10 (5.0)	6 (6.1)	4 (4.0)	
7: Death	12 (6.0)	5 (5.1)	7 (7.0)	
Seven-category scale at day 14 — no. of patients (%)				
2: Not hospitalized, but unable to resume normal activities	71 (35.7)	43 (43.4)	28 (28.0)	
3: Hospitalization, not requiring supplemental oxygen	32 (16.1)	8 (8.1)	24 (24.0)	
4: Hospitalization, requiring supplemental oxygen	45 (22.6)	25 (25.3)	20 (20.0)	
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation	11 (5.5)	5 (5.1)	6 (6.0)	
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both	8 (4.0)	3 (3.0)	5 (5.0)	
7: Death	32 (16.1)	15 (15.2)	17 (17.0)	

* Clinical improvement was defined as a decline of two categories on the modified seven-category ordinal scale of clinical status, or hospital discharge. ICU denotes intensive care unit.
† Differences were expressed as rate differences or median differences (Hodges–Lehmann estimate) and 95% confidence intervals.
‡ The hazard ratio for clinical improvement was estimated by Cox proportional-risk model.
§ This total includes 3 patients who died within 24 hours after randomization and did not receive lopinavir–ritonavir.

Table 4. Summary of Adverse Events in the Safety Population.*

Event	Lopinavir–Ritonavir (N=95)		Standard Care (N=99)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number (percent)			
Any adverse event	46 (48.4)	20 (21.1)	49 (49.5)	11 (11.1)
Lymphopenia	16 (16.8)	12 (12.6)	12 (12.1)	5 (5.1)
Nausea	9 (9.5)	1 (1.1)	0	0
Thrombocytopenia	6 (6.3)	1 (1.1)	10 (10.1)	2 (2.0)
Leukopenia	7 (7.4)	1 (1.1)	13 (13.1)	0
Vomiting	6 (6.3)	0	0	0
Increased aspartate aminotransferase	2 (2.1)	2 (2.1)	5 (5.1)	4 (4.0)
Abdominal discomfort	4 (4.2)	0	2 (2.1)	0
Diarrhea	4 (4.2)	0	0	0
Stomach ache	4 (4.2)	1 (1.1)	1 (1.0)	0
Neutropenia	4 (4.2)	1 (1.1)	8 (7.6)	0
Increased total bilirubin	3 (3.2)	3 (3.2)	3 (3.0)	2 (2.0)
Increased creatinine	2 (2.1)	2 (2.1)	7 (7.1)	6 (6.1)
Anemia	2 (2.1)	2 (2.1)	5 (5.0)	4 (4.0)
Rash	2 (2.1)	0	0	0
Hypoalbuminemia	1 (1.1)	1 (1.1)	4 (4.0)	1 (1.0)
Increased alanine aminotransferase	1 (1.1)	1 (1.1)	4 (4.0)	1 (1.0)
Increased creatine kinase	0	0	1 (1.0)	0
Decreased appetite	2 (2.1)	0	0	0
Prolonged QT interval	1 (1.1)	0	0	0
Sleep disorders and disturbances	1 (1.1)	0	0	0
Facial flushing	1 (1.1)	0	0	0
Serious adverse event	19 (20.0)	17 (17.9)	32 (32.3)	31 (31.3)
Respiratory failure or ARDS	12 (12.6)	12 (12.6)	27 (27.3)	27 (27.3)
Acute kidney injury	3 (3.2)	2 (2.1)	6 (6.1)	5 (5.1)
Secondary infection	1 (1.1)	1 (1.1)	6 (6.1)	6 (6.1)
Shock	2 (2.1)	2 (2.1)	2 (2.0)	2 (2.0)
Severe anemia	3 (3.2)	3 (3.2)	0	0
Acute gastritis	2 (2.1)	0	0	0
Hemorrhage of lower digestive tract	2 (2.1)	1 (1.1)	0	0
Pneumothorax	0	0	2 (2.0)	2 (2.0)
Unconsciousness	1 (1.1)	0	0	0
Disseminated intravascular coagulation	1 (1.1)	0	1 (1.0)	1 (1.0)
Sepsis	0	0	1 (1.0)	1 (1.0)
Acute heart failure	0	0	1 (1.0)	1 (1.0)

* Adverse events that occurred in more than 1 patient after randomization through day 28 are shown. Some patients had more than one adverse event. Since there are no adverse event grades criteria for serum levels of hypersensitivity troponin (cardiac biomarker) and serum lipid, the proportions of patients with values worse than baseline values are listed here. The proportion of increased hypersensitivity troponin was higher in the standard-care group than in the lopinavir–ritonavir group (14.1% vs. 9.5%). A total of 55 patients (52.4%) in the standard-care group and 65 (68.4%) in the lopinavir–ritonavir group had lipid levels that were normal at enrollment but abnormal after enrollment. All deaths were due to respiratory failure. ARDS indicates acute respiratory distress syndrome.

ELACOI Trial[51]

- Randomized, controlled study in Guangzhou of lopinavir/ritonavir vs. arbidol vs. control in mild/moderate COVID-19. This study found no benefit of lopinavir/ritonavir or arbidol compared with no antivirals for mild/moderate COVID-19.
- Patients were randomized 2:2:1 to lopinavir/ritonavir 400/100 mg PO BID x 7-14 days (N=21), arbidol 200 mg PO TID x 7-14 days (N=16), or control (no antivirals) (N=7).
- The median time of positive-to-negative conversion of SARS-CoV2 nucleic acid was 8.5 (IQR 3, 13) days in the LPV/r group, 7 (IQR 3, 10.5) days in the arbidol group and 4 (IQR 3, 10.5) days in the control group (P=0.751).

- The positive-to-negative conversion rates of SARS-CoV-2 nucleic acid at day 7 and 14 did not show significant differences in the LPV/r group (42.9%, 76.2%), the arbidol group (62.5%, 87.5%) and the control group (71.4%, 71.4%) (all P>0.53).
- No statistical differences were found among three groups in the rates of antipyresis, cough alleviation, improvement of chest CT or the deterioration rate of clinical status (all P > 0.05).
- Overall, 5 (23.8%) patients in the LPV/r group experienced adverse events during the follow-up period. No apparent adverse events occurred in the arbidol or control group.

Table 1: Baseline characteristics of the three treatment groups (intention-to-treat population)

Characteristic	LPV/r (n=21)	Arbidol (n=16)	Control (n=7)	*P* value
Gender (n, %)				0.914
Male	11(52.4%)	7(43.7%)	4(57.1%)	
Female	10(47.6%)	9(56.3%)	3(42.9%)	
Age, in years (mean, SD, range)	52.2(15.2;27-79)	49.4(14.6;30-73)	40.9(12.7;28-62)	0.218
Time from onset to treatment, in days (mean, SD, range)	4.3(3.3;1-15)	4.1(3.2;0.5-11)	5.6(3.0;1-8)	0.582
Underlying chronic diseases¶ (n, %)	7(33.3%)	7(43.8%)	1(14.3%)	0.530
Evidence of pneumonia based on chest CT imaging (n, %)	19(90.5%)	15(93.8%)	6(85.7%)	0.814
Clinical status (n, %)				0.814
mild	2(9.5%)	1(16.2%)	1(14.3%)	
moderate	19(90.5%)	15(93.8%)	6(85.7%)	
White blood cell count,10^9/L				0.929
<3.5 (n, %)	2(9.5%)	2(12.5%)	1(14.3%)	
3.5-9.5 (n, %)	19(90.5%)	14(87.5%)	6(85.7%)	
Lymphocyte count,10^9/L				0.861
<1.1 (n, %)	7(33.3%)	4(25.0%)	2(28.6%)	
1.1-3.2 (n, %)	14(66.7%)	12(75.0%)	5(71.4%)	
Neutrophil count,10^9/L				0.921
<3.5 (n, %)	2(9.5%)	2(12.5%)	1(14.3%)	
1.8-6.3 (n, %)	19(90.5%)	13(81.3%)	6(85.7%)	
>6.3(n, %)	0	1(6.3%)	0	
C-reactive protein,mg/L				0.06
<10 (n, %)	8(38.1%)	12(75.0%)	5(71.4%)	
>10(n, %)	13(61.9%)	4(25.0%)	2(28.6%)	
Procalcitonin, ng/mL				0.053
<0.05 (n, %)	10(47.6%)	13(81.3%)	6(85.7%)	
>0.05(n, %)	11(52.4%)	3(18.8%)	1(14.3%)	
Use of gamma globulin (%)	2/21(9.5%)	2/16(12.5%)	1/7(14.3%)	1.000
Use of glucocorticoids (%)	6/21(28.6%)	2/16(12.5%)	2/7(28.6%)	0.547
Oxygen therapy (%)				0.466
None	3/21(14.3%)	5/16(31.3%)	1/7(14.3%)	
Low flow oxygen supply	13/21(61.9%)	9/16(56.3%)	6/7(85.7%)	
High flow oxygen supply	5/21(23.8%)	2/16(12.5%)	0	

¶ list all the chronic diseases

Table 2: Outcomes of the three groups (intention-to-treat population)

Outcome	LPV/r	Arbidol	Control	*P* value	***Power***
Time to positive-to-negative conversion of SARS-CoV-2 nucleic acid in pharyngeal swab, in days (mean/SD, 95%CI)	8.70(6.00),(5.89,11.51)	7.63(5.32),(4.79,10.46)	7.00(5.94),(1.50,12.50)	0.751	0.47
Conversion rate from moderate to severe/critical clinical status (%)	8/21 (38.1%)	2/16(12.5%)	1/7(14.3%)	0.186	0.37
At 7 days after initiating treatment:					
Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid by pharyngeal swab (%)	9/21(42.9%)	10/16(62.5%)	5/7(71.4%)	0.942	0.28
Antipyresis rate (%)	8/11(72.7%)	5/9(55.6%)	2/2(100%)	0.536	0.72
Rate of cough alleviation (%)	9/19 (47.4%)	4/9(44.4%)	2/6(33.3%)	0.182	0.10
Rate of improvement on chest CT (%)	10/19(52.6%)	7/15(46.7%)	6/6 (100%)	0.074	0.86
At 14 days after initiating treatment:					
Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid by pharyngeal swab (%)	16/21(76.2%)	14/16(87.5%)	5/7(71.4%)	0.681	0.15
Antipyresis rate (%)	10/11 (90.9%)	9/9 (100%)	2/2 (100%)	1.000	0.30
Rate of cough alleviation (%)	17/19 (89.5%)	9/9 (100%)	5/6 (83.3%)	0.743	0.28
Rate of improvement on chest CT (%)	16/19(84.2%)	10/15(66.7%)	6/6 (100%)	0.193	0.58

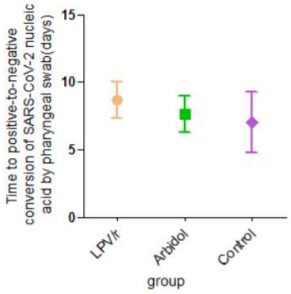


Figure 2. Time to positive-to-negative conversion of SARS-CoV-2 nucleic acid by pharyngeal swab in each of the treatment three groups during the 21-day follow-up period

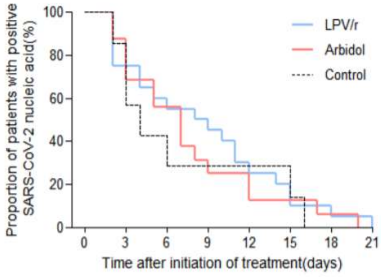


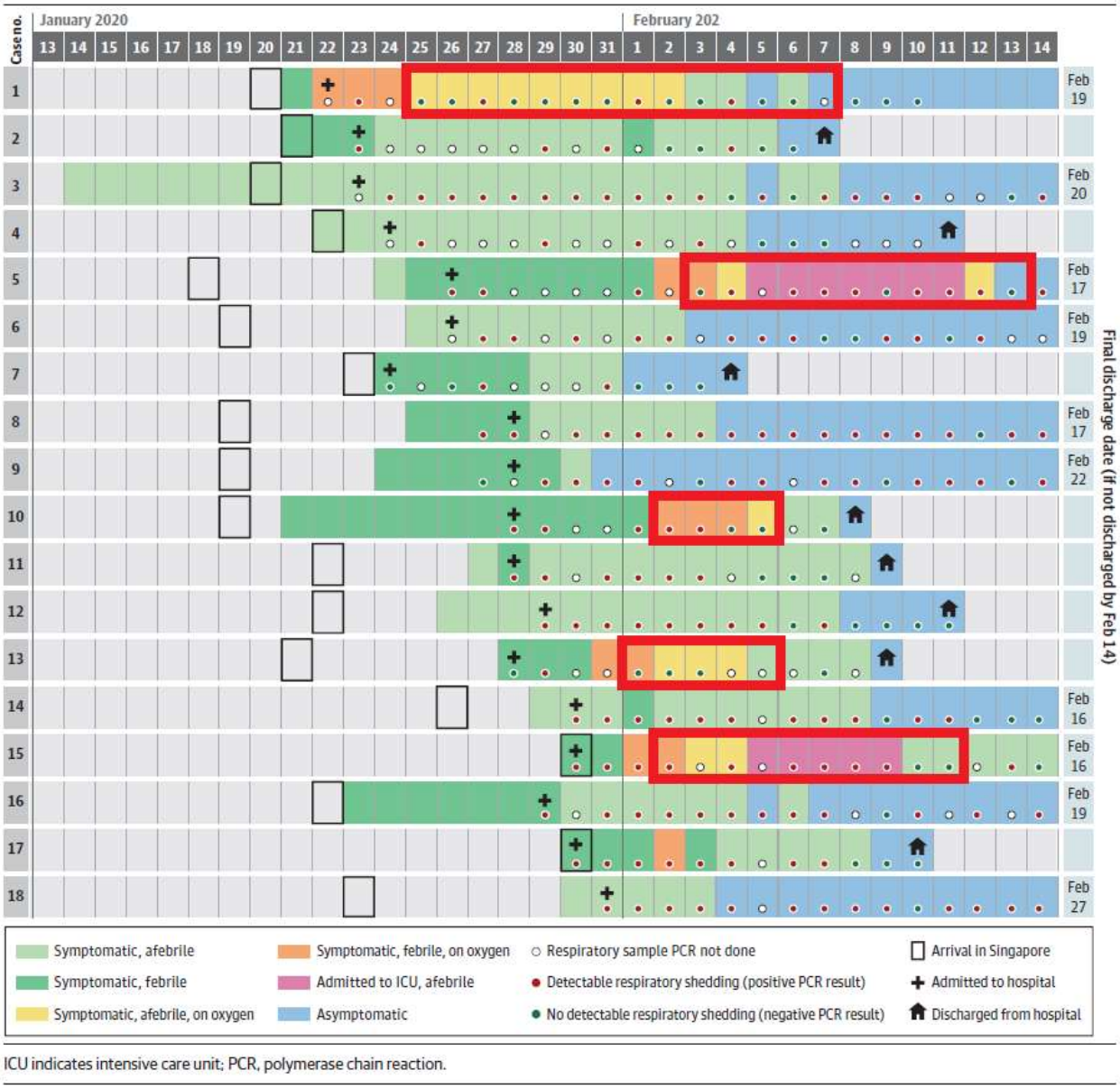
Figure 3. Proportion of patients in each of the three treatment groups with positive SARS-CoV-2 nucleic acid by pharyngeal swab during the 21-day follow-up period

Singapore Lopinavir/Ritonavir Study[52]

- A retrospective observational study of 18 patients with COVID-19 in Singapore, 5 of which received lopinavir/ritonavir, clinical benefit was deemed equivocal (3 patients had improved oxygenation of which 2 had clearance of nasopharyngeal viral detection within two days of treatment, the remaining 2 had progressive disease and one of these required intubation).
- Of note this study used a lower dose (200/100 mg twice daily) of lopinavir/ritonavir, did not use synergistic ribavirin that was used in prior studies of SARS, and patients who received lopinavir/ritonavir had a higher severity of disease compared to those that did not. (see below)

Red boxes indicate days on which patients (Cases 1, 5, 10, 13, and 15) received LPV/r

Figure 1. Time Course of Symptoms, Supplemental Oxygen Requirements, Hospital Admission, and Discharge of Patients Infected With SARS-CoV-2



ICU indicates intensive care unit; PCR, polymerase chain reaction.

Shanghai Case Series[53]

- In a study of 4 patients, 2 with mild, 2 with severe COVID-19 in Shanghai who received lopinavir/ritonavir (400/100mg PO BID x 6-15 days) along with other treatments including umifenovir (membrane fusion inhibitor and immunomodulator antiviral available in Asia) and traditional Chinese medicine, 3 improved, 2 of which had negative viral testing at end of data collection. The fourth patient, with severe COVID-19, showed signs of improvement at end of data collection. (see below)
- Of note, this study is a case series without comparator arm, used other adjunctive therapies (umifenovir, traditional Chinese medicine, and in one case IV immunoglobulin), did not describe terminal clinical outcome of 2 patients (cases 3 and 4)

Table 1. Demographics, baseline characteristics, and clinical outcomes of 4 patients admitted to Shanghai Public Health Clinical Center

Items	Case 1	Case 2	Case 3	Case 4
Age	32	19	63	63
Sex	Male	Male	Male	Female
Exposure history	Recent travel to Wuhan	Resident of Wuhan	Close contact with 2019-nCoV patient	Recent travel to Wuhan
Chronic medical illness	Fatty liver	None	None	None
Days from illness onset to diagnosis confirmation	11	6	1	2
Clinical outcome	Discharged	Discharged	Remained in hospital	Remained in hospital

Table 2. Clinical characteristics at presentation and treatment of patients with 2019-nCoV pneumonia

Items	Case 1	Case 2	Case 3	Case 4
Signs and symptoms				
Fever	Yes	Yes	Yes	Yes
Cough		Yes	Yes	Yes
Fatigue	Yes	Yes		
Dizziness	Yes			Yes
Nasal congestion		Yes		
Rhinorrhea		Yes		
Constipation	Yes			Yes
Respiratory rate	22/min	19/min	26/min	22/min
Lung auscultation	Rhonchi (left lower lobe)	No rhonchi	Rhonchi (right lower lobe)	Rhonchi (left lower lobe)
Chest CT findings				
Unilateral pneumonia		Yes	Yes	
Bilateral pneumonia	Yes			Yes
Treatment				
Oxygen therapy	Yes	Yes	Yes	Yes
Mechanical ventilation				Yes
Antibiotic treatment	Yes	Yes	Yes	Yes
Lopinavir/ritonavir/arbidol/SFJDC	Yes	Yes	Yes	Yes
Intravenous immunoglobulin therapy				Yes

Table 3. Clinical laboratory results of patients with 2019-nCoV pneumonia

Variable	Case 1		Case 2		Case 3		Case 4	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Blood, routine								
Leucocytes ($\times 10^9$ per L; normal range 3.5-9.5)	4.23	4.68	6.48	6.58	4.40	5.31	6.84	10.84
Neutrophils (%; normal range 50-70)	57.2	49.1	57.0	47.6	50.0	55.4	93	94
Lymphocytes (%; normal range 20-40)	30.3	37.1	30.6	39.4	24.5	25.0	6.10	3.2
Blood gas analysis								
pH (normal range 7.35-7.45)	7.33	7.33	7.43	7.33	7.40	7.36	7.44	7.33
PCO_2 (kPa, normal range 4.65-6.0)	5.42	6.05	4.55	5.96	5.45	5.59	4.23	5.52
PO_2 (kPa, normal range 10.6-13.3)	22.00	11.90	16.6	13.4	7.60	12.0	5.45	21.9

- Rapid advice guidelines for 2019-nCoV pneumonia from the Zhongnan Hospital of Wuhan Novel Coronavirus Management and Research Team published February 6, 2020 provided a weak recommendation for use of lopinavir/ritonavir based on benefits found in patients with SARS or MERS, especially with earlier administration.[54]

Studies in SARS:

- In a retrospective case control study of 75 patients with SARS, addition of lopinavir 400 mg/ritonavir 100 mg orally twice daily for 10-14 days as initial treatment showed association with lower death rate (2.3% vs 15.6%), intubation rate (0% vs 11.0%) compared with 634 matched controls. Excluded pregnancy, liver disease.[45]
- In a retrospective case control study of 41 patients with SARS who received LPV/r 400/100 mg orally twice daily x 14 days with ribavirin compared to 111 patients who received ribavirin only, incidence of ADRS or death was significantly lower in LPV/r group (2.4% vs. 28.8%, $p<0.001$) at day 21.[46]

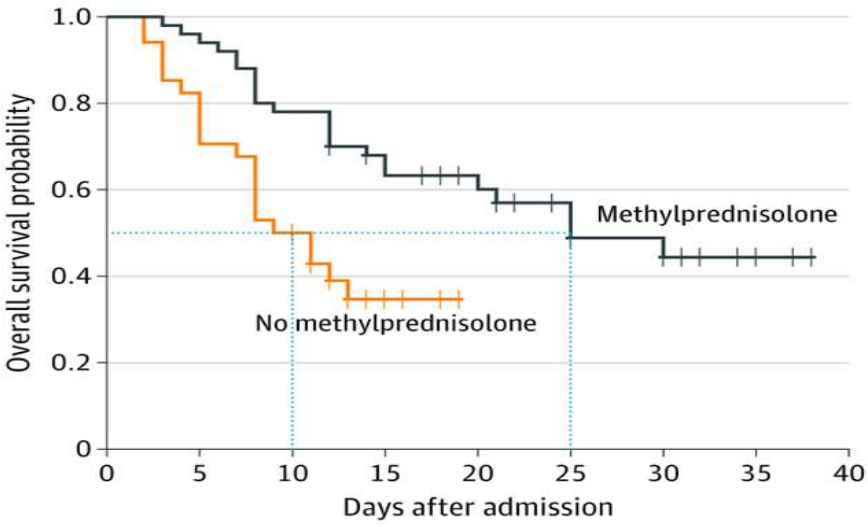
Adjunctive Therapy (Corticosteroids, Tocilizumab)

Corticosteroids

- Considerations:
  - Supporting evidence is conflicting on whether corticosteroid therapy is harmful, beneficial, or neutral to clinical outcomes in general (see supportive data)
- Dosage:
  - Chinese New Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 7th Edition) recommends methylprednisolone not to exceed 1-2mg/kg/day for 3-5 days
- Supportive Data:
  - Chinese New Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 7th Edition) provide a conditional recommendation (at clinician discretion) for adjunctive glucocorticoid therapy in patients with "progressively deteriorating oxygenation index, rapid imaging progression, and overactive inflammatory responses." They also acknowledge "immunosuppressive function of high-dose glucocorticoid may delay the clearance of coronavirus from the system".
  - In a study of 201 patients, 84 (41.8%) of which had ARDS, methylprednisolone administration decreased risk of death (HR, 0.38; 95% CI, 0.20-0.72) despite the fact that a higher proportion of patients who received methylprednisolone were classified into a higher grade on the Pneumonia Severity Index compared with patients who did not receive methylprednisolone (P = 0.01).[55] (see below)

Table 3. Clinical Characteristics and Initial Laboratory Indices Among Patients With and Without ARDS

	All patients				Patients with ARDS			
Clinical characteristics	Without ARDS, No. (%) (n = 117)	With ARDS, No. (%) (n = 84)	Difference (95% CI)[a]	P value[b]	Alive, No. (%) (n = 40)	Died, No. (%) (n = 44)	Difference (95% CI)[a]	P value[b]
Age, median (IQR), y	48.0 (40.0 to 54.0)	58.5 (50.0 to 69.0)	12.0 (8.0 to 16.0)	<.001	50.0 (40.3 to 56.8)	68.5 (59.3 to 75.0)	18.0 (13.0 to 23.0)	<.001
Highest patient temperature, median (IQR), °C	38.60 (38.2 to 39.0)	39.0 (38.5 to 39.6)	0.3 (0.0 to 0.5)	.004	39.0 (38.5 to 39.7)	38.9 (38.0 to 39.2)	−0.3 (−0.6 to 0.0)	.05
≥39 (high fever)	36 (36.4)	41 (57.7)	21.3 (5.3 to 37.5)	.006	27 (73.0)	14 (41.2)	−31.8 (−56.5 to −7.1)	.007
<39	63 (63.6)	30 (42.3)			10 (27.0)	20 (58.8)		
Gender								
Male	68 (58.1)	60 (71.4)	13.3 (−0.9 to 27.5)	.05	31 (77.5)	29 (65.9)	−11.6 (−33.0 to 9.9)	.24
Female	49 (41.9)	24 (28.6)			9 (22.5)	15 (34.1)		
Initial symptoms								
Fever	110 (94.0)	78 (92.9)	−1.2 (−9.2 to 6.8)	.74	39 (97.5)	39 (88.6)	−8.9 (−21.8 to 4.1)	.25
Cough	95 (81.2)	68 (81.0)	−0.2 (−11.5 to 11.0)	.97	35 (87.5)	33 (75.0)	−12.5 (−31.3 to 6.3)	.15
Productive cough	42 (35.9)	41 (48.8)	12.9 (−1.9 to 27.7)	.07	22 (55.0)	19 (43.2)	−11.8 (−35.5 to 11.8)	.28
Dyspnea	30 (25.6)	50 (59.5)	33.9 (19.7 to 48.1)	<.001	21 (52.5)	29 (65.9)	13.4 (−9.8 to 36.7)	.21
Fatigue or myalgia	38 (32.5)	27 (32.1)	−0.3 (−13.8 to 13.1)	.96	12 (30.0)	15 (34.1)	4.1 (−18.2 to 26.4)	.69
Comorbidities								
Hypertension	16 (13.7)	23 (27.4)	13.7 (1.3 to 26.1)	.02	7 (17.5)	16 (36.4)	18.9 (−2.0 to 39.7)	.05
Diabetes	6 (5.1)	16 (19.0)	13.9 (3.6 to 24.2)	.002	5 (12.5)	11 (25.0)	12.5 (−6.3 to 31.3)	.15
Cardiac disease	3 (2.6)	5 (6.0)	3.4 (−3.4 to 10.2)	.40	4 (10.0)	4 (9.1)	−0.9 (−14.4 to 12.6)	.13
Treatment in hospital								
Oxygen therapy[c]								
Nasal cannula	81 (69.2)	17 (20.2)	−49.0 (−62.0 to −36.0)	<.001	17 (42.5)	0	−42.5 (−60.2 to −24.8)	<.001
NMV	0	61 (72.6)	72.6 (62.1 to 83.2)		23 (57.5)	38 (86.4)	28.9 (8.1 to 49.6)	
IMV	0	5 (6.0)	6.0 (−0.1 to 12.0)		0	5 (11.4)	11.4 (−0.4 to 23.1)	
IMV with ECMO	0	1 (1.2)	1.2 (−2.2 to 4.5)		0	1 (2.3)	2.3 (−4.4 to 8.9)	
Methylprednisolone	12 (10.3)	50 (59.5)	49.3 (36.4 to 62.1)	<.001	27 (67.5)	23 (52.3)	−15.2 (−38.3 to 7.9)	.16
Antibiotic therapy	113 (96.6)	83 (98.8)	2.2 (−2.8 to 7.3)	.59	40 (100.0)	43 (97.7)	−2.3 (−8.9 to 4.4)	>.99
Antiviral therapy	106 (90.6)	64 (76.2)	−14.4 (−26.0 to −2.9)	.005	39 (97.5)	25 (56.8)	−40.7 (−58.5 to −22.9)	<.001



No. at risk

No methylprednisolone	34	28	17	4	0	0	0	0	0
Methylprednisolone	50	48	39	29	20	14	11	4	0

- In a study of 69 patients with COVID-19 in Wuhan, corticosteroid therapy was associated with increased rate of death, however, this could be due to an imbalance in patient characteristics and no regression or other analysis was performed to account for confounders.[56] (see below)

Table 2: Outcomes of COVID-19 patients treated with corticosteroids.

Prognosis	corticosteroids-treated group (n=10)	corticosteroids-untreated group (n=57)	p value
Hospitalization	3(30%)	41(72%)	<0.001
Discharge	3(30%)	15(26%)	..
Death	4(40%)	1(2%)	..

Abbreviations: COVID-19, coronavirus disease 2019. Data are n/N (%), where N is the total number of patients with available data. P values are comparing the corticosteroids-treated group and the corticosteroids-untreated group from χ^2 test. $P < 0.05$ was considered statistically significant.

Table 4: Treatments and outcomes of patients infected with SARS-CoV-2.

	All patients(n=67)	$SpO_2 \geq 90\%$(n=55)	$SpO_2 < 90\%$(n=12)	p value
Onset of symptom to admission	6.0(4.0-9.0)	6.0(4.0-9.0)	7.0(4.0-9.0)	0.928
Oxygen support	43(64.2%)	31(56.4%)	12(100.0%)	0.003
Prognosis				
Hospitalization	44(65.7%)	38(69.1%)	6(50.0%)	<0.001
Discharge	18(26.9%)	17(30.9%)	1(8.3%)	..
Death	5(7.5%)	0	5(41.7%)	..
Involved treatment				
Antiviral therapy	66(98.5%)	55(100.0%)	11(91.7%)	0.179
Antibiotic therapy	66(98.5%)	54(98.2%)	12(100.0%)	0.638
Antifungal therapy	8(11.9%)	3(5.5%)	5(41.7%)	<0.001
Use of corticosteroids	10(14.9%)	6(10.9%)	4(33.3%)	0.048
Arbidol	36(53.7%)	32(58.2%)	4(33.3%)	0.118

Abbreviations: SARS-CoV-2, 2019 severe acute respiratory syndrome coronavirus 2. Data are median (IQR) or n/N (%), where N is the total number of patients with available data. P values are comparing the $SpO_2 \geq 90\%$ group and the $SpO_2 < 90\%$ group from Mann-Whitney U test, χ^2 test, or Fisher's exact test. $P < 0.05$ was considered statistically significant.

- Of note, adjunctive corticosteroids have not shown clinical benefit and delayed viral RNA clearance in other coronavirus disease (SARS and MERS). Use has also been associated withan increased risk of side effects (e.g. psychosis, diabetes, avascular necrosis) and increased mortality in influenza.[57] (see below)

	Outcomes of corticosteroid therapy*	Comment
MERS-CoV	Delayed clearance of viral RNA from respiratory tract[3]	Adjusted hazard ratio 0·4 (95% CI 0·2–0·7)
SARS-CoV	Delayed clearance of viral RNA from blood[5]	Significant difference but effect size not quantified
SARS-CoV	Complication: psychosis[6]	Associated with higher cumulative dose, 10 975 mg *vs* 6780 mg hydrocortisone equivalent
SARS-CoV	Complication: diabetes[7]	33 (35%) of 95 patients treated with corticosteroid developed corticosteroid-induced diabetes
SARS-CoV	Complication: avascular necrosis in survivors[8]	Among 40 patients who survived after corticosteroid treatment, 12 (30%) had avascular necrosis and 30 (75%) had osteoporosis
Influenza	Increased mortality[9]	Risk ratio for mortality 1·75 (95% CI 1·3–2·4) in a meta-analysis of 6548 patients from ten studies
RSV	No clinical benefit in children[10,11]	No effect in largest randomised controlled trial of 600 children, of whom 305 (51%) had been treated with corticosteroids

CoV=coronavirus. MERS=Middle East respiratory syndrome. RSV=respiratory syncytial virus. SARS=severe acute respiratory syndrome. *Hydrocortisone, methylprednisolone, dexamethasone, and prednisolone.

Table: **Summary of clinical evidence to date**

- An open labelled, randomized, controlled trial of 48 patients will be conducted in China comparing corticosteroid therapy (methylprednisolone 1-2 mg/kg/day IV for 3 days) to a control group (no corticosteroid) in patients with severe COVID-19. Currently only the study protocol is published.[58]

Tocilizumab

- Considerations:
  - Recent revisions to Chinese guidance ("New Coronavirus Pneumonia Diagnosis and Treatment Scheme (Trial Version 7)") has proposed the use of tocilizumab for cytokine storm in patients with severe disease (e.g. acute respiratory distress syndrome) and elevated interleukin-6 levels.[59]

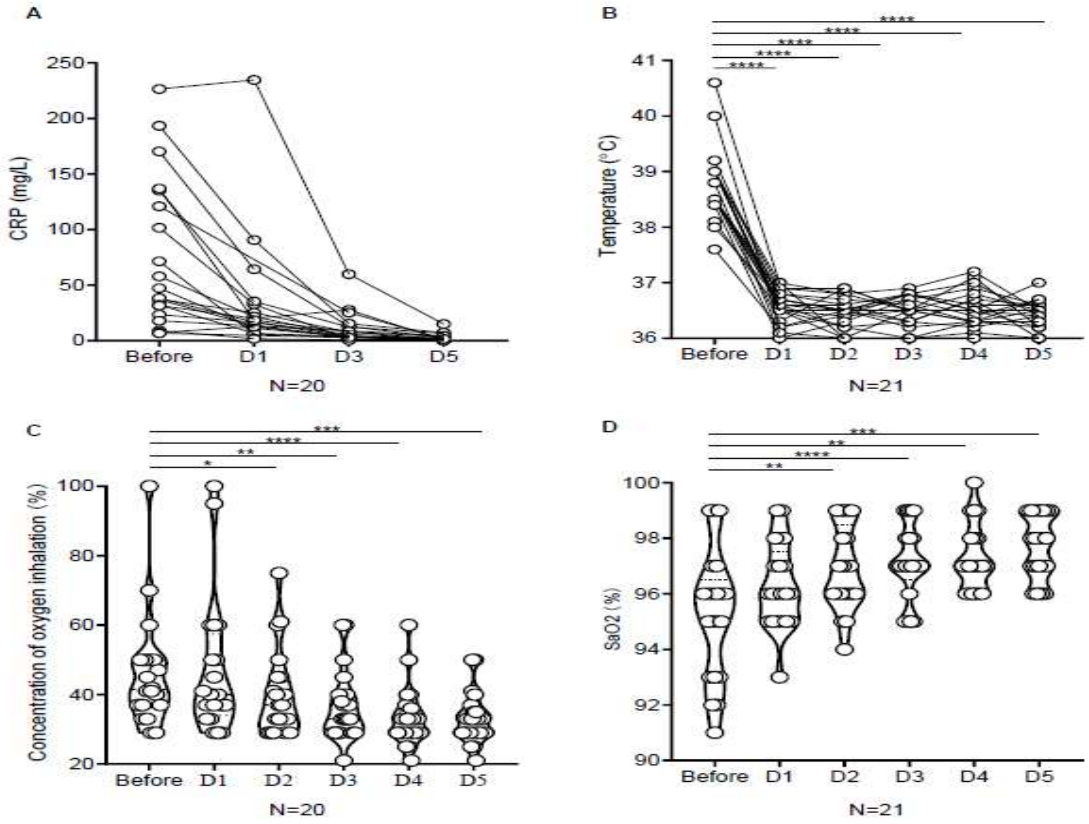
  - Benefit should be weighed against potential toxicities (see tolerability).
- Dosage:
  - Optimal dosing regimen is unclear
  - In a pre-peer review study of 21 patients with severe COVID, a single dose of 400 mg IV was used[60]
  - In cytokine release syndrome in the setting of CAR-T, a weight-based and severity-based dosing approach is taken, example:
    - Grade 2 CRS (Temp > 38 C, mild hypotension, no pressors, oxygenation via nasal cannula) – Tocilizumab 8 mg/kg (max 800 mg) IV x 1 dose
    - Grade 3 CRS (Temp > 38 C, requiring single vasopressor +/- vasopressin, oxygenation via mask or high flow) – Tocilizumab 8 mg/kg (max 800 mg) IV q4-6 hours (maximum 3 doses in 24 hours)
- Tolerability (all in setting of CAR-T, so clinical relevance in other patients unknown):[7]
  - GI perforation (typically secondary to diverticulitis)
  - Hematologic (neutropenia, thrombocytopenia)
  - Hepatic injury resulting in liver transplantation or death (may be delayed months to years after administration)
  - Secondary invasive fungal, bacterial, viral, protozoal, and other opportunistic infections due to immunosuppression
  - HSV reactivation
  - Tuberculosis, reactivation and new infection
  - Secondary malignancy (unclear association)
  - Hypersensitivity (to drug and excipients, notably polysorbate 80 [Tweens], which can result in delayed-type reaction)
- Supportive data:
  - In a pre-peer review study[60] of 21 patients in Wuhan with "severe" COVID (defined as RR ≥ 30 bpm, SpO2 ≤ 93% on RA, or PaO2/FiO2 ≤ 300 mmHg) tocilizumab was administered as a single IV dose of 400 mg.
    - Of note, despite the nomenclature, these patients could be considered mostly moderate in severity, with 16/21 (76%) on nasal cannula or high flow, and only 2/21 (10%) on invasive mechanical ventilation.
    - Patients also received lopinavir, methylprednisolone, "other symptom relievers," and oxygen therapy.
    - Fever curve, CRP, and oxygenation improved after tocilizumab therapy (see images below)
    - Concerns regarding interpretation of study findings are: (1) pre-peer review, (2) no comparator arm, (3) concomitant corticosteroid therapy, (4) mostly objectively moderate disease with only 2 patients on mechanical ventilation
    - Multiple studies are currently ongoing to evaluate the role of tocilizumab for management of COVID-19 (NCT04306705, ChiCTR2000029765, NCT04315480, NCT04317092, NCT04320615, NCT04322773

Table 2 Laboratory Tests before and after Tocilizumab

	Range	Before the tocilizumab	After the tocilizumab		
			D1	D3	D5
White-cell count, $\times 10^9$/L	3.5-9.5	6.30 ± 2.77 (4/20, 20.0%)	8.05 ± 4.39 (8/18, 44.4%)	6.02 ± 3.05 (9/21, 42.9%)	5.25 ± 2.11 (2/19, 10.5%)
Lymphocyte percentage, %	20-50	15.52 ± 8.89 (17/20, 85.0%)	11.78 ± 11.36 (16/18, 88.9%)	16.93 ± 13.59 (14/21, 66.7%)	22.62 ± 13.48 (9/19, 47.4%)
C-reactive protein, mg/L	0-5	75.06 ± 66.80 (20/20, 100%)	38.13 ± 54.21 (17/18, 94.4%)	10.61 ± 13.79 (10/20, 50.0%)	2.72 ± 3.60 (3/19, 15.8%)
Procalcitonin, ng/ml	0-0.5	0.33 ± 0.78 (2/20, 10.0%)	0.21 ± 0.35 (2/16, 12.5%)	0.09 ± 0.13 (1/19, 5.3%)	0.12 ± 0.15 (1/18,5.6%)

Data are means ± SD (abnomal no./total no., %).

Figure 2



Intravenous immunoglobulin (IVIG)

- Use of IVIG has been reported in case series[61,62] of COVID-19. However, because of the small numbers, limited reported data, and uncontrolled nature of these studies, the efficacy of IVIG cannot be adequately interpreted.
- In a randomized controlled trial of adjunctive anti-influenza hyperimmune IVIG in 313 patients (168 receiving IVIG vs. 161 receiving placebo), IVIG was not superior to placebo.[63]

- IVIG is associated with significant cost and can rarely cause adverse events including anaphylaxis, thromboembolism, aseptic meningitis, renal failure, hemolytic reactions, transfusion-associated lung injury, and other late reactions.[7,64]
- The Surviving Sepsis Campaign Guidelines for critically ill patients with COVID-19 recommend against the use of IVIG (weak recommendation, very low quality evidence).[64]

Supportive/Other Care (NSAID, ACEi/ARB)

NSAIDs (ibuprofen)

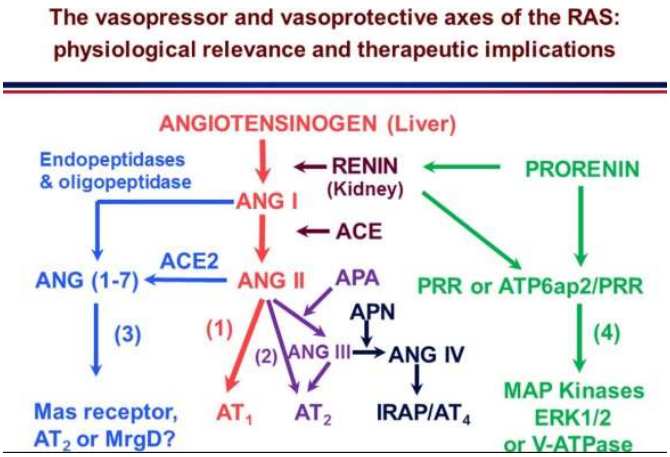
- Theoretical Risk in COVID-19:
  - While NSAIDs like ibuprofen can attenuate symptoms of COVID-19, it has been hypothesized that they can upregulate expression of angiotensin-converting enzyme 2 (ACE2), which is utilized by SARS-CoV-2 to bind to target cells (e.g. epithelial cells of the lung, intestine, kidney, and blood vessels), facilitating infection.[65]
  - It has also been hypothesized that NSAIDs impair neutrophil intrinsic functions, their recruitment to the inflammatory site, and the resolution of inflammatory processes after acute pulmonary bacterial challenge.[66]
- Clinical considerations:
  - There is no clinical data yet to support this hypothesis but alternative analgesic and antipyretic medications (e.g. acetaminophen) do exist and risk/benefit should be considered.
- Supporting data in other disease states
  - In a review of observational trials[66], data supported a strong association between pre-hospital NSAID exposure and a delayed hospital referral, a delayed administration of antibiotic therapy, and the occurrence of pleuropulmonary complications, even in the only study that has accounted for a protopathic bias. Other endpoints have been described including a longer duration of antibiotic therapy and a greater hospital length of stay.
  - In a population-based study[67] conducted using the Danish National Patient Registry to identify all patients (>15 yr old) with hospitalized CAP in the period 1997–2011 (N= 59,250 patients), clear association between NSAID intake and increased risk of pleuropulmonary complications, especially in young and healthy people. This was observed for both new and longer-term NSAID use, with the highest RRs among new users. Current NSAID users had a higher risk of pleuropulmonary complications (3.8%) compared with both former users (2.4%) and nonusers (2.3%). After adjustment for confounders, the aRR was 1.81 (95% confidence interval [CI], 1.60–2.05) for all current NSAID users, 1.51 (95% CI, 1.29–1.75) for current longer-term users, and 2.48 (95% CI, 2.09–2.94) for current new users. In contrast, the aRR was 1.10 (95% CI, 0.95–1.27) for former NSAID users. As a point of comparison, the complication aRR associated with current paracetamol use was 0.97 (95% CI, 0.86–1.09). Among current NSAID users, a stratified analysis showed the highest complication aRRs in young patients (18–44 yr; aRR = 3.48 [95% CI, 2.64–4.60]) and in patients without comorbidities (aRR = 2.29 [95% CI, 1.94–2.70]).
-
- Conflicting data in other disease states
  - In an exploratory analysis[68] of NSAIDs and aspirin use in 683 adult and 838 pediatric critically ill pandemic 2009 H1N1 influenza (pH1N1) patients. Mortality among 89 pediatric NSAID users and 749 nonusers did not differ significantly (10.1% and 8.8%, respectively). One of 16 pediatric ASA users died. Among pediatric patients, the adjusted relative risk estimate for NSAID use and 90-day mortality was higher when influenza vaccination was included in the model (risk ratio [RR] = 1.5; 95% confidence

interval, 0.7–3.2), although not statistically significant. Among adults, RR estimates did not change appreciably after adjusting for age, sex, health status, or vaccine status.

- In an in vitro model[69], indomethacin was found to have potent direct antiviral activity against the coronaviruses SARS-CoV and Canine CoV. Indomethacin did not affect coronavirus binding or entry into host cells, but acted by blocking viral RNA synthesis at cytoprotective doses.

ACEi/ARB

- It has been shown that ACE inhibitors and ARBs increase expression of angiotensin-converting enzyme 2 (ACE2)[70] (see image right). It has been hypothesized that upregulated ACE2, which is utilized by SARS-CoV-2 to bind to target cells (e.g. epithelial cells of the lung, intestine, kidney, and blood vessels), could facilitate infection.[65]



- There is no clinical data yet to support this hypothesis
- The American Heart Association, Heart Failure Society of America, and American College of Cardiologists have published a statement instructing patients to remain on ACEis and ARBs unless otherwise directed to stop by their physician. They acknowledge the lack of experimental and clinical evidence supporting the theoretical risk and need for complete evaluation and treatment of cardiovascular disease.[71]

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