COVID-19 – FAQs

This document outlines the frequently asked questions (FAQs) that may arise during the COVID-19 pandemic. In the document below, sections are separated into general questions and treatment options.

This is a living document and will be updated as needed. Information added since the last update will be highlighted in yellow. The date of last update is included at the end of the file name and in the footer of this document.

Note: COVID-19 will be used throughout the document to refer to the illness caused by SARS-CoV-2.

ABBREVIATIONS

HCoV = human coronavirus; IV = intravenous; LPV/r = lopinavir/ritonavir; MERS-CoV = Middle East respiratory syndrome coronavirus; PO = by mouth; SARS = severe acute respiratory syndrome; SARS-CoV = severe acute respiratory syndrome coronavirus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, the virus that causes COVID-19

General Questions

1. What is COVID-19?

"Coronavirus is a large family of viruses that cause illnesses ranging from the common cold to more serious disease such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). Coronaviruses are zoonotic, meaning they are transmitted between animals and people."[1]

The current disease, COVID-19, is caused by SARS-CoV-2, which is a virus not previously identified in humans.[1,2]

2. What are the main symptoms of COVID-19? How can it be differentiated from seasonal influenza or the common cold?

Common symptoms of COVID-19 are fever, cough, shortness of breath, and other breathing difficulties.[1,2] Sneezing is not a symptom of COVID-19. Symptoms appear within 2-14 days of exposure; recovery times are not yet known.[2]

Common symptoms of seasonal influenza (flu) are fever, chills, cough, sore throat, runny/stuffy nose, muscle or body aches, headache, fatigue/tiredness, and some patients may experience diarrhea and vomiting. Patients with the flu typically notice an abrupt onset of symptoms and recover after a few days to less than 2 weeks.[3]

Symptoms of the common cold include fatigue/weakness, sneezing, stuffy nose, sore throat, while some patients may also experience cough. Fever and headache are rare. Onset of symptoms occur gradually and patients recover after a few days to less than 2 weeks.[3,4]

3. How does COVID-19 spread?

COVID-19 is spread through close (i.e. within 6-feet) person-to-person contact and through respiratory droplets when an infected person coughs/sneezes. An analysis from the Imperial College of London estimates each case person will infect an average of 2.6 people (range 1.3-3.5).[1] Additionally, touching contaminated surfaces may also spread the virus. Though is not the main method of viral spread, the CDC advises persons to avoid touching their own faces/noses/eyes/mouths to prevent spreading through contamination.[2] Doremalen and colleagues performed an *in vitro* study analyzing the viability of the COVID-19 virus on various surfaces; COVID-19 remained viable in aerosol for 3 hours, 24 hours on cardboard, and 72 hours on plastic and stainless steel.[3]

4. What guidance has been given regarding the use of face masks or respirators to prevent viral spreading?

Facemasks prevent the wearer from transferring droplets into the environment. Respirators (NIOSH approved N95 respirators) protect the wearer from droplets within the environment.[1] N95 respirators are not recommended for use by the general public, as they require special fit testing.[2]

For persons that are sick, the CDC and WHO recommend wearing a facemask when around other people and before entering a healthcare provider's office.[3,4]

For persons that are not sick, facemasks are not necessary, unless caring for a person that is sick and unable to wear a facemask themselves.[3,4] There has been no evidence to suggest facemasks worn by healthy individuals are effective in preventing illness.[2] Facemasks may be in short supply and should be reserved for healthcare providers and caregivers.[3,4]

5. What are considerations that healthcare personnel should take when caring for patients with suspected or confirmed COVID-19?

The World Health Organization (WHO) discusses recommended PPE during the outbreak of COVID-19 according to setting, personnel, and type of activity being performed in the healthcare setting. These recommendations are outlined for healthcare facilities in Table 1.[1]

Table 1. Recommended personal PPE during the outbreak of COVID-19 outbreak, according to the setting, personnel, and type of activity[a,1]

Setting	Target personnel or patients	Activity	Type of PPE or procedure
Inpatient Facilities			
Patient room	Healthcare workers	Providing direct care to COVID-19 patients	Medical mask Gown Gloves Eye protection (goggles or face shield)
		Aerosol-generating procedures performed on COVID-19 patients	Respirator N95 or FFP2 standard, or equivalent Gown

Setting	Target personnel or patients	Activity	Type of PPE or procedure
			Gloves Eye protection Apron
	Cleaners	Entering the room of COVID-19 patients	Medical mask Gown Heavy duty gloves Eye protection (if risk of splash from organic material or chemicals) Boots or closed work shoes
	Visitors[b]	Entering the room of COVID-19 patients	Medical mask Gown Gloves
Other areas of patient transit (e.g. wards, corridors)	All staff, including health care workers	Any activity that does not involve contact with COVID-19 patients	No PPE required
Triage	Healthcare workers	Preliminary screening not involving direct contact[c]	Maintain spatial distance of at least 1 metre. No PPE required
	Patients with respiratory symptoms	Any	Maintain spatial distance of at least 1 metre. Provide medical mask if tolerated by patient.
	Patients without respiratory symptoms	Any	No PPE required
Laboratory	Lab technician	Manipulation of respiratory samples	Medical mask Gown Gloves Eye protection (if risk of splash)
Administrative areas	All staff, including health care workers.	Administrative tasks that do not involve contact with COVID-19 patients	No PPE required
Outpatient Facilities			
Consultation room	Healthcare workers	Physical examination of patient with respiratory symptoms	Medical mask Gown Gloves Eye protection
	Healthcare workers	Physical examination of patients without respiratory symptoms	PPE according to standard precautions and risk assessment.
	Patients with respiratory symptoms	Any	Provide medical mask if tolerated.
	Patients without respiratory symptoms	Any	No PPE required
	Cleaners	After and between consultations with patients with respiratory symptoms.	Medical mask Gown Heavy duty gloves Eye protection (if risk of splash from organic material or chemicals). Boots or closed work shoes
Waiting room	Patients with respiratory symptoms	Any	Provide medical mask if tolerated.

Setting	Target personnel or patients	Activity	Type of PPE or procedure
			Immediately move the patient to an isolation room or separate area away from others; if this is not feasible, ensure spatial distance of at least 1 metre from other patients.
	Patients without respiratory symptoms	Any	No PPE required
Administrative areas	All staff, including health care workers	Administrative tasks	No PPE required
Triage	Healthcare workers	Preliminary screening not involving direct contact[c]	Maintain spatial distance of at least 1 metre. No PPE required
	Patients with respiratory symptoms	Any	Maintain spatial distance of at least 1 metre. Provide medical mask if tolerated.
	Patients without respiratory symptoms	Any	No PPE required

[a]In addition to using the appropriate PPE, frequent hand hygiene and respiratory hygiene should always be performed. PPE should be discarded in an appropriate waste container after use, and hand hygiene should be performed before putting on and after taking off PPE.
[b]The number of visitors should be restricted. If visitors must enter a COVID-19 patient's room, they should be provided with clear instructions about how to put on and remove PPE and about performing hand hygiene before putting on and after removing PPE; this should be supervised by a health care worker.
[c]This category includes the use of no-touch thermometers, thermal imaging cameras, and limited observation and questioning, all while maintaining a spatial distance of at least 1 m.
For PPE specifications, refer to WHO's disease commodity package, located here.

Additionally, the WHO recommends appropriate doffing and disposal of all PPE after patient care activities along with proper hand hygiene. A new set of PPE is needed when care is given to a different patient. Equipment should be either single-use or disposable or dedicated equipment (e.g. stethoscopes, blood pressure cuffs and thermometers). If equipment needs to be shared among patients, clean and disinfect it between use for each individual patient (e.g. by using ethyl alcohol 70%).[2]

The WHO has also created a tool for healthcare worker exposure risk assessment and management in the context of COVID-19. This tool gauges healthcare workers risk after COVID-19 exposure along with what the appropriate actions are if a worker is deemed high risk. The tool can be found here.[3]

6. What is the guidance on the use of PPE for patient care with regards to supply challenges?

The rational, correct, and consistent use of PPE helps reduce the spread of pathogens. PPE effectiveness depends strongly on adequate and regular supplies, adequate staff training, appropriate hand hygiene, and appropriate human behavior.[1] The WHO recommends strategies to optimize the availability of PPE that are summarized in Table 2.

Table 2. Strategies to optimize the availability of personal protective equipment (PPE)[1]

Minimize PPE need	Ensure PPE use is rational and appropriate	Coordinate PPE supply chain
• Consider using telemedicine to evaluate suspected cases of COVID-192, thus minimizing the	• Respirators (e.g. N95, FFP2 or equivalent standard) have been used for an extended time	• Using PPE forecasts based on rational quantification models

Minimize PPE need	Ensure PPE use is rational and appropriate	Coordinate PPE supply chain
need for these persons to go to health care facilities for evaluation. • Use physical barriers to reduce exposure to the COVID-19 virus, such as glass or plastic windows. This approach can be implemented in areas of the health care setting where patients will first present, such as triage areas, the registration desk at the emergency department, or at the pharmacy window where medication is collected. • Restrict health care workers from entering the rooms of COVID-19 patients if they are not involved in direct care. Consider bundling activities to minimize the number of times a room is entered (e.g. check vital signs during medication administration or have food delivered by health care workers while they are performing other care) and plan which activities will be performed at the bedside.	during previous public health emergencies involving acute respiratory illness when PPE was in short supply. This refers to wearing the same respirator while caring for multiple patients who have the same diagnosis without removing it, and evidence indicates that respirators maintain their protection when used for extended periods. However, using one respirator for longer than 4 hours can lead to discomfort and should be avoided. • Among the general public, persons with respiratory symptoms or those caring for COVID-19 patients at home should receive medical masks. • For persons without symptoms, wearing a mask of any type is not recommended. Wearing medical masks when they are not indicated may cause unnecessary cost and a procurement burden and create a false sense of security that can lead to the neglect of other essential preventive measures.	to ensure the rationalization of requested supplies • Monitoring and controlling PPE requests from countries and large responders • Promoting a centralized request management approach to avoid duplication of stock and ensuring strict adherence to essential stock management rules to limit wastage, overstock, and stock ruptures • Monitoring the end-to-end distribution of PPE • Monitoring and controlling the distribution of PPE from medical facilities stores

7. What is the guidance on the use of PPE for sterile compounding?

The United States Pharmacopeia (USP) has drafted a response to address shortages of garb and PPE for sterile compounding during the COVID-19 pandemic.[1] USP supports State Boards and other regulators using risk-based enforcement discretion related to the implementation of USP compounding standards. Further recommendations are outlined in Table 3.

Table 3. USP Response to Garb and PPE Shortage for Sterile Compounding during COVID-19 Pandemic[1]

Conserve garb and PPE • Garb for direct patient care personnel should take priority. • Prioritize availability of sterile gloves above other garb for sterile compounding activities because direct contact contamination is the highest risk to the CSP. • Inventory supply of garb to prepare and implement a temporary garb and PPE action plan. Ensure staff are properly trained to implement changes in garbing procedures. Check with suppliers on expected availability. • Limit staff performing sterile compounding.

○ Schedule staff to maximize compounding time and limit number of compounders per day or shift. ○ Modify staging activities to minimize passage into and out of the compounding areas. • If necessary, establish and document deviations from existing Standard Operating Procedures (SOPs).
Shortages of garb used for sterile non-hazardous drug compounding • Face mask ○ Reuse of face masks is not recommended because of the risk of introducing microbial bioburden from used masks. Storage in bags (e.g., plastic or paper) is not recommended because they may contain bioburden and may generate particles and microbial contamination. ○ Use clean fabric (e.g., polyester) to cover nose and mouth (e.g., bandana, washable face mask). Don a clean face cover each time before entering the compounding area. • Gown ○ Use clean, washable, dedicated non-disposable garments (e.g., gowns, lab coats). Long-sleeved garments are preferred, and if not available, wear sleeve covers. Preferably, wash garments after each shift or sooner when visibly soiled. ○ Retain and reuse disposable gowns as long as they are intact and not visibly soiled. Preferably, discard used disposable gowns each day. ○ Store garments in a manner that minimizes contamination. - Maintain garments inside of classified area or within the perimeter of the segregated compounding area (SCA). • Head and hair cover ○ Use clean fabric to cover head and hair. Preferably, wash after each shift or sooner when visibly soiled. • Shoe cover shortages • Implement dedicated shoes for the compounding area. Preferably, dedicated shoes should be cleaned regularly.
For shortages of PPE used for sterile hazardous drug compounding • Prioritize gowns and chemotherapy gloves for preparing antineoplastic agents in Table 1 of the NIOSH list. • PPE is designed to minimize exposure of healthcare personnel to HDs. PPE should not be reused when compounding antineoplastic drugs in Table 1 of the NIOSH list.
If facilities are not able to obtain garb or PPE • Adopt a risk-based approach and limit anticipatory compounding • Storage times should be assigned conservatively based on patient need and the type of garb mitigation strategy that is used. Use the shortest feasible beyond-use dates (BUDs) while giving consideration to avoiding drug shortages and maintaining patient access to essential medications. • Where feasible, increase cleaning and disinfecting frequency. • Consider increasing frequency of surface sampling in the primary engineering control to determine effectiveness of cleaning procedures and work practices. ○ If any changes are needed, promptly remediate and consider assigning shorter BUDs.

8. How is COVID-19 tested/confirmed?

Laboratories test for COVID-19 using polymerase chain reaction (PCR) technology. The WHO and CDC currently recommend collection of respiratory specimens, though blood may also be collected.[1,2] All 50 states have at least 1 laboratory performing verified COVID diagnostic testing. Healthcare providers should contact local and state health departments to coordinate testing or for additional testing information.[3]

9. What evidence is available for the use of commercially available medications for treatment of COVID-19?

Hydroxychloroquine (HCQ)/chloroquine (CQ)

Overall recommendation = likely beneficial, clinical trials ongoing; a summary of recommended doses is as follows:

- CQ = 500 mg PO twice daily x 10 days[1,2] –OR–
  - 600 mg PO loading dose followed by 300 mg PO on Day 1, then 300 mg PO twice daily on Days 2-5[2]
- HCQ = 200 mg PO twice daily x 10 days[2] –OR–
  - 400 mg PO once daily x 10 days[3] –OR–
  - 400 mg PO twice daily on Day 1, then 200 mg PO twice daily on Days 2-5[4] –OR–
  - 200 mg PO three times daily x 10 days +/- azithromycin 500 mg PO on day 1, then 250 mg PO per day for the next 4 days[8]

After *in vitro* studies of CQ proved activity against SARS-CoV-2, Chinese hospitals launched several clinical trials; first results of over 100 patients have shown superiority of CQ over the control groups in reduction of exacerbation of pneumonia, duration of symptoms, and delay of viral clearance, with no mention of severe adverse events. Therefore, CQ is included in the Chinese recommendations for prevention and treatment of COVID-19 pneumonia.[2,5] Analysis from Chinese scientists determined the *in vitro* activity of CQ against SARS-CoV-2 to be 1.13 micromolar and 6.9 micromolar for inhibition of 50% and 90% of viral activity, respectfully.[6] Therefore, with recommended CQ doses of 500 mg twice daily for 10 days (in mild, moderate, and severe COVID-19), therapeutic concentrations may be reached.[1]

Table 1. EC_{50} (in micromolar) for CQ and HCQ Against SARS-CoV-2, as Reported from *In Vitro* Trials[4,7]

Trial	CQ	HCQ
Yao 2020	5.47	0.72
Liu 2020	7.36	12.96

EC_{50} = effective concentration in which drug inhibits 50% of viral replication , with higher numbers meaning higher concentrations of drug are necessary to inhibit viral replication

Though *in vitro* studies have produced conflicting data on which agent (CQ or HCQ) is more effective for inhibiting viral replication of SARS-CoV-2, both agents have shown effective viral inhibition at therapeutically achievable concentrations.[4,7] After studying a few different dosing regimens, Yao et al recommends HCQ dosing of 400 mg twice daily on Day 1 and 200 mg twice daily on Days 2-5, citing efficacy, safety, and patient compliance considerations. (see Table 2).[4]

Table 2. Dosing regimens and free lung tissue trough concentrations, per Yao et al

Drug	Dosing Regimen	Ratio of free lung tissue trough concentration/EC_{50}			
		Day 1	Day 3	Day 5	Day 10
CQ	500 mg BID (Days 1-10)	2.38	5.92	18.9	40.7
HCQ	800 mg+400 mg (Day 1) 400 mg once daily (Days 2-10)	33.3	55.1	103	168
HCQ	600 mg BID (Day 1) 400 mg once daily (Days 2-10)	31.7	54.7	103	169
HCQ	600 mg BID (Day 1) 200 mg BID (Days 2-10)	31.7	53.1	101	167
HCQ	400 mg BID (Day 1) 200 mg BID (Days 2-10)	21.0	38.9	85.4	154
HCQ	400 mg BID (Day 1) 200 mg BID (Days 2-5)	21.0	38.9	85.4	83.3

BID = twice daily; CQ = chloroquine; EC_{50}= effective concentration to inhibit viral replication by 50%; HCQ = hydroxychloroquine

Because the mechanism of CQ and HCQ are identical, and HCQ is more tolerable used for longer periods, HCQ is the optimal first choice for therapy.[1] Additionally, both CQ and HCQ can increase the QT interval, leading the Chinese panel to recommend routine electrocardiography and the avoidance of concomitant therapies known to increase the QT interval.[2] A group of Korean physicians recommends considering CQ 500 mg PO twice daily in older COVID-19 patients or in those with underlying conditions/serious symptoms; if CQ is not available, HCQ 400 mg PO once daily is recommended. Per this group of physicians, the use of antiviral medications is not recommended in younger COVID-19 patients with mild symptoms and no underlying comorbid conditions.[3]

In a preliminary analysis, 8/14 patients treated with HCQ only (200 mg PO three times daily x 10 days) and 6/6 patients treated with HCQ + azithromycin (500 mg on day 1, then 250 mg per day for the next 4 days) had virological clearance from nasal swabs at 6 days post inclusion compared to 2/16 patients in the control group. After addition of azithromycin to HCQ in 1 HCQ only patient remaining positive at Day 6 post inclusion, virologic clearance resulted after 1 day of combination therapy. However, 1 patient who tested negative at Day 6 in the HCQ + azithromycin group subsequently tested positive for the virus (at low titers) on Day 8. The authors suggest a synergistic effect of HCQ + azithromycin but caution of increased QT prolongation with the combination, as both drugs have been known to increase the QT interval individually. Nevertheless, additional studies are needed to determine the utility of adding azithromycin to HCQ to reduce the risk of superinfection.[8]

Cortegiani et al performed a systematic review of CQ use in COVID-19 including 6 articles and noted 23 ongoing studies in China. Studies demonstrated that CQ was effective in reducing viral replication and appropriate concentrations can be accomplished with standard dosing due to favorable tissue penetration, including into lung tissues. A Dutch Center for Disease Control public document recommends supportive care and consideration for use of CQ, with adult dose recommendations of 600 mg, followed by 300 mg after 12 hours on Day 1, then 300 mg twice daily on Days 2-5, encouraging ending treatment at 5 days due to adverse events. An Italian Society of Infectious and Tropical Diseases document recommends use of CQ 500 mg twice daily or HCQ 200 mg twice daily for 10 days, with variations in treatment duration from 5-20 days; target populations from this document included "patients with mild respiratory symptoms and comorbidities to patients with severe respiratory failure".[2]

Tamiflu (oseltamivir)/Xofluza (baloxavir)

Overall recommendation = NOT recommended for use in COVID-19

Oseltamivir is a neuraminidase inhibitor that prevents release of viral particles from the cellular envelope of the influenza virus.[1] Though most COVID-positive patients (>85%) are being given antivirals (including oseltamivir 75 mg PO twice daily), no effective outcomes have been observed. [2,3] In an *in vitro* study, Tan et al found insufficient inhibition of the cytopathic effect of SARS-CoV-1 with oseltamivir after 3 days (meaning insufficient activity against SARS-CoV-1).[4] As of March 17, 2020, 2 ongoing trials are studying the use of oseltamivir in combination with other antivirals or chloroquine.[5]

Baloxavir is a viral polymerase inhibitor that prevents transcription of the viral genome and thus viral replication.[1] No data could be found regarding the current use of baloxavir COVID-19 patients. In China, 1 trial is ongoing, studying baloxavir in combination with favipiravir for the treatment of COVID-19.[6]

Ribavirin

Overall recommendation = potentially beneficial in combination with lopinavir/ritonavir (LPV/r) (ribavirin should not be used as monotherapy), clinical trials ongoing

- Dosing varies among clinical trials (e.g. 400 mg PO twice daily OR 2 grams IV loading dose, then 400-600 mg PO every 8 hours)

Ribavirin is an antiviral medication that inhibits RNA polymerase activity and is most commonly used in Hepatitis C infections.[1] Ribavirin was studied for use in the original SARS-CoV but did not show meaningful activity against the virus in cell culture.[2] In an *in vitro* study by Tan et al, ribavirin showed inhibitory activity at all 3 SARS-CoV-1 viral load levels but only at high drug concentrations; because these high drug concentrations also caused cellular toxicity, the authors consider ribavirin alone to be inactive against SARS-CoV-1.[3] As expected, *in vitro* data for SARS-CoV-2 shows high ribavirin concentrations are necessary to inhibit the virus, with a concentration of 109.5 micromolar required to effectively inhibit 50% of viral replication.[4] However, Elfiky showed high binding affinity of ribavirin to the RNA-dependent RNA polymerase of COVID-19, thus creating the potential for ribavirin to work in combination with other therapies to synergistically inhibit the virus.[2,5]

The combination of ribavirin/interferon was commonly used in the treatment of MERS-CoV, showing efficacy in reducing MERS-CoV viral replication in animals.[6,7] The combination of ribavirin + LPV/r showed superior outcomes (e.g. reduced viral load, lower death rate) in a small group of SARS-CoV-1 positive patients compared to ribavirin alone.[8] Based on its previous use in these other viruses, the office of the National Health Commission of the People's Republic of China released guidance including recommendations for the use of ribavirin in combination with LPV/r for the treatment of COVID-19. As of March 17, 2020, no evidence in humans could be found for the use of ribavirin in COVID-19, but trials are ongoing.[7,9]

Kaletra (lopinavir/ritonavir, LPV/r)

Overall recommendation = possibly beneficial (potential for increased benefit when used with ribavirin), clinical trials ongoing; can be used with or without ribavirin (see above)

- Recommended adult dosing = 400/100 mg PO twice daily (with or without ribavirin)
- University of Michigan recommendations for pediatric dosing[1]
    - 14 days to 6 months old: lopinavir component 16 mg/kg PO twice daily
    - 6 months to 18 years:

- 15-25 kg: 200/50 mg PO twice daily
- 26-35 kg: 300/75 mg PO twice daily
- >35 kg: 400/100 mg PO twice daily

Kaletra is a combination of lopinavir and ritonavir commonly used for HIV treatment. Due to its successful use in the previous SARS-CoV outbreak, LPV/r has shown promise for use in COVID-19.[2,3] Lim et al reports a case of a 54-year old male COVID patient given 10 days of LPV/r therapy (400/100 mg PO twice daily), beginning on hospital day 8 (illness day 10). On the second day of LPV/r therapy, the patient's viral loads began to decline and remained negative on Days 8-10 of therapy. The authors note that given the timing of the illness (illness Day 10 once LPV/r therapy was started), it is possible that the patient's healing could have been due to the natural course of the illness (patient's fever was already starting to improve). Nevertheless, this case shows promise for LPV/r therapy in the management of COVID-19 patients.[4] A different course of events was described by Young et al when 5 COVID-19-postitive patients in Singapore were given LPV/r (200/100 mg PO twice daily for up to 14 days). Though supplemental oxygen requirements decreased for 3/5 patients and clearance of viral shedding from nasal swabs was seen for 2/5 patients, 2/5 patients subsequently deteriorated and experienced progressive respiratory failure, and viral detection persisted on nasal swabs/endotracheal aspirate for 2/5 patients for the duration of their admission to intensive care. Additionally, 4/5 patients experienced nausea/vomiting/diarrhea, and 3 developed abnormal liver tests (all of which are known adverse events of this medication); as a result of these adverse events, 4/5 patients did not finish the 14-day course of therapy.[5]

In a randomized, controlled, open-label trial, hospitalized, severe, COVID-19-positive patients were treated with LPV/r (400/100 mg PO twice daily for 14 days) + standard of care (n=99) or standard of care alone (n=100). Median age of enrollees was 58 years old with an average of 13 days between illness onset and randomization; 95% were also treated with antibiotic regimens. Selected outcomes are shown in **Table 3** below. Across various time points, similar percentages of patients in each group had detectable viral loads. SARS-CoV-2 was still detectable in 40.7% of patients in the LPV/r group at Day 28 (vs 42.3% in the control group). Approximately 14% of LPV/r patients discontinued treatment early due to adverse events. Overall, the benefit of LPV/r therapy in COVID-19 patients remains undetermined.[6] Though this trial did not produce positive results, it is important to note that the median time from illness onset to enrollment was 13 days; additional evidence is needed to determine if earlier initiation of treatment produces a more substantial effect.

Table 3. Results of LPV/r Therapy vs Standard Care Alone, per Cao et al[6]

	LPV/r + standard care (n=99)	Standard care alone (n=100)	Statistical Outcomes (95% CI)
Time to clinical improvement (median days)	16	16	HR 1.31 (0.95, 1.85)
Modified intent to treat*: time to clinical improvement (median days)	15	16	HR 1.39 (1.00, 1.91)
Subgroup: initiation of LPV/r therapy within 12 days on symptom onset: time to clinical improvement (median days)	12	15	HR 1.25 (0.77, 2.05)
Mortality at 28 days	19.2%	25.0%	-5.8% (-17.3, 5.7)
ICU length of stay (median days)	6	11	-5 (IQR 9, 0)

	LPV/r + standard care (n=99)	Standard care alone (n=100)	Statistical Outcomes (95% CI)
Time from illness onset to randomization (median days)	13	13	---
Time from randomization to discharge (median days)	12	14	1 (IQR 0, 3)
Adverse reactions (% patients) between randomization at Day 28	48.4%	49.5%	---
Serious adverse events (% patients) between randomization at Day 28	20.0%	32.3%	---

*modified intent to treat population excluded 3 early deaths within 24 hours of enrollment; CI = confidence interval; HR = hazard ratio; IQR = interquartile range

In the previous SARS outbreak (SARS-CoV-1), Chu et al evaluated the use of ribavirin (4 g oral loading dose followed by 1.2 g every 8 hours x 14 days, or 8 mg/kg intravenously every 8 hours if the patient could not tolerate oral treatment, x 14 days) + LPV/r (400/100 mg BID x 14 days) in patients positive for SARS-CoV. Forty-one patients were enrolled in the ritonavir + LPV/r group, and 111 patients were enrolled in the ritonavir only control group. At Day 21, 7/111 patients in the ribavirin only group had died compared to 0/41 in the LPV/r + ribavirin group. Patients given LPV/r + ribavirin continued to show a decline in viral load (4.7×10^4/mL on Day 5 to undetectable on Day 10) whereas patients in the ritonavir only group continued to show detectable virus (6.3×10^3/mL) at Day 20. The authors concluded that results of this study supported further trials using the combination of LPV/r + ribavirin in the treatment of SARS-CoV patients.[2] Given the unclear results of the above LPV/r trials, the addition of ribavirin may synergize the effects of LPV/r enough to provide benefit in the treatment of COVID-19, but additional data is necessary to bolster this hypothesis.

10. What medications are in clinical trials for COVID-19?

Remdesivir

Overall recommendation = likely beneficial, must apply for compassionate use through manufacturer (form link, email)

- Dosage used in clinical trials = 200 mg IV on Day 1, then 100 mg IV once daily[1]

Remdesivir (Gilead Sciences) is an experimental nucleotide analog given via intravenous infusion and previously studied for use in SARS, MERS, and Ebola viruses.[2] *In vitro* data shows high selectivity for SARS-CoV-2, with a remdesivir concentration of only 0.77 micromolar to effectively inhibit 50% of viral activity, making remdesivir a promising candidate for *in vivo* use.[3] As of March 17, 2020, 6 clinical trials are ongoing for the use of remdesivir in COVID-19 (mild/moderate and severe).[1] A New England Journal of Medicine article reports the use of remdesivir in the first COVID-19-positive US patient; in the case report, the patient's status appeared to improve upon remdesivir administration (though viral levels were already declining). However, final results for the patient were not available.[4] An additional report of a woman treated with remdesivir at UC Davis shows promise for use of remdesivir, with doctors reporting "the patient is doing well."[5] A news article by Keown cautioned the safety of remdesivir use, as preliminary reports of increased liver enzymes and gastrointestinal distress have surfaced (though these have not been verified).[6] Results from the ongoing clinical trials will provide important evidence regarding the safety and efficacy of remdesivir for the treatment of COVID-19.

Others

Over 40 other medication candidates are in preclinical evaluation for the treatment and/or prevention of COVID-19.

11. What are the recommendations surrounding adjunctive medications for supportive care?

Actemra (tocilizumab)

Overall recommendation = likely beneficial in severe patients, clinical trials ongoing[1,2]

- Recommended dosing is not clear; Xu et al used 400 mg IV once, with the option of a second 400 mg dose if fever[3]
    - China recommends 4-8 mg/kg IV (with 400 mg dose recommended) for initial dose, with second dose allowed if poor response to first one (max single dose 800 mg)[4]
    - University of Washington recommends 8 mg/kg IV x 1[5]
    - University of Michigan lists a more specific dosing regimen based on patient weight (seen here, 3.20.2020)
    - Package insert dosing for cytokine storm is 8 mg/kg IV (≥30 kg) or 12 mg/kg IV (<30 kg), with a max dose of 800 mg; additional dose may be administered with ≥8 hours in between doses[6]

Tocilizumab inhibits a receptor of pro-inflammatory cytokine interleukin 6 (IL-6) and was used in the US to treat rheumatoid arthritis; however, in 2017, the FDA approved its use in cytokine release syndrome (CRS).[1] Some COVID-19-positive patients have shown increased levels of inflammatory markers, causing authors to urge providers to consider the potential for harmful effects from cytokine storms.[7-9] In a retrospective analysis of 191 COVID-19-positive patients from 2 China hospitals, elevated IL-6 was associated with death, with higher levels found in non-survivors compared to survivors; results are shown in **Table 4.**[8]

Table 4. Comparison of IL-6 Levels in Survivors and Non-Survivors[8]

Day of Illness	Survivor	Non-Survivor
4	5.5	9.5
7	6.8	12.0
10	6.6	10.7
13	6.1	11.7
16	6.3	17.2
19	7.0	26.4

*IL-6 levels reported in picograms/mL

Upon analysis of IL-6 levels in 69 severe COVID-19-positive patients in China, researchers found significantly higher baseline IL-6 levels in severe patients compared to non-severe patients, with higher IL-6 levels trending towards higher severity (i.e. the higher the IL-6 level, the shorter time from symptom onset to pneumonia diagnosis). Additionally, a positive correlation was found between IL-6 level and bilateral/interstitial pulmonary involvement. In a subgroup of patients whose IL-6 levels were assessed before and after treatment, 26/30 patients experienced significant decreases in IL-6 levels and improvements in CT function after treatment (e.g. LPV/r, oxygen, immunoglobulin, oseltamivir, antibiotics, ribavirin, etc). Though the relationship between IL-6 and the pathogenesis of COVID-19 remains unknown, the correlation of IL-6 levels with disease severity makes IL-6 a possible marker for disease.[10]

The only human data of tocilizumab use comes from a small report of 21 severe COVID-19 patients. All patients received standard care (lopinavir, methylprednisolone, oxygen therapy, etc) in addition to tocilizumab 400 mg IV once; 3 patients received a second dose due to fever within 12 hours. Fevers resided in all patients on the first day after receiving tocilizumab; 15/20 patients lowered their oxygen requirements and 1 patient was able to be removed from the ventilator on the first day after tocilizumab therapy. On the 5th day of treatment, 17/19 patients had normal white blood cell counts and 16/19 patients reached normal levels of C-reactive protein. At the time of publication, 19/21 patients were discharged and remained stable; 2/21 patients remained under hospital observation, with normal body temperatures and improvement in symptoms. No adverse events were reported with tocilizumab therapy. The authors concluded that tocilizumab successfully improves clinical symptoms and "represses the deterioration of severe COVID-19 patients".[3]

Recommendations from the People's Republic of China state that tocilizumab therapy may be attempted in patients with extensive and bilateral lung disease and severely ill patients with elevated IL-6. Initial dosing should be 4-8 mg/kg, with maintenance dosing of 400 mg per day. Tocilizumab should be diluted to 100 mL with normal saline and infused over 1 hour; the dose may be repeated after 12 hours if the response to the first dose was poor (max 2 doses, or 800 mg).[4]

Kevzara (sarilumab)

Overall recommendation = unknown benefit; clinical trials ongoing; no dosing recommendation available

Based on the data surrounding IL-6 levels mentioned above in the tocilizumab section, sarilumab is also being studied for use in COVID-19.[1,2] Regeneron and Sanofi have begun recruitment for their 2 part trial. Part 1 is a Phase II study randomizing patients to high dose sarilumab, low dose sarilumab, or placebo; results from this part will help determine dosage, endpoints, and patient numbers for the Phase III trial (part 2). Only severe hospitalized patients will be enrolled in these trials, including a requirement for pneumonia and fever.[2]

Nitric oxide

In progress

Azithromycin

In progress

Doxycycline

In progress

12. What vaccines are in clinical trials for COVID-19?

mRNA-1273

mRNA-1273 (Moderna, Inc.) is a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized spike (S) protein of SARS-CoV-2.[1] Previous studies in SARS and MERS allowed for the quick development of mRNA-1273.[2] A Phase 1 clinical trial for the vaccine started in March 2020. The study will include 45 healthy, adult participants who will receive 25 mcg, 100 mcg, or 250 mcg of mRNA-1273 administered through 0.5 mL intramuscular injection in the deltoid

muscle on Days 1 and 29. Follow-up will be through 12 months post second vaccination.[1] A phase 2 trial could begin in a few months.[3]

BNT162

BNT162 (BioNTech and Pfizer) is an mRNA-based vaccine for COVID-19. Clinical testing is expected to begin by the end of April 2020.[4]

INO-4800

INO-4800 (INOVIO Pharmaceuticals, Inc. and Beijing Advaccine Biotechnology Co.) is an intradermal DNA-based vaccine for COVID-19. Phase 1 clinical trials in the U.S. are expected to begin in April 2020.[5-6]

Ad5-nCoV

Ad5-nCoV (CanSino Biologics, Inc. and Bejing Institute of Biotechnology) is a recombinant COVID-19 vaccine that incorporates Adenovirus Type 5 Vector. A Phase 1 clinical trial in China has begun.[7]

Others

Over 30 other vaccine candidates are in preclinical evaluation for COVID-19.

Janssen in collaboration with Beth Israel Deaconess Medical Center (BIDMC) hope to identify a candidate by the end of March 2020 and begin a Phase 1 clinical trial by the end of 2020.[8]

Altimmune is developing a single-dose intranasal vaccine for COVID-19. Clinical trials could begin as early as August 2020.[9]

CureVac plans to start clinical trials with its mRNA-based COVID-19 vaccine by early summer 2020.[9]

13. What evidence is available regarding the worsening of COVID-19 infection by certain FDA-approved medications?

Ibuprofen

Overall recommendation = does NOT increase infection risk; some may still use acetaminophen over ibuprofen for fever control but no evidence to suggest ibuprofen increases infection risk

The original discussion of avoiding ibuprofen arose after the French Health Minister recommended acetaminophen use over NSAIDs in treating fever in COVID-19 patients, citing evidence suggesting an association between ibuprofen and more severe illness and complications.[1] Another argument surrounded the mechanism of COVID-19 infection in human cells; COVID-19 binds target cells through angiotensin converting enzyme-2 (ACE2), which is expressed in many human cells including the epithelial lining of the lungs, gastrointestinal tract, kidney, and blood vessels. Because ibuprofen may increase the expression of ACE2, discussion of increased risk of COVID-19 infection arose.[2] However, there is not enough evidence to suggest the use of ibuprofen increases the risk of COVID-19 infection.[3,4]

ACE-inhibitors/ARBs

Overall recommendation = does NOT increase infection risk; do NOT discontinue treatment unless recommended by physician

The points around avoiding angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are the same as mentioned above for ibuprofen: COVID-19 binds to ACE2 in human cells.[1] Like ibuprofen, there is no evidence to support the avoidance of ACEIs/ARBs; the European

Society of Cardiology (ESC) Council on Hypertension, American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) all report that patients currently receiving treatment with ACEIs/ARBs should NOT discontinue treatment, unless recommended by their physician.[2]

14. Is there evidence comparing the use of multi-dose inhalers versus nebulized respiratory medications for supportive care? Which is safer?

Virus transmission via respiratory secretions in the form of droplets (>5 microns) or aerosols (< 5 microns) appears to be likely, as SARS-CoV-2 has been detected in upper and lower respiratory tract samples of infected patients.[1,2] As mentioned previously, van Doremalen et al showed that COVID-19 remained viable in aerosols for up to 3 hours and was most stable on plastic and stainless steel with viable virus detectable for up to 72 hours post application.[3] Given the aerosolized viability of COVID-19, it is likely good practice to avoid use of nebulizers in patients that can use alternative methods of treatment such as metered dose inhalers (MDIs). These practices may result in a reduced number of aerosolized transmissions of COVID-19. Tellier et al discusses recognition of aerosol transmission of infectious agents and briefly mentions the use of nebulizer therapy. For influenza specifically, carefully controlling the use and exposure to respiratory assist devices (high-flow oxygen masks, nebulizers) should only take place in designated, containment areas or rooms. Airflows expelled from side vents of oxygen masks and nebulizers contain mixtures of patient exhaled air (which could be carrying airborne pathogens) and incoming high flow oxygen or air carrying nebulized drugs. These vented airflows could then act as a potential sources of airborne pathogens.[4] Furthermore, per communications between health systems regarding this question, many are moving forward with policies to implement switching from nebulizer therapy to MDIs in patients with confirmed or suspected COVID-19 so long as patients can tolerate MDI therapy.

15. What does the evidence say regarding use of corticosteroids? Does using them increase infection risk?

Routine use of systemic corticosteroids is not recommended.[1-3] One review showed no survival benefit and possible harm with the use of corticosteroids in SARS patients while another review found a higher risk of mortality and secondary infections in patients with influenza.[2,3] Arabi et al found no difference in mortality between patient's receiving corticosteroids (vs no corticosteroids) but did find delayed clearance of viral RNA from respiratory tract secretions (**HR 0.4, 95% CI 0.2-0.7**).[4] While these data are not referring to patients infected with COVID-19 (e.g. SARS-CoV-1, MERS-CoV, influenza, etc), there is no data suggesting patients infected with COVID-19 are expected to act differently or benefit from corticosteroids.[3] Corticosteroids should be avoided unless they are indicated for another reason (e.g., COPD exacerbation, refractory septic shock following Surviving Sepsis Campaign Guidelines).[1-3]

Note: data above is in reference to systemic corticosteroid use, not inhaled corticosteroids. None of the asthma medications (inhaled corticosteroids, biologics, etc) have been shown to increase the risk of contracting COVID-19.[5] In an *in vitro* study, Matsuyama et al showed suppressed replication of MERS-CoV, SARS-CoV and HCoV-229E viruses with inhaled ciclesonide and mometasone but not fluticasone. Ciclesonide and mometasone reduced RNA replication of SARS-CoV-2 at rates similar to lopinavir when exposed for 6 hours post-inoculation; only ciclesonide was studied at 27 hours post-inoculation, showing an effective concentration of 6.3 micromolar to inhibit SARS-CoV-2 replication.[6]

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Hydroxychloroquine/chloroquine

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Tamiflu (oseltamivir)/Xofluza (baloxavir)

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Ribavirin

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Kevzara (sarilumab)

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Nitric oxide

1. In progress

Azithromycin

1. In progress

Doxycycline

1. In progress

12. What vaccines are in clinical trials for COVID-19?

mRNA-1273

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13. What evidence is available regarding the worsening of COVID-19 infection by certain FDA-approved medications?

Ibuprofen

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