

Resources and Use of Approved Therapies for Treatment of n-CoViD-19 Disease

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Disclaimer: all references and text should be verified prior to incorporating into your practice. This is not meant to endorse any specific treatment, or even any antiviral therapy at all - supportive care is the current standard of care.

Therapies Approved by US FDA for Other Conditions

The following interventions have some in vitro/mechanism-based support, but lack substantial supporting clinical data	The following interventions are considered less likely to be useful in most situations based on in vitro data, mechanism of action, or clinical experience to date
Chloroquine/Hydroxychloroquine	Oseltamivir
Lopinavir/ritonavir	Ribavirin
Darunavir/cobicistat	Steroids
alpha-interferon	Angiotensin II Receptor Blockers
Nitazoxanide	Sarilumab
Nelfinavir	
Baricitinib	
Tocilizumab	

NOTE: most data is likely to be extrapolated from other coronaviruses

Resources

COVID-19 Guidelines & Handbooks
Practical Clinical Resources
Webinars / Grand Rounds
General Resources

COVID-19 Guidelines & Handbooks

- [Society of Critical Care Medicine \(SCCM\) Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with COVID-19](#) (Published March 20, 2020)
- [Interim Clinical Guidance for Patients Suspected of/Confirmed with COVID-19 in Belgium](#) (Updated March 19, 2020)
- [Zhejiang University School of Medicine Handbook of COVID-19 Prevention and Treatment](#) (Published March 18, 2020)
 - Collaboration with the Jack Ma Foundation to provide recommendations for isolation area management, diagnosis, treatment (antivirals, ECMO, lung transplantation, etc.), and nursing care.
 - This hospital had no fatalities and a 96% recovery rate.
- [The Australian and New Zealand Intensive Care Society \(ANZICS\) COVID-19 Guidelines: Version 1](#) (Published March 16, 2020)
- [Italian Society of Infectious and Tropical Diseases Handbook for the Care of People with Coronavirus](#) (Published March 13, 2020)
- [Chinese Government Novel Coronavirus Pneumonia Diagnosis and Treatment Plan \(Provisional 7th Edition\): WHO English Translation](#) (Published March 3, 2020)
- [Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team, Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care \(CPAM\): A Rapid Advice Guideline for the Diagnosis and Treatment of 2019 Novel Coronavirus \(2019-NCoV\) Infected Pneumonia \(Standard Version\)](#) (Published February 6, 2020)
- [World Health Organization \(WHO\) Clinical management of severe acute respiratory infection when novel coronavirus \(2019-nCoV\) infection is suspected](#) (Published January 28, 2020)
- Institutional Guidelines
 - [University of Washington \(UW Medicine\) Treatment Guidelines](#)

- [University of Michigan \(Michigan Medicine\) Inpatient Guidance for Diagnosis and Treatment of COVID-19 in Adults & Children](#)
- [Penn Medicine Treatment Guidelines for Adult Patients with Laboratory-Confirmed SARS-CoV-2 \(COVID-19\) Infection](#)
- [Brigham and Women's Hospital COVID-19 Critical Care Clinical Guidelines](#)
- **COVID-19 ICU Net: A Call for Guidelines: [email guidelines@coronavirus-icu.net](mailto:guidelines@coronavirus-icu.net) to contribute your institution's guideline!**

Practical Clinical Resources

- [ASHP Assessment of Evidence for COVID-19-Related Treatments](#)
- [EmCrit Project Internet Book of Critical Care: COVID-19 Chapter](#)
- [ID Stewardship: COVID-19 Resources for Pharmacists](#)
- [University of Liverpool Drug Interactions Database for Experimental COVID-19 Therapeutics](#)
- [University of Liverpool Experimental COVID-19 Therapeutics: Administration in Cases of Swallowing Difficulties](#)
- [American Academy of Ophthalmology: Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy](#)

Webinars/Grand Rounds

- [Society of Infectious Diseases Pharmacists: Treatment Options for COVID-19](#) (Uploaded March 23, 2020 by Jason Pogue, PharmD, BCPS, BCIDP)
- [Conference on Retroviruses and Opportunistic Infections \(CROI\) 2020 COVID-19 Webinar](#) (Broadcasted March 10, 2020)
- [Harvard University/Massachusetts General Hospital Medical Grand Rounds: A Coordinated Boston Response to COVID-19](#) (Broadcasted March 12, 2020)

General Resources

- Martinez, Miguel Angel. [Compounds with Therapeutic Potential against Novel Respiratory 2019 Coronavirus](#). *Antimicrob Agents Chemother* 9 March 2020.
- Lu, Hongzhou. [Drug Treatment Options for the 2019-New Coronavirus \(2019-NCoV\)](#). *BioScience Trends* 28 Jan 2020 (adv pub).
- Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. [The proximal origin of SARS-CoV-2](#). *Nature Medicine* 17 Mar 2020.
 - For your conspiracy theorist Facebook friends who think COVID-19 was man-made (hint: it wasn't!)

- Harrison, Charlotte. "[Coronavirus Puts Drug Repurposing on the Fast Track.](#)" *Nature Biotechnology* 27 Feb 2020.
- Li, Guangdi, and Erik De Clercq. "[Therapeutic Options for the 2019 Novel Coronavirus \(2019-NCoV\).](#)" *Nature Reviews Drug Discovery* 10 Feb 10, 2020.
 - Contains supplementary appendix with large number of investigational agents
- [WHO R&D Blueprint Report](#): Informal consultation on prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection. 27 Jan 2020
- [Guide to drugs and vaccines in development](#) (Published March 2, 2020)
 - Not primary literature, but a concise overview of the pipeline
- Lai C-C et al. [Severe acute respiratory syndrome coronavirus 2 \(SARS-CoV-2\) and coronavirus disease-2019 \(COVID-19\): The epidemic and the challenges.](#) *Int J Antimicrob Agents* 2020; In press.
 - Review of treatment options
- Guo L et al. [Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease \(COVID-19\).](#) *Clin Infect Dis* 21 Mar 2020.
 - Role of IgM in diagnosis along with PCR
- [Inhibition of SARS Coronavirus Infection In Vitro with Clinically Approved Drugs \(NOT COVID-19\)](#); 4 Apr 2004)
 - Neuraminidase inhibitors/protease inhibitors had no effect
 - Concentrations of ribavirin needed may not be clinically achievable

Chloroquine/Hydroxychloroquine

- Gautret P et al. [Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial.](#) *Int J Antimicrob Agents* 17 Mar 2020.

Citation	Gautret P et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. <i>Int J Antimicrob Agents</i> 2020. doi: 10.1016/j.ijantimicag.2020.105949
Study design	Open-label, non-randomized clinical trial (N=36)
Patients	<p>Inclusion</p> <ul style="list-style-type: none"> ● Age > 12 years ● PCR documented SARS-CoV-2 carriage in nasopharyngeal sample at admission <p>Exclusion</p> <ul style="list-style-type: none"> ● Hydroxychloroquine or chloroquine allergy ● G6PD deficiency ● QT prolongation ● Retinopathy ● Breastfeeding

	<ul style="list-style-type: none"> • Pregnancy
Treatments	<ul style="list-style-type: none"> • Hydroxychloroquine (HCQ) 200 mg TID x 10 days with daily viral load testing via nasopharyngeal swab ± azithromycin (AZI) (dosed as 500 mg on day 1, followed by 250 mg on days 2-4) depending on clinical presentation (N=26; 14 HCQ monotherapy, 6 HCQ+AZ, 6 not included in analysis due to poor outcome) • Controls (N=16)
Results	<ul style="list-style-type: none"> • Greater reduction in viral carriage at D6 post-inclusion in HCQ/AZI treated patients (100% virologic cure) compared to 57.1% in HCQ only patients and 12.5% in controls • Lower average carrying duration than reported of untreated patients in the literature • Azithromycin added to HCQ significantly more effective for virus elimination
Conclusion	<p>HCQ may be efficient in clearing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients in 3-6 days, and AZI in combination may help prevent severe respiratory tract infections in patients with viral infection</p>
Discussion	<p>Very thoughtful discussion and analysis of this study here by SIDP President Jason Pogue (additional video interview and transcript here), points below:</p> <ul style="list-style-type: none"> • Only 20/26 patients in HCQ group included in analysis (5 failures?) <ul style="list-style-type: none"> ○ 3 transferred to ICU while still PCR positive ○ 1 died (PCR negative) ○ 1 left the hospital (PCR negative) ○ 1 withdrew due to nausea (PCR positive) • Cycle threshold (Ct): number of cycles to be run for PCR test to turn positive--meaning the <i>lower</i> the Ct, the <i>more</i> virus is present (the less numbers of cycle to hit threshold) <ul style="list-style-type: none"> ○ HCQ+AZI patients have baseline Ct values ≥ 24, whereas 5 patients in monotherapy arm have values < 23 ○ This subset of patients in the monotherapy arm would need a greater antiviral effect to reach “negative” or undetectable virus (defined as Ct > 35 in this study; negative is often defined as Ct $> 40!$) • Eradication rates at day 6 <ul style="list-style-type: none"> ○ HCQ monotherapy (Ct < 23): 1/5 (20%) ○ HCQ monotherapy (Ct 23+): 7/9 (78%) ○ HCQ + Azithro (all Ct ≥ 24): 6/6 (100%) • Study used nasopharyngeal swab, which is less sensitive than both sputum and BAL for detection of COVID-19

	<ul style="list-style-type: none"> Other obvious limitations/considerations: not randomized, not blinded, small sample size, groups not similar at baseline, drug combination requires close QTc monitoring
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- Cortegiani A, Ingoglia G, Ippolito M, Einav S. [A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19](#). *J Crit Care*. In Press (10 Mar 2020).
- Colson P, Rolain J, Laiger J, Brouqui P, Raoult D. [Chloroquine and hydroxychloroquine as available weapons to fight COVID-19](#). *Int J Antimicrob Agents* (4 Mar 2020).
- Gao, Jianjun, Zhenxue Tian, and Xu Yang. [Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies](#). *BioScience Trends* (ePub 19 Feb 2020).
- Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. [Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia](#). *Zhonghua Jiehe He Huxi Zazhi = Chinese Journal of Tuberculosis and Respiratory Diseases* 43(0):E019 (20 Feb 2020).

Mechanism/Virology/In vitro data (specific to COVID-19)

- Yao X, Ye F, Zhang M et al. [In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 \(SARS-CoV-2\)](#). *Clin Infect Dis* (9 Mar 2020, pre-publication).
- Wang M, Cao R, Zhang L et al. [Remdesivir and Chloroquine Effectively Inhibit the Recently Emerged Novel Coronavirus \(2019-nCoV\) in Vitro](#). *Cell Research* (4 Feb 2020).
 - Proposed mechanism: “Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV”
 - “The EC90 value of chloroquine against the 2019-nCoV in Vero E6 cells was 6.90 μM, which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration”

*Mechanism/Virology/In vitro data (extrapolated from SARS-CoV; **NOT COVID-19**)*

- Keyaerts E, Vijgen L, Maes P et al. (2004). [In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine](#). *Biochem Biophys Res Commun* 323: 264.
- Vincent MJ, Bergeron E, Benjannet S et al. (2005). [Chloroquine is a potent inhibitor of SARS coronavirus infection and spread](#). *Virology* 2: 69.
- Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. [Effects of chloroquine on viral infections: an old drug against today's diseases](#). *Lancet Infect Dis*. 2003; 3:722- 727.
- Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A. [New insights into the antiviral effects of chloroquine](#). *Lancet Infect Dis*. 2006; 6(2):67-9.

Animal Models

- Keyaerts E, Li S, Vijgen L et al. (2009). [Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice](#). *Antimicrob Agents Chemother* 53: 3416. **(NOT COVID-19)**

Pharmacokinetics/Administration

- McHenry AR et al. [Stability of Extemporaneously Prepared Hydroxychloroquine Sulfate 25-Mg/ML Suspensions in Plastic Bottles and Syringes](#). *Int J Pharmaceutical Compounding* (2017)
- Pesko LJ. *Am Druggist*, 1993, 207(4):57.

Trials in Progress

- Hydroxychloroquine
 - Treatment
 - [NCT04261517](#): Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV)
 - Hydroxychloroquine 400 mg PO daily x 5 days vs. standard of care
 - Status: Recruiting (as of 3/4/2020)
 - [NCT04315896](#): Hydroxychloroquine Treatment for Severe COVID-19 Pulmonary Infection (HYDRA trial)
 - Hydroxychloroquine 200 mg BID x 10 days
 - Status: Not yet recruiting (as of 3/23/2020)
 - Prophylaxis
 - [NCT04318015](#): Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact with COVID-19 Patients (PHYDRA trial)
 - Hydroxychloroquine 200 mg PO daily x 60 days
 - Status: Not yet recruiting (as of 3/23/2020)
 - [NCT04308668](#): Post-exposure Prophylaxis for SARS-Coronavirus-2

- 800 mg orally once, followed in 6 to 8 hours by 600 mg, then 600 mg once a day for 4 consecutive days compared to placebo
 - Status: Recruiting (as of 3/16/2020)
- Hydroxychloroquine vs. Lopinavir/ritonavir
 - [NCT04307693](#): Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients with Mild Coronavirus Disease (COVID-19)
 - Lopinavir/ritonavir 200mg/100mg 2 tablets PO BID for 7-10 days vs hydroxychloroquine 200mg 2 tablets PO BID for 7-10 days
 - Status: Recruiting (as of 3/23/2020)
- Carrimycin
 - [NCT04286503](#): The Clinical Study of Carrimycin on Treatment Patients With COVID-19
 - Active comparator: lopinavir/ritonavir tablets or Arbidol or chloroquine phosphate
 - Status: Not yet recruiting (as of 3/10/2020)

Lopinavir/ritonavir (Kaletra®)

Completed Clinical Trials

- [LOTUS Trial](#)

Citation	Cao B, Wang Y, Wen D et al. A trial of lopinavir–ritonavir in adults hospitalized with severe COVID-19. <i>N Eng J Med</i> 18 Mar 2020.
Study design	Open label RCT (N=199)
Patients	<p>Inclusion</p> <ul style="list-style-type: none"> ● Hospitalized adults with confirmed SARS-CoV-2 ● SaO₂ ≤ while breathing ambient air, or PaO₂/FiO₂ < 300 mmHg <p>Exclusion</p> <ul style="list-style-type: none"> ● Pregnancy ● Breastfeeding ● HIV infection ● Known allergy/hypersensitivity ● Severe liver disease (AST/ALT >5x ULN, cirrhosis) ● Medications known to interact with study drug ● Physician discretion
Treatments	<ul style="list-style-type: none"> ● Lopinavir/ritonavir 400-100 mg BID (4 tablets/day) x 14 days and standard of care (N=99) ● Standard of care alone x 14 days (N=100) ● Randomization stratified by oxygen support (e.g. nasal cannula, HFNC, ventilation)
Baseline	<ul style="list-style-type: none"> ● Mean age: 58 years

characteristics	<ul style="list-style-type: none"> • Concurrent glucocorticoid treatment: 33% lopinavir-ritonavir group vs. 35.7% standard of care • Median time between symptom onset and randomization: 13 days (IQR 11-16 days) • Mean viral load (log₁₀ copies/mL at day 1): 4.4% lopinavir-ritonavir group vs. 3.7% standard of care
Results	<p>Primary</p> <ul style="list-style-type: none"> • Treatment with lopinavir-ritonavir not associated with a difference from standard of care in time to clinical improvement (HR 1.24; 95% CI 0.90-1.72) <p>Secondary</p> <ul style="list-style-type: none"> • 28-day mortality similar (19.2% vs. 25.0%; difference, -5.8%; 95% CI, -17.3 to 5.7) • Percentages of patients with detectable viral RNA at various time points were similar; viral RNA detected in 40.7% of lopinavir-ritonavir group at day 28 • In a modified ITT analysis, lopinavir-ritonavir led to a median time to clinical improvement that was shorter by 1 day (HR 1.39; 95% CI, 1.00-1.91) • In a post-hoc analysis, patients treated within 12 days of sx onset had slight decrease in time to clinical recovery (16d vs. 17d) and reduced mortality (19% vs. 27.1%) • ICU LOS shorter by 1 day in treatment group (95% CI, -9 to 0 days) and hospital LOS shorter by 1 day (95% CI -3 to 0 days) for survivors • 14% of lopinavir-ritonavir arm DC'd due to ADEs (anorexia, nausea, abdominal discomfort, diarrhea, acute gastritis) • Serious ADEs more common in standard-care group • Lopinavir-ritonavir stopped early in 13 patients (13.8%) d/t ADEs
Conclusion	<p>The addition of lopinavir-ritonavir to standard care was not associated with clinical improvement in seriously ill patients with COVID-19, nor did it reduce mortality or throat viral RNA</p>
Discussion	<ul style="list-style-type: none"> • Underpowered for both primary and secondary endpoints; thus unable to truly make any conclusions • Trial extended, then terminated early due to alternative therapy becoming available, without establishing futility • Uncertain relevance to ICU cohort—only 16% of patients were on high flow oxygen or mechanical ventilation at time of randomization • Median interval time between symptom onset and randomization (and thus initiation of therapy) was 13 days (IQR 11-16); unclear if benefit would have been seen if treatment had been initiated earlier • Given the higher throat viral loads in the lopinavir-ritonavir group, this group may have had more viral replication • Lopinavir-ritonavir remains experimental, but at a time when resources are overwhelmed, even small improvements in time to discharge from ICU and hospital may have great implications for hospital resource availability and patient throughput; larger trials

	are needed to confirm whether lopinavir-ritonavir is associated with shorter hospital and/or ICU LOS
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Mechanism/Virology/In vitro data

- Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. [A Systematic Review of Lopinavir Therapy for SARS Coronavirus and MERS Coronavirus-A Possible Reference for Coronavirus Disease-19 Treatment Option](#). *J Med Virol* 27 Feb 2020.
- Chang, Yu-Chuan, Yi-An Tung, Ko-Han Lee, Ting-Fu Chen, Yu-Chun Hsiao, Hung-Ching Chang, Tsung-Ting Hsieh et al. [Potential Therapeutic Agents for COVID-19 Based on the Analysis of Protease and RNA Polymerase Docking](#). *Preprints* (not peer reviewed) 17 Feb 2020.

Animal Models in MERS-CoV (NOT COVID-19)

- Chan JF et al. [Treatment With Lopinavir/Ritonavir or Interferon-B1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset](#). *J Infect Dis* 212, no. 12 (December 15, 2015): 1904–13.
 - Improved clinical scores and lower viral loads in necroscopied lungs in animals treated with lopinavir/ritonavir OR interferon
 - Pathology of MMF and untreated lungs much more extensive than lopinavir/ritonavir and interferon
 - Worsened disease and viral load in animals treated with mycophenolate
- Sheahan TP, Sims AC, Leist SR et al. [Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV](#). *Nat Commun*. 10 Jan 2020;11.
 - Includes both *in vitro* (human lung cell) and *in vivo* (transgenic mouse model) of MERS-CoV
 - TL;DR: high EC50 + low levels of free LPV in plasma → authors conclude that LPV is unlikely to be efficacious against MERS-CoV in human host

Clinical Reports

- Zhou F, Yu T, Du R et al. [Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study](#). *Lancet* 9 Mar 2020.

- **Study design:** Retrospective, multicenter cohort study including all adult inpatients with laboratory confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary hospital who had been discharged or died by 1/31/20
 - **Patients:** N=191 (137 of whom were discharged; 54 died in-hospital)
 - **Statistical analysis:** Included univariable and multivariable logistic regression to evaluate risk factors associated with in-hospital death
 - **Results:** 41 (21%) received antiviral therapy (LPV/r). Among 29 patients who received LPV/r and were discharged (survived), the median time from illness onset to initiation of therapy was 14 days and the median duration of viral shedding was 22 days. The median duration of viral shedding was 20 days among all 137 survivors.
 - **Conclusion:** This study did not observe shortening of viral shedding duration after LPV/r.
- Chan KS et al. [Treatment of Severe Acute Respiratory Syndrome with Lopinavir/Ritonavir: A Multicentre Retrospective Matched Cohort Study](#). *Hong Kong Med J* 2003.
 - **Study design:** Retrospective matched cohort study of treatment of SARS-CoV (**NOT COVID-19**) in which patients who received LPV/r as initial therapy OR LPV/r as rescue therapy were compared to controls
 - **Conclusion:** “The addition of lopinavir/ritonavir to a standard treatment protocol as an initial treatment for severe acute respiratory syndrome appeared to be associated with improved clinical outcome.”
- Chu CM, Cheng VCC, Hung IFN et al. [Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings](#). *Thorax*. 2004;59(3):252-256.
 - **Study design:** Retrospective case control study of 41 patients who received LPV/r + ribavirin compared to 111 patients who received ribavirin only
 - **Results:** “The adverse clinical outcome (ARDS or death) was significantly lower in the treatment group than in the historical controls (2.4% v 28.8%, p<0.001) at day 21 after the onset of symptoms...Lopinavir/ritonavir treatment was associated with a better outcome even when adjusted for baseline lactate dehydrogenase level.” Of note, both the treatment group and control group also received ribavirin (x14 days; dose 4 g oral loading dose followed by 1.2 g every 8 hour or IV if unable to take PO)
- Young BE, Ong SWX, Kalimuddin S et al. [Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore](#). *JAMA* 3 Mar 2020.

- Singapore descriptive case series of 18 cases. Five of six patients requiring supplemental oxygen were given lopinavir/ritonavir 200mg/100 mg BID for up to 14 days.
- Only one individual finished 14 days due to adverse events (N/V/increased LFTs). Two patients continued to deteriorate and shed virus. Two of the five cleared viral shedding in two days, three of the five had decreases in supplemental oxygen requirement.
- “Evidence of clinical benefit equivocal. Decline in viral load as indicated by the cycle threshold value from nasopharyngeal swabs also appeared similar between those treated and not treated with lopinavir-ritonavir.”

Trials in Progress

- [NCT04252885](#): The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection (ELACOI)
 - [NCT04307693](#): Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients with Mild Coronavirus Disease (COVID-19)
 - Lopinavir/ritonavir 200mg/100mg 2 tablets PO BID for 7-10 days vs hydroxychloroquine 200mg 2 tablets PO BID for 7-10 days
 - Status: Recruiting (as of 3/23/2020)
 - [ChiCTR2000029308](#): A randomized, open-label, blank-controlled trial for the efficacy and safety of **lopinavir-ritonavir and interferon-alpha 2b** in hospitalized patients with novel coronavirus pneumonia (COVID-19)
 - Ongoing trial in China, registered 1/23/2020
 - [ChiCTR2000029387](#): Comparative effectiveness and safety of ribavirin plus interferon-alpha 1b, lopinavir/ritonavir plus interferon-alpha 1b, and ribavirin plus lopinavir/ritonavir plus interferon-alpha 1b in patients with mild to moderate novel coronavirus pneumonia
 - Ongoing trial in China, registered 1/29/2020
 - Zeng Y, Xu X, He X, Tang S, Li Y, Huang Y, Harypursat V, Chen Y. [Comparative Effectiveness and Safety of Ribavirin plus Interferon-Alpha, Lopinavir/Ritonavir plus Interferon-Alpha, and Ribavirin plus Lopinavir/Ritonavir plus Interferon-Alpha in in Patients with Mild to Moderate Novel Coronavirus Pneumonia](#). *Chinese Medical Journal* (1 Mar 2020, prepub).
 - [NCT02845843](#): MERS-CoV Infection tReated With A Combination of Lopinavir/Ritonavir and Interferon Beta-1b (MIRACLE) (**NOT COVID-19**)
 - RCT comparing LPV/r + interferon beta-1b x 14 days for treatment of MERS-CoV. Recruitment is ongoing. No results posted.
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Darunavir/cobicistat (Prezcobix®)

Mechanism/Virology/In vitro data

- [Coronavirus outbreak: Top coronavirus drugs and vaccines in development](#)
 - “Janssen has no in vitro or clinical data to support the use of darunavir as a treatment for Covid-19. The drug is in the process of being evaluated in vitro for any potential activity against the coronavirus.”
- [Johnson & Johnson: Lack of evidence to support use of darunavir-based treatments for SARS-CoV-2](#)

Animal Models

Clinical Reports

Trials in Progress

- [NCT04252274](#): Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV (DACO-nCoV)
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alpha-interferon (Intron® A)

Mechanism/Virology/In vitro data

- Falzarano D, de Wit E, Martellaro C, Callison J, Vincent J. Munster, and Heinz Feldmann. [Inhibition of Novel \$\beta\$ Coronavirus Replication by a Combination of Interferon-A2b and Ribavirin](#). *Scientific Reports* 3 (April 18, 2013).

Animal Models

Clinical Reports

Trials in Progress

- [ChiCTR2000029387](#): Comparative effectiveness and safety of ribavirin plus interferon-alpha 1b, lopinavir/ritonavir plus interferon-alpha 1b, and ribavirin plus lopinavir/ritonavir plus interferon-alpha 1b in patients with mild to moderate novel coronavirus pneumonia
 - Ongoing trial in China, registered 1/29/2020

- Zeng Y, Xu X, He X, Tang S, Li Y, Huang Y, Harypursat V, Chen Y. [Comparative Effectiveness and Safety of Ribavirin plus Interferon-Alpha, Lopinavir/Ritonavir plus Interferon-Alpha, and Ribavirin plus Lopinavir/Ritonavir plus Interferon-Alpha in Patients with Mild to Moderate Novel Coronavirus Pneumonia](#). *Chinese Medical Journal* (1 Mar 2020, prepub).
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Nitazoxanide (Alinia®)

Mechanism/Virology/In vitro data

- Cao J, Forrest JC, Zhang X (2015). [A screen of the NIH Clinical Collection small molecule library identifies potential anti-coronavirus drugs](#). *Antiviral Res*, 114;
- Wang M et al. [Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus \(2019-nCoV\) in vitro](#). *Cell Research*. 2020 30;269-71.
 - Nitazoxanide also demonstrated promise in this in vitro assay

Animal Models

Clinical Reports

- Gamiño-Arroyo AE, Guerrero ML, McCarthy S et al. [Efficacy and Safety of Nitazoxanide in Addition to Standard of Care for the Treatment of Severe Acute Respiratory Illness](#), *Clin Infect Dis* 2019 Nov 13;69(11):1903-1911. doi: 10.1093/cid/ciz100.
 - A clinical trial that demonstrated no value in its use, though only 5 patients with a coronavirus were identified. At the very least, safety appeared comparable.

Trials in Progress

Nelfinavir (Viracept®)

- Xu Y, Peng C, Shi Y et al. [Nelfinavir was predicted to be a potential inhibitor of 2019-nCov main protease by an integrative approach combining homology modelling, molecular docking and binding free energy calculation](#). *bioRxiv* 2020 (preprint, **NOT peer reviewed**).
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Baricitinib (Olumiant®)

- Stebbing J et al. [COVID-19: combining antiviral and anti-inflammatory treatments](#). *Lancet Infect Dis* 27 Feb 2020.

- Benevolent AI's proprietary artificial intelligence (AI)-derived knowledge graph
 - NAK inhibitor, with a particularly high affinity for AAK1, a pivotal regulator of clathrin-mediated endocytosis
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Tocilizumab (Actemra®)

Proposed mechanism

- Mehta P et al. [COVID-19: consider cytokine storm syndromes and immunosuppression](#). *Lancet* 2 Mar 2020.
- Liu T, Zhang j, Yang Y, Ma H, Li Z, Zhang J, Cheng J et al. [The Potential Role of IL-6 in Monitoring Severe Case of Coronavirus Disease 2019](#). *medRxiv* 2 Mar 2020 (preprint, **NOT peer reviewed**).
- Liu A. "[China turns Roche arthritis drug Actemra against COVID-19 in new treatment guidelines](#)." *Fierce Pharma* 4 Mar 2020.
 - LAY PRESS REPORT: IL-6 inhibitor used for CRS in CAR-T patients
 - IL-6 inhibition -> reduction in cytokine storm driving severe disease.
- [Italian guidelines](#) page 11

Clinical data

- Xu X, Han M, Li T et al. [Effective treatment of severe COVID-19 patients with Tocilizumab](#). chinaXiv (preprint report, **NOT peer reviewed**).
 - **Study design:** Single-arm trial of 21 patients with severe or critical (e.g. SpO2 <93%, intubated) COVID-19 who received tocilizumab 400 mg IV x 1 in addition to standard of care; 3 patients (14.3%) got an additional dose 12 hr later d/t fever
 - **Results:** 75% with improved respiratory function after treatment
 - **Limitations:** very short f/u (average 2 weeks)

Trials in progress

- [NCT04315480](#): Tocilizumab for SARS-CoV2 Severe Pneumonitis
 - Open label phase II trial in Italy of tocilizumab as a single 8 mg/kg dose in patients with severe multifocal interstitial pneumonia correlated to COVID-19
 - Posted 3/19/2020, estimated enrollment up to 30 patients, not yet recruiting
- [NCT04306705](#): Tocilizumab vs CRRT in Management of Cytokine Release Syndrome (CRS) in COVID-19 (TACOS)
 - Retrospective study comparing a tocilizumab as a single 8 mg/kg dose to CRRT
 - Posted 3/13/2020, estimated enrollment 120 patients, recruiting

- [NCT04310228](#) / [ChiCTR2000030894](#): Favipiravir Combined With Tocilizumab in the Treatment of novel coronavirus pneumonia (COVID-19) - A Multicenter, Randomized, Controlled Trial
 - Multicenter, randomized, open-label, 150-patient trial led by Hong Zhao of Peking University First Hospital, registered 3/16/2020
 - [ChiCTR2000029765](#): A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19)
 - A 188-patient trial led by Dongsheng Wang of The First Affiliated Hospital of University of science and technology of China (Anhui Provincial Hospital), registered 2/13/2020
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Oseltamivir (Tamiflu®)

Mechanism/Virology/In vitro data

- Role of neuraminidase in influenza: cleaves sialic acid from cell surface and progeny virions, facilitating virus release from infected cells
- Unlike influenza A/B, coronaviruses are not known to utilize neuraminidase as part of viral replication and so oseltamivir is unlikely to be of therapeutic value.
- Fehr AR, Perlman S. [Coronaviruses: An Overview of Their Replication and Pathogenesis](#). *Methods Mol Biol*. 2015;1282:1-23.
- Matrosovich MN, Matrosovich TY, Gray T, Roberts NA, Klenk H-D. [Neuraminidase Is Important for the Initiation of Influenza Virus Infection in Human Airway Epithelium](#). *J Virol*. 2004;78(22):12665-12667.

Animal Models

Clinical Reports

Trials in Progress

- [NCT04261270](#): A Randomized, Open, Controlled Clinical Study to Evaluate the Efficacy of ASC09F and Ritonavir for 2019-nCoV Pneumonia
 - Note that oseltamivir appears to be the “control” arm in this study
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Ribavirin (Rebetol®)

Mechanism/Virology/In vitro data

Animal Models

Clinical Reports

- Chu CM, Cheng VCC, Hung IFN et al. [Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings](#). *Thorax*. 2004;59(3):252-256.
 - Retrospective case control study of 41 patients who received LPV/r + ribavirin compared to 111 patients who received ribavirin only
 - “The adverse clinical outcome (ARDS or death) was significantly lower in the treatment group than in the historical controls (2.4% v 28.8%, p<0.001) at day 21 after the onset of symptoms...Lopinavir/ritonavir treatment was associated with a better outcome even when adjusted for baseline lactate dehydrogenase level.”
 - Of note, both groups also received ribavirin x14 days: dose 4 g PO loading dose followed by 1.2 g q8h (or IV if unable to take PO)

Trials in Progress

- [ChiCTR2000029387](#): Comparative effectiveness and safety of ribavirin plus interferon-alpha 1b, lopinavir/ritonavir plus interferon-alpha 1b, and ribavirin plus lopinavir/ritonavir plus interferon-alpha 1b in patients with mild to moderate novel coronavirus pneumonia
 - Ongoing trial in China, registered 1/29/2020
 - Zeng Y, Xu X, He X, Tang S, Li Y, Huang Y, Harypursat V, Chen Y. [Comparative Effectiveness and Safety of Ribavirin plus Interferon-Alpha, Lopinavir/Ritonavir plus Interferon-Alpha, and Ribavirin plus Lopinavir/Ritonavir plus Interferon-Alpha in in Patients with Mild to Moderate Novel Coronavirus Pneumonia](#). *Chinese Medical Journal* (1 Mar 2020, prepub).

Steroids

- Wu C, Chen X, Cai Y et al. [Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China](#). *JAMA Intern Med* 13 Mar 2020. doi:10.1001/jamainternmed.2020.0994

- Retrospective cohort study of 201 patients with confirmed COVID-19 pneumonia admitted to Wuhan Jinyintan Hospital in China between December 25, 2019, and Jan 26, 2020.
 - Among patients with ARDS, treatment with methylprednisolone decreased the risk of death (46% vs. 61.8%, HR 0.38; 95% CI, 0.20-0.72).
 - Potential bias: drug used in sickest patients
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Angiotensin II Receptor Blockers

Mechanism/Virology/In vitro data

- Fang L, Karakiulakis G, Roth M. [Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?](#) *Lancet Respir Med* 11 Mar 2020.
- Zheng Y, Ma Y, Zhang J. et al. [COVID-19 and the cardiovascular system.](#) *Nat Rev Cardiol* 5 Mar 2020.
- Gurwitz D. [Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics.](#) *Drug Dev Res* 4 Mar 2020.
- [HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19](#)
- [Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers](#)

Animal Models

Clinical Reports

Trials in Progress

- [NCT04312009](#): Losartan for Patients With COVID-19 Requiring Hospitalization
 - Multi-center, double-blinded study comparing losartan 25 mg PO daily or placebo for 7 days or until hospital discharge
 - Status: Not yet recruiting (as of 3/23/2020)
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Sarilumab (Kevzara®)

Mechanism/Virology/In vitro data

- “Currently, no known published clinical trial evidence supporting efficacy or safety against Coronavirus. However, based on encouraging results in China with a similar

drug, tocilizumab, a U.S.-based, phase II/III, randomized, double-blind, placebo-controlled study evaluating efficacy and safety of sarilumab in patients hospitalized with severe COVID-19 is currently underway.”

Animal Models

Clinical Reports

Trials in Progress

- [NCT04315298](#): Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19
 - Phase II/III, randomized, double-blind, placebo-controlled trial assessing efficacy and safety of sarilumab as a single IV dose
 - Status: Recruiting (as of 3/19/2020)
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