



Coronavirus (COVID-19)

Last Updated: June 17, 2020

Prior versions: April 8, 2020; April 24, 2020; May 8, 2020; June 12, 2020; June 15, 2020

The June 17, 2020 update includes the following major changes:

1. Revised guidance with upgrading of the glucocorticosteroid recommendation to be provisionally recommended [Recommended, Insufficient Evidence (I)]. The provisional designation is based on the UK's reported findings, pending publication of final data.
2. Revised guidance with downgrading of the hydroxychloroquine and chloroquine recommendations to be provisionally not recommended [Not Recommended, Insufficient Evidence (I)]. The provisional designation is based on the UK's reported findings, pending publication of final data.

The June 12, 2020 update included the following major changes:

1. Inclusion of remdesivir randomized controlled trial data and upgrading of the remdesivir recommendation to Level C evidence [1].
2. A new recommendation for combination therapy with lopinavir, ritonavir, ribavirin, and interferon beta-1b (Level C evidence).
3. Increase in the categorizations of COVID-19 disease to include pre-clinical infections. The six categories are asymptomatic, subclinical, pre-symptomatic, upper respiratory tract infection, lower respiratory tract infection/pneumonia, and acute respiratory distress syndrome. It is important to separately recognize subclinical infections as an important avenue for prevention of disease spread (e.g., using daily electronic symptom screeners).
4. Updated epidemiological data, including the Center for Disease Control and Prevention's most recent estimates of $R_0=2.5$; overall symptomatic case fatality ratio is 0.004, or 1 in 250; 40% of transmission occurs prior to symptom onset; and the infectiousness is estimated to be comparable between asymptomatic and symptomatic individuals [2].

5. Viral inactivation experimental data, including that sunlight rapidly deactivates the virus in experimental data with simulated saliva (90% was inactivated every 6.8 minutes at solstice sunlight ultraviolet intensity at 40 degrees latitude) [3].
6. Inclusion of hydroxychloroquine prophylaxis study data, which suggested a non-statistically significant 17% reduction in risk, among mostly healthcare workers who had been exposed (11.8% vs. 14.3%, 17.5% reduction, p=0.35) [4].

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Strength of Evidence Ratings

Strength of Evidence ratings are used to designate the quality and amount of evidence that supports a specific guideline recommendation, when taking into account the entire body of relevant evidence found in the literature search. The body of evidence on a topic consists of all studies found that were relevant to the specific clinical question and of acceptable quality. In general, the highest quality of evidence found should be used by the Panel as the basis for the guideline recommendation, unless other factors, such as the potential for harm, are an overriding consideration. When multiple studies of similar quality and relevance are found on a topic, these studies should be evaluated as a group; if results are generally consistent, they would be considered either Strong Evidence (for high quality studies) or Moderate Evidence (for moderate quality studies). In all cases, the rationale for each recommendation and scientific studies used as evidence, should be documented by the Panel.

A	Strong evidence-base: Two or more high-quality studies. ¹
B	Moderate evidence-base: At least one high-quality study or multiple moderate-quality studies ² relevant to the topic and the working population.
C	Limited evidence-base: At least one study of moderate quality.
I	Insufficient Evidence: Evidence is insufficient or irreconcilable.

For treatment, the criteria used by evidence reviewers to categorize the quality of individual randomized controlled trials as high, moderate, or low quality are: adequate randomization, concealed treatment allocation, baseline cohort comparability, patient blinded, provider blinded, assessor blinded, controlled for co-interventions, compliance acceptable, dropout rate acceptable, timing of assessments equivalent, data analyzed by intention to treat, and lack of bias.³ Each criterion receives a score of 0, 0.5, or 1. See [Table B in the Methodology](#) for a definition of each criterion and scoring level. Studies are considered of low quality if they are rated 3.5 or less, moderate quality if they are rated 4-7.5, and high quality if they are rated 8-11.

Please see <https://info.mdguidelines.com/wp-content/uploads/2019/08/Methodology-2017-Update.pdf> for our full [methodology](#).

¹ For therapy and prevention, randomized controlled trials (RCTs) with narrow confidence intervals and minimal heterogeneity. For diagnosis and screening, cross-sectional studies using independent gold standards.

For prognosis, etiology or harms, prospective cohort studies with minimal heterogeneity.

² For therapy and prevention, a well-conducted review of cohort studies. For prognosis, etiology or harms, a well-conducted review of retrospective cohort studies or untreated control arms of RCTs.

³ van Tulder M, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the Cochrane Collaboration back review group. *Spine*. 2003;28(12):1290-9.

Introduction

Note: This guideline and its recommendations were last reviewed and updated on **June 17, 2020**.

This guideline has previously undergone extensive peer review. However, the total depth and breadth of quality literature for the treatment of COVID-19 is quite limited. Some of the studies underlying this guideline are particularly fluid due to the pace of change in knowledge. Research data, especially those associated with treatments, are being published prior to peer review. Under normal circumstances, such data would not be considered for an evidence-based guideline. However, the severity, urgency, and mortality associated with this pandemic do not allow the luxury of time to await the completion of peer review. The literature will continue to be monitored and this guideline will be updated as needed in response to new research reports, changes in prior reports caused by peer review, and any retractions.

Novel coronavirus 2019 (COVID-19) is an acute respiratory infection caused by a new strain of coronavirus. The virus has been named “SARS-CoV-2” and the disease it causes has been named “coronavirus disease 2019” (abbreviated “COVID-19”) [5]. Because it is new, limited but increasing information is available about the virus.

The pandemic began in Wuhan, China in October-November 2019, then expanded markedly throughout the Wuhan region. The Chinese New Year likely accelerated the spread of the virus through global travel and hastened the development of a pandemic. Quarantines were likely ineffective at preventing the pandemic [6] for several reasons, including the number of undiagnosed, mild, or asymptomatic patients spreading the virus [2, 7]; animals’ susceptibility and involvement; and the spread of cases in a region prior to the recognition of COVID-19 within that area [8]. Public health management of this pandemic has varied across countries and jurisdictions, typically using various combinations of approaches, including the quarantine of affected individuals, contact tracing, isolation, stay-at-home orders, social distancing, mask use, and the closure of non-essential businesses. There is considerable and growing controversy regarding efficacy of these various measures, especially closure of businesses and schools; quality data are weak and some countries (e.g., Japan, South Korea, Sweden) have instituted less stringent measures with seemingly somewhat comparable results [9-19]. The pandemic continues to provide numerous challenges, including surge prevention and mitigation; healthcare and first-responder personal protective equipment availability; COVID-19 diagnostic testing availability, capacities, and limitations; unique treatment challenges and sparse evidence of efficacy; growing public restlessness with restrictions; and increasing business/economic concerns.

Other coronavirus outbreaks have occurred in the past, such as severe acute respiratory syndrome (SARS) in 2003-04 and Middle East respiratory syndrome (MERS) in 2012-15 [20, 21].

When a virus mutates or changes, studies must be performed to determine the new strain's virulence (i.e., its ability to infect humans). Based on prior research and experience with coronavirus infections, the origin of this epidemic is thought to be traced to bats near Wuhan, China. COVID-19's SARS-CoV-2 virus can now be found in humans on all continents around the world except Antarctica [22, 23].

Virus Characteristics

Contagiousness

COVID-19's SARS-CoV-2 virus appears to be more contagious than the prior coronaviruses. The virus is thought to be mostly spread by respiratory droplets and direct hand-to-mucous membrane contact. However, a committee of the National Academy of Sciences has concluded there is some limited evidence that it is also spread by respiratory aerosols [24-32]. Aerosols can remain suspended in the air for a longer time and well beyond the commonly quoted 6-foot (or 1-meter, per the World Health Organization) physical distancing guideline [33].

The contagiousness and virulence of the SARS-CoV-2 virus appears to be about 3-fold greater than that of influenza. Estimates of the contagiousness or transmission rate without interventions (e.g., physical distancing) range from 2.0 to 3.9—that is, 2 to 3.9 new cases arise from each known case [34], which is far higher than typical influenza transmission rate of ~1.3 [35]. The most recent Centers for Disease Control and Prevention (CDC) estimate for the United States is 2.5 [2]. More precise estimates of transmission rates will become known with time, particularly as testing rates escalate. Collectively, although global next-generation sequencing results indicate that SARS-CoV-2 genomes are relatively stable, dynamic mutations can be selected in symptomatic individuals [36]. A more recent publication documented changes in the SARS-CoV-2 spike protein D614G due to recombination between locally circulating strains, which is now the dominant pandemic form in many countries. This new version is associated with higher viral loads and suggests that it is more transmissible, although there was no significant correlation found between D614G status and hospitalization status (i.e., severity of disease) [37].

Future studies will need to further quantify factors, such as how many people become infected when they are close to someone with the virus, how many asymptomatic cases occur, how many clinical infections occur, and how many fatalities occur.

The virus's survivability on surfaces varies depending on the material; it has been estimated to survive up to 9 days [38]. The total viable viral counts decline with time [33]. The survival time of the virus was reported to differ by surface type, with approximate upper limits of detection being 4 hours on copper, 24 hours on cardboard, 48 hours on stainless steel, and 72 hours on plastic. [38]. Survival of the virus in aerosols is thought to be at least 3 hours. However, it is still unclear how much virus is needed to infect a human from either surfaces or aerosols.

Some preliminary data suggest spread may be optimal in indoor and/or cooler climate conditions [39-41], and prior data on the SARS coronavirus are corroborative [42]. Experimental

evidence suggests that simulated sunlight rapidly inactivates the virus. At a simulated sunlight intensity of the summer solstice at 40 degrees of latitude, the inactivation rate was 90% inactivated every 6.8 minutes [3]. This suggests highly variable disease transmission risks based on seasonality and in indoor compared with outdoor environments. Taken together, these data indirectly suggest the potential for a wave of spread in northern latitudes in fall 2020 [40], assuming the viral epidemic does not tail off and/or sufficient herd immunity does not occur in the meantime.

Incubation and period of infectious viral shedding

The incubation period is the amount of time that occurs between exposure and the onset of symptoms. The incubation period of the SARS-CoV-2 virus is estimated to be approximately 6 days [2, 43, 44], with infrequent cases of up to 14 days [23, 45]. The time between symptom onset in an individual and symptom onset in a second person infected by that individual also averages 6 days [2]. Viral shedding may antedate symptoms by 1–2 days, and viral titers are highest in the earliest phases of infection.

A detailed virological analysis of nine cases of COVID-19 demonstrated active virus replication in the upper respiratory tract. Pharyngeal virus shedding was very high during the first week of symptoms, with a peak at 7.11×10^8 RNA copies per throat swab on day 4. Infectious virus was isolated from pharyngeal and sputum samples, but not from stool samples, despite high concentrations of viral RNA. Blood and urine samples never yielded virus. Active replication in the throat was confirmed by the presence of viral replicative RNA intermediates in pharyngeal samples. In one patient, sequence-distinct virus populations were detected in throat and lung samples, demonstrating independent replication. Infectious virus was no longer detected from 9 to 22 days after symptom onset [46].

The length of time an infected person sheds virus is affected by severity of illness. A recent study showed that no infectious virus was detected 10 days after symptom onset. A retrospective study of 113 patients with severe illness admitted to two hospitals outside of Wuhan reported that the median duration of viral shedding measured by PCR was 17 days (13 – 22). Longer viral shedding was associated with male sex, age ≥ 54.5 years, hypertension, delayed admission after symptom onset, and mechanical ventilation [47]. A different study of 147 patients in Changsha, China, similarly found a median duration of viral shedding of 17 days (range: 12–21 days), with longer viral shedding from those more severely affected, as measured by higher temperature on admission, longer duration of symptoms before admission, and longer hospital stay [48]. However, detection of virus by PCR does not necessarily mean that the virus is infectious, as PCR may also detect non-infectious viral particles [46].

Clinical Presentation

There are at least six distinct types or clinical presentations of COVID-19's SARS-CoV-2 virus infections, the first and third of which incur no healthcare visits; pre-symptomatic individuals may or may not incur healthcare visits [2]:

1. Asymptomatic

2. Pre-symptomatic
3. Mild, subclinical infection (e.g., mild rhinorrhea)
4. Upper respiratory tract infection (URI), which also may include gastrointestinal symptoms
5. Lower respiratory tract infection, including pneumonia
6. Acute respiratory distress syndrome (ARDS)

Treatments differ for each presentation (see Treatment section for more details).

Symptoms and Signs

The symptoms of COVID-19 vary but are generally typical of respiratory infections, such as fever and cough. COVID-19 symptoms may include the following [49-51]:

- Fever (low or high grade) (80-88%)
- Dry cough [23, 52] (63-69%)
- Loss of appetite (39-84% [53])
- Fatigue (38-46%)
- Sputum production (33-42%)
- Chest pain or pressure (28-36%)
- Dyspnea (shortness of breath) (19-35%)
- Myalgia and/or arthralgia (muscle and joint pain) (15-33%)
- Sore throat (12-14%)
- Headache (11-15%)
- Chills (6-11%)
- Nausea or vomiting (5-10%)
- Diarrhea (4-29% [53])
- Nasal congestion (4-5%)
- Abdominal pain (4%)
- Conjunctivitis (pink eye) [54] (1%)
- Hemoptysis (1%)
- Rhinorrhea (runny nose)
- Anosmia and dysgeusia (loss of smell and taste) (85% moderate/severe or anosmic) [55]

Cardiovascular symptoms and signs may also be noted on initial presentation [56-60].

Coagulopathy associated with antiphospholipid antibodies and multiple infarcts have been reported in three elderly patients with COVID-19 infection and multiple comorbidities [61]. Five patients in New York City, ranging in age from 33 to 49, presented with large vessel strokes as the manifestation of COVID-19 infection [62]. There also have been reports of dermatological abnormalities such as urticaria, vasculitides, and pityriasis rosea [63-66]. Various neurological presentations including stroke-like symptoms have been reported [67-73]. While the prevalence of direct kidney involvement in COVID-19 disease ranges from 3 to 15%, it is a marker for multiple organ failure and severe disease [74]. Acute kidney injury is thought to be triggered by cytokine storm. In addition, the ACE2 receptor, essential for viral uptake, is highly

expressed on podocytes and tubule epithelial cells. Albuminuria and hematuria have been detected in COVID-19 infection, along with the isolation of viral RNA from urine [75].

Because the symptoms for most patients are typical of nonspecific respiratory tract infections, they can be difficult to distinguish from other diseases [76, 77]. The disease commonly begins with mild symptoms for several days, which may readily facilitate its spread to other individuals. A minority of patients then develop more severe symptoms and may require ICU care [78]. These more severe cases of COVID-19 involve additional symptoms that typically accompany pneumonia, such as shortness of breath. Respiratory problems may further progress to severe dyspnea, require oxygen supplementation, and develop into acute respiratory distress syndrome (ARDS). Patients with pneumonia may have tissue hypoxia, tachypnea, tachycardia, and crackles on chest examination. Severe cases may present with shock and respiratory failure.

The virus infection may also cause no symptoms; however, asymptomatic and pre-symptomatic individuals may still pass the virus to others, who may then develop symptoms [7, 78, 79]. The CDC estimates that 40% of transmission occurs prior to symptom onset and that the infectiousness is comparable between asymptomatic and symptomatic individuals [2, 7]. Children tend to be asymptomatic or have milder symptoms, which suggests a mechanism that may accelerate disease transmission throughout the population [78]. However, a pediatric multisystem inflammatory syndrome has been reported in 50 children who presented with persistent fever and features of Kawasaki disease or toxic shock in New York City. Most of those patients tested positive for the COVID-19 virus or for antibodies to the virus, suggesting a post-infection immune response. None of the children have died, but several have required mechanical ventilation [80].

Mortality

The mortality of COVID-19 was estimated to be approximately 10-fold higher than that of typical seasonal influenza [81]. More recently, severity estimates have been reported as low enough to be comparable with prior influenza epidemics [82-85], with a range of infection fatality rates of 0.03–0.5% and corrected rates of 0.02–0.4% [86]. The current CDC estimate of the overall *symptomatic* case fatality ratio is 0.004, or 1 in 250 [2].

Mortality risks increase sharply with age, with a symptomatic case fatality ratio of 1 in 2000 among those 0–49 years of age, 1 in 500 among those 50–64 years of age, and 1 in 77 among those 65+ years of age [2]. The mortality rate for males is 57–64% higher than that for females. Nursing home residence is a particularly potent fatality risk [87-91]. The risk of severe disease and/or death is also correlated with other underlying conditions, such as heart disease, hypertension, diabetes mellitus, chronic renal disease, dialysis, liver disease, chronic obstructive pulmonary disease [COPD], smoking, and obesity [92-95]; however, approximately 1% of fatalities occur in previously healthy patients [96]. Past outbreaks of coronavirus infections had considerably higher mortality rates: 34% for MERS and 10% for SARS. However, the mortality rate is not the only factor in determining the seriousness of a disease; a high rate of infectivity

and/or easy transmissibility could result in many more total deaths despite a lower case fatality rate.

Business Considerations

The actions an employer can take to mitigate the risk of COVID-19 infection center primarily on the virus's potential respiratory and contact spread. There are multiple domains for an employer's actions. Please see the following sections on:

1. Employee issues (e.g., education and medical surveillance)
2. Travel issues
3. Social distancing methods
4. Disinfection practices and contact spread measures
5. Personal protective equipment (e.g., masks, gloves, and face shields)
6. Ventilation issues
7. Policies and procedures
8. Industry-specific recommendations

The education of workers in each of these areas is advised as appropriate.

A business with broad geographic interests may also wish to incorporate geographic-specific risks. McKinsey suggested risks for a given jurisdiction should be related to four metrics assessing the strength of test, trace, and quarantine efforts (adapted from [97]):

1. *Test positivity rate*, a measure of testing systems' abilities to capture all cases. The World Health Organization recommends a target of <10% positivity.
2. *Tests per million population*, a measure of the depth of testing.
3. *Average number of contacts identified per case*, a measure of how effective contact-tracing systems are at identifying and isolating the likely next generation of cases. The figures are expected to trend lower in lockdown settings than when people are moving and interacting freely.
4. *Fraction of cases arising from contact lists*, a measure of the portion of cases arising from known sources versus undetected community transmission.

(Note: Always check for current guidance from the Centers for Disease Control and Prevention.)

Employee Issues

COVID-19 surveillance

Employers are recommended to implement a surveillance system that at minimum includes education of workers and screening to avoid having workers with potential early and/or symptomatic but subclinical COVID symptoms enter the workplace premises. Options for larger employers and/or jobs with greater risks (e.g., mission-critical jobs; a workforce where one ill worker could infect an essential group of workers, which would shut down the workplace)

include either daily/periodic electronic questionnaires with or without temperature measurements. Electronic questionnaires are likely to be more effective than temperature measurements, as 69% of those seriously ill are afebrile [98], and temperature measurements are also likely to miss all subclinical but symptomatic cases [2]. Diagnostic testing should be performed on those with symptoms, most commonly through the local healthcare or public health systems. Diagnostic testing may also be performed to ascertain asymptomatic spread, especially among essential workers. Considerations also include providing communications and expectations to subcontractors, suppliers, and others who may have significant interactions with the employer (e.g., assurance of policies to address symptomatic employees, surveillance).

Employees with possible COVID symptoms

Sick employees (including those with minimal symptoms) should stay home from work, as it is important to eliminate all contact between the healthy workers in the workplace and anyone with potentially infectious symptoms [99]. If there is believed to be COVID-19's SARS-CoV-2 virus transmission in the area (currently true of essentially all US urban and many rural areas), then anyone with even mild symptoms of a respiratory tract infection (e.g., cough, fever, fatigue) should stay home to be sure they do not progress to a clear, readily transmissible, and potentially severe COVID-19 infection [78], as well as to prevent transmission to others. Sick employees should also be encouraged to undergo testing if available. They should be instructed to call a provider or healthcare organization in advance, discuss the symptoms, seek testing if available (especially at outdoor tents), and put on a mask prior to entering any clinic or hospital.

Any questions about potential COVID-19 infections should be directed to the local health department, which has the expertise and personnel to investigate outbreaks and perform contact tracings (provided they are not overwhelmed by the current epidemic). It is important to recognize that return-to-work recommendations for essential workers, especially healthcare workers, may need to be modified during the course of the epidemic for practical reasons in response to acute workforce shortages in key jobs and sectors.

CDC recommendations for healthcare workers have been revised to address the removal of exposed workers who had relatively low risks for conversion during potential incubation periods, as it affected the capacity for patient care [100]. Current guidance includes the following [100]:

- A symptom-based strategy for symptomatic workers, who are recommended to be excluded from work until there has been at least 3 days since recovery, improvement in respiratory symptoms, and at least 10 days since the symptoms first appeared.
- A test-based strategy for symptomatic workers, who are recommended to be excluded from work until there is resolution of fever, improvement in respiratory symptoms, and negative COVID-19 results for at least 2 consecutive tests. (There is a risk of ongoing positive test results in a minority of workers of uncertain significance.)

- A time-based strategy for confirmed but asymptomatic employees, who are recommended to be excluded from work for 10 days since the positive test result.
- A test-based strategy for confirmed but asymptomatic employees, who are recommended to be excluded from work until at least 2 consecutive tests are negative 24+ hours apart. (There is risk of ongoing positive test results in a minority of workers of uncertain significance.)

Although the above recommendations are official CDC guidance, it is also advisable for a healthcare employer to consider factors including staffing needs, manpower, infection rates, and individualized assessment of the degree of that person's contact with susceptible patients (especially those with comorbidities). Furthermore, it is advisable that the other CDC guidance be followed [100]. Depending on those factors, more conservative or more liberal return-to-work timeframes may be advisable to balance the risks of infecting patients with the ability to staff and care for patients.

What to do if an employee tests positive for COVID-19

The sick employee should follow current CDC guidelines, quarantining at home (if able). A symptom-based approach recommends recording temperatures twice daily until 72 hours (3 days) have passed without fever or treatment with any fever-reducing medications. In order to leave quarantine, it is advised that a minimum of 7 days must have passed since the onset of symptoms, with then 3 subsequent days of no fever and improvement in symptoms. A testing-based approach requires two negative PCR viral tests obtained at least 24 hours apart. The areas where the sick employee worked, including conference rooms and common areas, should undergo deep cleaning and decontamination to prevent spread to other employees.

Employees in contact with an infected coworker

Employees in contact with an infected coworker should continue to undergo medical screening. Close contacts are defined as any individual who was within 6 feet of an infected person for at least 15 minutes starting from 2 days before illness onset (or, for asymptomatic patients, 2 days prior to positive specimen collection) until the time that the patient is isolated [101]. Risk assessment should include the duration of contact with the sick employee, whether they were using any personal protective equipment, and the type of personal protective equipment used (e.g., cloth face covering vs. respirator) [102]. Attempt to maintain confidentiality regarding an ill employee's identity. Employers may wish to apply more or less restrictive policies depending on their individual business requirements, organizational characteristics (e.g., closeness and numbers of other workers), and risk tolerances. For higher risk exposures with greater business considerations, the most conservative approach is to have employees who could be in the incubation stage work from home for at least 2 weeks after the possible exposure.

Yet, in certain manpower shortage situations, medical centers and critical service workers are being allowed to work while asymptomatic with twice-daily temperature checks, self-surveillance for symptoms, social distancing, disinfection of work spaces, and consistent mask-wearing instead of being quarantined for 14 days [103]. This option is controversial and not without considerable risks as pre-symptomatic spread is believed to be a primary source of

epidemic spread. This option should be carefully weighed between the industry sector, criticality of the job, job requirements, and risks of an infectious individual in that particular workplace. This option is likely unduly risky if the workforce or work group is mission critical.

High-Risk Employee Issues

For the purposes of these recommendations, high-risk individuals have any of the following conditions [98, 104]:

- Age 65 years and older
- Chronic lung disease, including moderate to severe asthma
- Serious heart condition (e.g., history of heart attack or heart failure)
- Immunocompromised (e.g., having had bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS; using corticosteroids or other immune-modulating medications, undergoing cancer treatment)
- Smoking, current or former
- Obesity, especially severe
- Diabetes mellitus
- Chronic kidney disease, especially those undergoing dialysis
- Liver disease
- Hypertension
- Current cancer
- Neurological diseases, including stroke and dementia

Generally, the risks associated with the above conditions are greater as the severity of the conditions increase. The presence of multiple conditions increases risks of severe disease [105].

Employers should attempt to reduce exposures to higher-risk situations for workers who self-identify as high-risk, while being cognizant of the implications of the Americans with Disabilities Act and amendments. A full- or part-time medical director and medical department may help to interface between the worker and management to effect these risk assessments and potential risk reductions. Examples of reductions in exposure (beyond electronic questionnaires with or without temperature checks) include the following:

- Emphasize distance-based work methods, including telecommuting where feasible
- Place high-risk individuals behind barriers
- Reduce public-facing work
- Use personal protective equipment (PPE) to protect from exposure
- Use masks (evidence from randomized controlled trials has suggested a surgical mask is equally effective as an N95 respirator for prevention of influenza) [106].
- Consider placing high-risk individuals closer to ventilation that provides fresh air
- Regular disinfection of surfaces

Travel Issues

Travel risks include those associated with travel to and from a site, as well as business conducted at those sites [107]. Risks differ considerably by mode of transportation, geographic locations, and current state of the epidemic in any given locale. Businesses need to weigh the value of the travel against the risks associated with that travel. Such valuations should include costs associated with any potential illness and any post-trip quarantine period. Caution is especially advised for all non-essential travel to any locales with outbreaks or community spread in progress [107], which currently includes most urban and many rural US areas (see map to help with other risk considerations:

<https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6>) [108]. International trips are currently similarly affected, with somewhat increased risk estimates due to the length of the transit. Any trips that can be canceled or postponed should be. As risks are reduced, travel to lower-risk locales may increasingly be acceptable (e.g., New Zealand).

Employees returning from, or having traveled through, areas known to have COVID-19 infections

For employees returning from personal or work-related travel, the safest course of action is to self-quarantine and work from home for a minimum of 2 weeks⁴ and avoid direct contact with other workers [45], especially for travel to higher-risk areas compared with travel by personal automobile to an unaffected rural area. If that worker becomes ill, he or she should promptly call a healthcare provider before appearing in a clinic or hospital (i.e., to arrange which entrance to use, to be given an appropriate type of mask before entering the building). The person should also avoid all contact with other people. Wearing a surgical-type mask when ill, such as in transit to a healthcare facility, may help to reduce the spread of the virus from the wearer's sneezes or coughs.

Social Distancing Methods

The following are some social distancing options to consider:

- Work from home when feasible to help improve social distancing.
- Consider rotating workers between home and work settings to reduce workplace population densities while facilitating functions that are best to be performed at work to continue.
- Improve social distancing at work (e.g., increase distances between workers, install temporary barriers, mark 6-foot distances on the floor between co-workers).
- Consider either social spacing in cafeterias, closing cafeterias and offering individual prepackaged meals, and/or having workers eat their own food at their workstations.
- Where there are two options for walking through a workplace, consider one-way walkways.
- Reorganize shifts to spatially- and temporally-spread workers.

⁴ See data above regarding outlier cases of >14 days for incubation. A company must weigh the risks vs. their risk tolerance. Four weeks is a safer course of action.

- Route shifts of workers to enter through one entrance that is a different entrance than that being used to exit the premises.
- Provide protection for those who interact with the general public (e.g., install temporary barriers to prevent respiratory transmission, install barriers to physically require social distancing of 6+ feet).
- Consider discouraging carpooling and mass transit, or encouraging the use of masks if using either of those options.
- Minimize reasons for external individuals and the public to enter a workplace (e.g., curbside deliveries, web-based meetings). If there are multiple options for meetings onsite, attempt to limit which rooms are used and have them cleaned after every use.

Personal Protective Equipment

PPE measures (masks, gloves, and face shields) are lower on the list of controls, but still may help to slow spread of the COVID virus and include the following:

- Have healthy individuals wear a face covering or mask, as there is evidence of COVID-19's SARS-CoV-2 virus spreading by asymptomatic and presymptomatic individuals [109, 110].
- Use face shields, especially where there is potential for human-related splashes or droplet exposures.
- Follow OSHA guidance regarding requirements for fit testing of PPE and to assure proper use, donning, and doffing [111, 112].
- Appropriate PPE for cleaning a workspace contaminated by the virus is thought to normally be a face mask and gloves. If there are concerns about aerosols (e.g., an infected worker was in the room, especially with coughing, sneezing, and/or for an extended time), an option may be to leave the room overnight before cleaning it; otherwise, an N95 mask would ideally be recommended (P100 is not an appropriate mask for these purposes).

Ventilation Issues

Ventilation issues (general and local) have been underutilized as potential COVID controls. Local ventilation can provide a relatively safe zone for workers:

- Use local ventilation to supply clean air to a worker's workspace
- Utilize increased air exchanges in the HVAC system to dilute the general ambient air (including HEPA filters in the HVAC system).
- Where possible, use portable air purification systems for small work areas.

Disinfection Practices and Contact Spread Measures

The following disinfection practices may help to slow spread by contact:

- Train staff on how to disinfect workplaces

- Clean commonly touched worksite surfaces frequently (e.g., hourly or between shifts), including machine controls, door handles, bathroom doors, bathroom fixtures, faucet handles, lunch tabletops, breakrooms, etc.
- Consider propping open bathroom and other doors to reduce handling or touching.
- Avoid shared equipment when possible (e.g., keyboards), and clean common surfaces between shifts or between worker usage.
- Clean surfaces with an EPA-approved virucidal agent and follow manufacturer's instructions for use. Reports include agents containing 62-71% ethanol, 0.5% hydrogen peroxide, 0.1% sodium hypochlorite for at least 1 minute [38], although some agents will require longer contact times. It is important to allow sufficient time for sanitizing agents to work, and directions should be carefully followed. The EPA has a list of products active against human coronavirus, with recommendations for the duration of contact time [113].
- Encourage frequent hand hygiene (hand washing or use of alcohol-based hand disinfectants) with appropriate techniques [114].
- Provide ample hand sanitizer and hand-sanitizer stations.

Policies and Procedures

The following are potential policies and procedures to consider:

- Inform and seek authorization for the plan from the organization's leadership.
- Develop a plan in conjunction with occupational health and safety professionals, government regulations, and public health authorities (including CDC).
- Ensure affected workers have sufficient paid leave to observe a quarantine period or are able to stay home as indicated.
- Continue to monitor sickness absence, but expand sick leave provisions to allow employees to stay at home if ill and to care for sick family members.
- Educate and place posters throughout workplace to remind employees to avoid touching their eyes, nose, and/or mouth with unwashed hands (e.g., CDC poster).
- Teach workers to use tissues to catch a cough or sneeze, then throw that tissue away and wash their hands.
- Avoid scheduled aggregate meetings and encourage physical distancing within group settings, ideally a distance of at least 6 feet. Encourage use of teleconferences and/or other virtual meeting formats.
- Encourage early reporting of any symptoms consistent with COVID-19 to the medical department, designated employer representative, and/or supervisor, following the company's established policies. It is preferable to preclude all symptomatic workers, including those who are mildly symptomatic, from physically entering all workplaces; electronic questionnaires may be useful to facilitate this. Place posters prominently to help remind workers of procedures (e.g., CDC posters).
- Have employees who develop symptoms stay away from the workplace until clinically evaluated and/or until the symptoms are resolved and any quarantining period has expired.

- Consider having employees who could be in the incubation stage work from home for at least 2 weeks after the possible exposure.
- In certain manpower shortage situations, medical centers and critical service workers are being allowed to work while asymptomatic with twice-daily temperature checks, self-surveillance for symptoms, and consistent mask-wearing instead of being quarantined for 14 days. However, this has some residual risks of transmission and may not be compatible with mission-critical operations (e.g., dispatch center; air traffic control tower).
- If there is a confirmed case in your workplace, have the worker identify his or her most common contacts in collaboration with public health officials while attempting to maintain confidentiality. Using business risk tolerance procedures, identify whether any further actions are required other than increased monitoring (see above) and increased cleaning and disinfection of commonly used areas.
- Antibody testing is becoming available, but the sensitivity and specificity vary greatly between kits (see Diagnostic Testing). Their usefulness is limited in areas where the prevalence of disease is around 1 to 3%, and, in this setting and even with 95% specificity, the majority of positive tests will be false positives. With further validation, antibody testing may likely become useful in assessing possible susceptibility to infection versus protective response to prior infection. Currently, however, antibody testing is not able to provide that information and cannot be reliably used for that purpose. In the future, COVID-19 serology can determine infection risk in critical and susceptible populations (under medical direction to ensure proper implementation, interpretation, and management). Examples of these critical populations include employees in health care settings, on oil drilling platforms, commercial maritime, food preparation, cruise lines, airlines, and assembly lines with workforces working closely together.
- Provide proactive assistance to support mental health for the workforce.
- Identify and train workplace coordinators who will be responsible for implementing and monitoring the plan.

Industry-Specific Recommendations

Below are select industry guidelines, which are in addition to the general guidance above. Further guidance is available from the CDC [115].

Restaurants

- Provide social distancing between tables. Be alert to local ventilation issues that may cause downwind exposures beyond 6 feet.
- Barriers between tables allow for seating closer than 6 feet.
- Outdoor seating may allow distancing that is closer than 6 feet.
- Menus should be either disposable or laminated and sanitized after each customer contact.
- Clean and disinfect chairs and tables after each customer use (see Disinfection).

- Assign high-risk employees with multiple co-morbidities or concerns to low-exposure areas, such as working in non-customer-facing areas as much as possible.
- Wear protective masks while in the restaurant and kitchen.
- When possible, designate non-high-risk employees to bus tables.
- Housekeeping in public areas should ideally be performed by lower-risk employees.
- Encourage drive-through and carryout options to promote social distancing.

Retail

- When possible, preferentially assign low-risk employees to cashiering and other customer-facing work.
- Stocking by high-risk individuals should ideally be done when customers are not present.
- Returns that cannot be disinfected should best be handled by low-risk employees.
- Clothing from dressing rooms should ideally be restocked by low-risk employees.
- Housekeeping in public areas should ideally be assigned to lower-risk employees.
- Limit total number of customers within enclosed dwellings or structures at one time to allow for social distancing.
- Encourage customers to use personal respiratory protection and provide PPE to customers where feasible.

Hospitality

- Eliminate handling of luggage and other customer items. Otherwise, use gloves.
- Valet services should be provided by lower-risk employees if possible. Gloves should be used.
- Room keys should be disinfected between employee and customer usage.
- Housekeeping in public areas should ideally be assigned to lower-risk employees.

Personal Services (hair, tattoo, nail salons)

- Use physical barriers where possible.
- Employees should use aprons, gloves, eye, and face protection in addition to protective masks.

Home Repair

- Where clothing may be potentially contaminated from SARS-Cov-2, protective coverings (e.g., Tyvek or disposable smocks) should be worn to protect clothing from surface exposure.

Gyms

- Locker room and gym housekeeping should ideally be performed by low-risk employees.

- Employees should avoid using a public water fountain. Employees should be provided with bottled water.
- Towel service and other laundry should ideally be handled by low-risk employees.
- Housekeeping in public areas should be assigned to lower-risk employees.
- Saunas and steam rooms should be limited in use and ideally cleaned only by low-risk employees.

Construction

- Assure cleanliness and frequent cleaning of portable restrooms.
- Face coverings should be used when performing maneuvers that require close contact with co-workers or within confined spaces.
- Avoid sharing tools or disinfect between users.
- Reduce unnecessary shared rides; disinfect heavy equipment cabs between operators.
- Designate a COVID-19 coordinator for large jobsites, with the responsibility to coordinate prevention efforts for all contractors, subcontractors, and crafts on site.
- Provide handwashing or issue hand sanitizer to be used for donning/doffing respiratory PPE.

Manufacturing

- Install physical barriers when physical distancing is not possible.
- When possible, consider wearing gloves while assembling parts.

Food Production Facilities

These have been hot spots of virus infection due to structural and socioeconomic challenges in meat and poultry processing facilities. Difficulties to overcome include workers speaking many different primary languages, an incentive to work while ill as a result of limited medical leave and disability policies, and attendance bonuses that could encourage working while sick. At home, many workers live in crowded, multigenerational settings and may share transportation to and from work, increasing risk for transmission of disease [116]. Recommended potential changes in facility practice include the following:

- Adjust start and stop times of breaks and shifts, add outdoor breakrooms. Avoid en masse movements of workers.
- Install physical barriers between workers.
- Screen all workers and visitors, isolate workers who become ill at work.
- Require universal face coverings and provide training on donning and doffing PPE.
- Assign additional staff to sanitize high-touch areas.
- Add hand-sanitizer dispensers and handwashing stations.
- Develop culturally informed messaging.
- Include messaging about behaviors to limit spread of virus at home.
- Add additional vehicles to shuttle routes.
- Provide additional medical leave and disability benefits; remove attendance bonuses.

More details regarding business concerns are available from the CDC [115].

Disability and Return-to-Work Considerations

Disability will be better defined with studies over time. Extrapolation using recovery from other conditions, such as pneumonia and ARDS, may provide some preliminary estimates.

Return-to-work evaluations should consider the worker's current status as compared with the physical requirements of the job, mental demands of the job, safety-critical work functions, current treatments, use of impairing medication, residual effects of the virus, requirements for personal protective equipment, potential risk to others if returned too early, and protection of other employees if additional risk is identified. Many of these complex cases will need to be addressed by occupational and environmental medicine physicians.

Currently, for patients without hospitalization, there are no quality data on returning to work, short-term disability, or long-term disability. Regarding short-term disability and return to work, recovery from post-infection fatigue is estimated to take approximately 2–3 weeks and appears to correlate with clinical duration and severity. For patients with mild to moderate pneumonia treated with oxygen supplementation, recovery is estimated to require 4–8 weeks after hospitalization or clinical recovery. Severe pneumonia and ARDS have worse prognoses.

The overall trajectory of recovery from COVID-19 remains unclear. Prior experience with diseases that have similar manifestations, such as ARDS, suggest there is significant risk of delayed return to work and long-term disability, as approximately 50% of individuals surviving ARDS have not returned to work after 1 year [117, 118]. ARDS is also associated with approximately 20% reductions in spirometry and lung volume, which resolve at about 6 months based on prior H7N9 influenza data [119]. Lung diffusion abnormalities can take up to 5 years to resolve in ARDS cases [119, 120]. Cognitive impairments and psychiatric abnormalities related to ARDS may be projected to occur in 30–55% and 40–60% of patients, respectively; the duration of these impairments is unclear, but other causes of ARDS raise considerable concerns about long-term disability [118-124]. Generalized skeletal muscle deconditioning is expected in patients who are intubated for any extended duration; these patients require exercise programs and possibly rehabilitation, which often results in residual incapacity [118, 121, 125, 126]. Cardiac problems are common with COVID-19, with cardiomyopathy, arrhythmia, and direct cardiac muscle injury affecting approximately 30%, 20%, and 10% of patients, respectively [127].

In general, for patients who are intubated and survive, recovery of the cardiorespiratory systems and endurance are estimated to take at least several months. It currently appears likely that some hospitalized and severely affected individuals will incur long-term disability with permanent impairments of the cardiac, respiratory, neurological, and/or musculoskeletal systems. [118-122]. The potential for a minority of patients to be permanently totally impaired cannot be excluded [122].

Cardiac, respiratory, and neurological disability measures include:

- Metabolic stress ECHO
- Full pulmonary function testing with impedance booth or washout testing
- Functional capacity testing
- Neuropsychological testing

Ratings for impairment can be found in the AMA Guides 5th Edition [128] and 6th Edition [129].

Diagnostic Approach

Laboratory Tests

COVID-19 has a widely varying clinical presentation. Depending on the extent of infection and the organ systems affected, any or all of the following may be found [76, 77]:

- Lymphopenia (a fairly unique and characteristic finding)
- Elevated liver enzymes
- Elevated lactate dehydrogenase (LDH)
- Elevated direct bilirubin
- Elevated pancreatic enzymes
- Elevated prothrombin time (PT)
- Elevated troponin
- Elevated creatine phosphokinase (CPK)
- Elevated inflammatory markers (e.g., C-reactive protein [CRP], ferritin)
- Elevated D-dimer
- Elevated fibrinogen
- Elevated creatinine
- Elevated blood urea nitrogen
- Hypoxemia

A risk prediction model has been developed to predict the development of severe disease [105]. The 10 variables included in the model are: 1) chest radiographic abnormality (odds ratio [OR]: 3.39), age (OR: 1.03), hemoptysis (OR: 4.53), dyspnea (OR: 1.88), unconsciousness (OR: 4.71), number of comorbidities (OR: 1.60), cancer history (OR: 4.07), neutrophil:lymphocyte ratio (OR: 1.06), lactate dehydrogenase (OR: 1.002), and direct bilirubin (OR: 1.15). A free online risk calculator is available [130].

Diagnostic Testing

There are two main types of diagnostic testing that are used for COVID-19: (1) polymerase chain reaction (PCR)-based test, typically using swabs [131] and (2) antibody testing of blood serum. Only the PCR testing is considered to be diagnostic of the infection because it detects the actual virus or viral particles. Antibody testing detects prior infection.

Work is progressing on the development of a saliva test for SARS-CoV-2 detection, which is appealing for ease of collection and is not limited by the shortages of swabs. One study detected higher SARS-CoV-2 titers in saliva compared to nasopharyngeal swabs, with less longitudinal variability [132]. If validated, saliva testing could provide near universal sampling coverage for both symptomatic and asymptomatic patients [133]. Currently, saliva testing is considered to be investigational.

PCR Testing

PCR samples and testing techniques amplify viral particles to identify relatively small amounts of virus, with the nucleocapsid antigen test being the most sensitive for detecting early infection [134]. Because they also amplify viral fragments, they can show recent infection among those who are still clearing the viral particles; thus, they may not reflect active viral shedding. Thus, these tests can indicate the RNA debris of coronavirus and may reflect non-viable virus remnants.

Importantly, the risks of false-negative and false-positive test results change as a pandemic progresses. For example, as an epidemic progresses and disease becomes more common, individuals who present with symptoms but test negative are increasingly most likely to represent false negatives. Thus, once an epidemic disease becomes highly pervasive and there is not a common competing cause of similar symptoms, diagnostic testing is often unnecessary for typical cases because it does not materially alter the post-test probability. At an epidemic's peak, the testing of unusual cases is ideally performed with highly accurate tests, as such cases may represent unusual presentations that should be distinguished from non-COVID-19 causes. As the SARS-CoV-2 virus causes such a wide spectrum of disease, from asymptomatic infection to life-threatening infection, along with the possibility of other co-circulating respiratory viruses at various times (e.g., influenza), this makes the issue of diagnostics for SARS-CoV-2 one of paramount importance for the foreseeable future, particularly in fall-winter 2020-21 with the anticipation of another epidemic wave(s) at that time.

Most of the limited evidence suggests that nasopharyngeal and oropharyngeal samples are comparable for the first week, but then the nasopharyngeal sample is more sensitive [135, 136]:

- From days 0–7, oropharyngeal and nasopharyngeal sensitivities are 61/60% and 72/73% for mild/severe disease, respectively.
- On days 8–14, oropharyngeal and nasopharyngeal sensitivities are approximately 30/50% and 54/72% for mild/severe disease, respectively [137].

PCR testing is recommended for the diagnosis of COVID-19. Testing should be performed either at the time of Covid-19-like symptom onset or ideally within several days of the onset of symptoms consistent with a COVID-19 infection.

PCR testing is also recommended for inpatient and outpatient preoperative assessments.

Preoperative tests must be ordered sufficiently ahead of surgery such that the results are received in time to address/respond to the results (generally 72–96 hours before surgery). Preoperative tests may be needed both for those without any history of symptoms, as well as for those with prior infections to assure the person is no longer infectious.

Antibody Testing

Antibody testing detects the body’s humeral response to the virus [138-140]. Most antibody tests detect IgG, although some attempt to also detect IgM or IgA. The median IgM seroconversion is 11–13 days (or 5–7 days after symptoms onset), while the median seroconversion for IgG is 14 days (or 8 days after symptoms onset), but then IgG persists for a far longer period of time [141]. Antibody tests are in early stages of deployment and reported reliability varies widely [138-140]. Because there is no reference standard and widespread testing of large populations have not been reported, the determination of test accuracy, sensitivity, and specificity are still somewhat problematic.

It is aspirational that immune status testing (IgG, IgM) will eventually be the most important test for population-based risk assessments, such as herd immunity. This requires considerable research, including determinations of sensitivity, specificity, reliability, timing, persistence of the immunoglobulins, and whether the immunoglobulin status identified by testing will be associated with true immunity. Theoretically, this testing may also help designate workers who may more safely interact with the public. If proven, antibody testing may be used to assure a workplace that a previously infected worker is safe to return to work (i.e., that they are not actively infected and unlikely to be shedding virus). However, the currently available antibody studies have yet to be sufficiently validated on a widespread basis. Inaccuracies are increasingly reported to be problematic [142, 143]. Once these problems are addressed, it is anticipated that antibody testing may become widespread if not universal in many workplaces and other populations of concern (e.g., nursing homes, mission-critical workers, irreplaceable workers, dispatch centers, C-suite executives).

Immune status determination, if proven, may be of major importance for workplace populations in many, if not all, sectors. Workforces with the greatest needs for immune status testing include those with isolated populations, risk of transmission to vulnerable populations, high worker densities, and/or distance from and lack of access to appropriate healthcare (e.g., oil platform drilling, commercial maritime, cruise lines, overseas workforces, airlines, rail, trucking, mining).

Antibody testing is selectively recommended for assessing immune status regarding the potential for COVID-19. These tests should be interpreted by someone thoroughly knowledgeable about numerous factors, including: the specific chosen test, that specific test’s reported testing performance (e.g., sensitivity, specificity), prevalence of COVID-19 in the specific community, principles of testing, Bayes’ theorem, and assessment of pre-test probability and post-test odds. In general, only mission-critical workers and special populations

should be tested with antibody testing at this point. As the experience with these tests improves, the populations assessed are likely to markedly expand.

Imaging

Although x-rays are usually abnormal for individuals with pulmonary involvement, radiography in general should not be used as a standalone screening tool for COVID-19. X-ray abnormalities peak at 10–12 days after onset of symptoms [76, 144]. One series reported that chest radiographs most commonly show either consolidation (47%) or ground glass abnormalities (33%). The same series noted that 41% were peripheral, 50% were lower distribution, and 50% were bilateral [144]. **X-rays are recommended for the diagnostic evaluation of COVID-19.**

Computerized tomograms are commonly performed [145, 146] and show patchy infiltrates and ground glass opacities [147-151]. One series reported 72% of cases with ground glass appearance, 12% with consolidation, 12% with crazy paving patterns, 37% with interlobular thickening, 56% with adjacent pleural thickening, and 61% with linear opacities [77]. **CT scans are recommended for the diagnostic evaluation of COVID-19.**

Treatment Recommendations

Treatment is currently guided by preliminary studies; many additional studies are underway. No treatment is indicated for asymptomatic cases or individuals with a URI. The three main classes of interventions for more serious infections are anti-viral treatments, cytokine storm-reducing agents, and ventilatory support (both non-invasive and invasive). Only glucocorticosteroids have thus far been reported to reduce mortality [244, 245]. Only remdesivir has been proven to be modestly effective at shortening intensive care unit (ICU) stays in a large trial [1]. The FDA has provided support for the use of convalescent plasma antibodies from survivors of COVID-19 through either randomized controlled trials (RCTs) or expanded use, although it was noted that antibodies are an unproven treatment for COVID-19 [177]. No other medications are currently approved for the treatment of COVID-19, although other anti-viral drugs are also under investigation (e.g., lopinavir-ritonavir). Although a trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19 did not improve outcomes [178], another trial of these agents combined with ribavirin and interferon beta-1b suggested efficacy [179]. The FDA has provided unprecedented flexibility to accelerate the development of new drugs and testing [180].

If individuals develop more severe symptoms or have complications (e.g., ARDS or respiratory failure), they are primarily treated with non-invasive ventilatory support measures, glucocorticosteroids, anti-cytokine storm agents, mechanical ventilation (including prone ventilation), other respiratory support measures, and DVT prophylaxis [181]. Evaluations should include exclusion of other causes (e.g., influenza). Glucocorticosteroids have reportedly been effective at reducing fatalities in hospitalized patients in a large UK trial using dexamethasone

to treat severely ill patients who were using supplemental oxygen and/or a ventilator [182, 244, 245]. The efficacy of glucocorticoids appears to be related to the stage of the COVID-19 infection. Glucocorticosteroids used early in the time course of infection do not appear to improve outcomes, and in theory could potentially allow viral replication to increase. In contrast, glucocorticosteroids appear to be effective in later, more severe stages of the infection, when the host inflammatory response is at its peak and may potentiate organ failure. In the United States, a trial evaluating the effectiveness of methylprednisolone (1 mg/kg/day IV for 7 days) for hospitalized patients is currently registered with ClinicalTrials.gov.

Although multiple agents addressing the cytokine storm are under investigation, most of the publications are centered around interleukin-6 (IL-6) [183]. Suppressing the cytokine storm to improve outcomes in an acute infection is not a new concept [246]. Although many cytokines are involved in the cytokine release syndrome (IL-2, IL-7, G-CSF, IFN- γ inducible protein 10, MIP 1- α , TNF- α), IL-6 has been shown to play a central role in orchestrating the inflammatory response in several coronavirus diseases, including SARS-CoV, MERS-CoV, and most recently SARS-CoV-2. IL-6 receptor blocker tocilizumab (Actemra) has been reported to reduce mortality in SARS-CoV-2 infection [250], and other trials are ongoing.

A recent short report described the use of pooled human high-dose polyclonal immunoglobulin G in 3 patients with severe COVID-19 pneumonia. Intravenous immunoglobulin was administered at 0.3–0.5 g per kg weight per day for 5 days, a dose based on previous use in immune modulation therapy for neuromuscular disorders and autoimmune thrombocytopenic purpura. There were no adverse events, and all patients clinically improved shortly after starting treatment. Their temperature returned to normal in 1–2 days and breathing difficulties alleviated in 3–5 days [184]. Thus, trials suggest that in selected patients with severe, COVID-19 pneumonia, tempering an excessive immune response to the virus is associated with clinical improvement.

Anti-viral medications may have minimal to no role in advanced pneumonia or ARDS [175], and one trial's subgroup analysis suggested that anti-viral treatment is needed within the first 7 days after symptom onset [179]. However, antiviral medications are typically prescribed in later phases due to the theoretical potential that there may be some ongoing viral replication. To date, there appears to be no registered trials (of >2,000) that assess the efficacy of an anti-viral medication within the first 1–2 days of the onset of symptoms [247].

A potential hierarchical protocol for antiviral treatment being discussed for COVID-19 is as follows:

1. Remdesivir
2. Combination therapy (interferon beta-1b, lopinavir-ritonavir and ribavirin)

A potential hierarchical treatment protocol for pneumonia/ARDS (in addition to possible anti-viral treatment) includes the following:

1. Oxygen supplementation
2. Glucocorticosteroid
3. Prone positioning (due to shunting) and/or non-invasive ventilation (NIV)
4. Interleukin-6 inhibition
5. Mechanical ventilation, prone
6. Extracorporeal membrane oxygenation (ECMO)

Mechanical ventilation has been associated with a survival rate of approximately 30% (and the short- to intermediate-term quality of life of those survivors is in considerable doubt). Thus, the prevention of severe outcomes should be the primary treatment emphasis [185, 186], and there is an increasing emphasis on noninvasive ventilatory measures.

There is no vaccine for COVID-19 [99], but development has begun. There are efforts underway using at least four types of vaccine classes or approaches against this infection (virus, viral vector, nucleic acid, and protein-based) [187]. Vaccine development is estimated to require 12–18+ months if successful [188].

Mental health issues are increasingly recognized as problematic, both among those infected as well as those otherwise impacted by the epidemic but not infected. Several references are available [189-195].

Hydroxychloroquine for Treatment of COVID-19

Not Recommended.

Hydroxychloroquine is provisionally not recommended for the supervised treatment of selected patients with COVID-19 (pending publication of UK trial data [248]).

Strength of Evidence – Not Recommended, Insufficient Evidence (I) ⁵

Level of Confidence – Low

Rationale:

A large, but as-yet unpublished, placebo-controlled UK trial (n=1542 HCQ vs. n=3132 usual care) has reported no reductions in fatalities among patients hospitalized with COVID-19 (25.7% vs. 23.5%, p=0.10) [248].

One moderate-quality RCT showed 31.0% fewer fever days, 35.5% fewer cough days, and 47.1% improved pneumonia on CT scan compared with placebo [175]; they also showed 0% vs. 12.9% progressed to severe disease. A second moderate-quality study found minimally faster improvements in symptoms, lymphopenia, and C-reactive protein [201]; however, the average administration began at 16–17 days in the treatment course, which was likely after viral replication had largely ceased and thus the primary outcome of viral clearance rate did not exceed that of standard care [202].

⁵ Provisional recommendation pending publication of UK trial data [176]

A large-scale pre/post intervention study showed that adjunctive use of zinc to hydroxychloroquine was associated with a 44–49% decreased need for ventilation, admission to the ICU, mortality or transfer to hospice, and increased the frequency of being discharged home [196].

One RCT without placebo control compared very high doses of HCQ (12 g over 10 days) to lower doses and was terminated early for arrhythmias [199]. The dose used was approximately 4 times the typical dose used in other studies.

Early outpatient treatment has been reported to result in low fatality rates in large case series and comparative trials that typically have used adjunctive azithromycin. Comparative trials also suggest earlier viral clearance with adjunctive treatment with azithromycin [157, 203][204, 205].

There are many in vitro studies suggesting antiviral activity [155, 156, 162, 166, 168, 176, 206-208]. However, although in vitro studies generally show efficacy for a medication to be effective in humans, that is not necessarily a definitive measure of efficacy in humans; such studies have sometimes failed to support treatment in human trials for other diseases [209, 210].

In contrast with the bulk of the RCTs, comparative trials, and pre/post interventional studies, there are multiple large-scale, non-randomized case series that have uniformly suggested a lack of efficacy of HCQ [198, 211-213]. In all cases, the HCQ-treated patients are shown to have been more ill with many measures of multiple organ systems than those not treated with HCQ. Although these studies have typically attempted to adjust for various patient severity measure(s), whether such adjustments are adequate and can completely adjust for the severity is unknown. Thus, the RCT evidence is the highest level of evidence to address efficacy [214], and large-scale RCT results are expected later in 2020.

The largest trial purportedly has found a lack of efficacy of HCQ among hospitalized patients [248]. Thus, based on reports of this large trial, this is a provisional recommendation against HCQ in hospitalized patients. To date, there are no quality data regarding potential (in)efficacy for those within the first 1-2 days of symptoms to attempt to abort the trajectory towards hospitalization.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to April 2020 using the following terms: hydroxychloroquine; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized

controlled trials as topics. We found and reviewed 2 articles in PubMed, 64 in Scopus, 4 in CINAHL, 4 in Cochrane Library, 1,914 in Google Scholar, and 5 from other sources[†]. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 10 from Google Scholar, and 5 from other sources. Of the 15 articles considered for inclusion, 3 randomized trials, 2 non-randomized trials, 5 case series, 2 retrospective studies and 4 systematic reviews met the inclusion criteria. There were no exclusion criteria.

[†]The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens, then the remaining articles are not reviewed due to a lack of relevancy.

Chloroquine for Treatment of COVID-19

Not Recommended.

Chloroquine is provisionally not recommended for the supervised treatment of selected patients with COVID-19, primarily based on the evidence for hydroxychloroquine (pending publication of UK trial data [248]).

Strength of Evidence – Not Recommended, Insufficient Evidence (I) ⁶

Level of Confidence – Low

Rationale:

A large, but as-yet unpublished, placebo-controlled UK trial of HCQ (n=1542 HCQ vs. n=3132 usual care) has reported no reductions in fatalities among patients hospitalized with COVID (25.7% vs. 23.5%, p=0.10) [248].

One small, low-quality, likely underpowered comparative RCT of chloroquine with lopinavir/ritonavir has showed trends for earlier improvement of CT scans and earlier hospital discharge with chloroquine [215]. One moderate-quality RCT of hydroxychloroquine showed 31.0% fewer fever days, 35.5% fewer cough days, and 47.1% improved pneumonia on CT scan compared with placebo [175]; they also showed 0% vs. 12.9% progressed to severe disease. There are unpublished reports suggesting efficacy has been demonstrated in trials in China, but these have neither been published in English nor apparently peer reviewed [168].

A large-scale pre/post intervention study showed that adjunctive use of zinc with hydroxychloroquine was associated with 44–49% lower need for ventilation, admission to the ICU, morality or transfer to hospice and increased the frequency of being discharged home [196].

⁶ Provisional recommendation pending publication of UK trial data [176]

One RCT without placebo control compared very high doses of HCQ (12 g over 10 days) to lower doses and was terminated early for arrhythmias [199]. The dose used was approximately 4 times the typical dose used in other studies.

Early outpatient treatment with HCQ has been reported to result in low fatality rates in a large case series and comparative trials that typically have used adjunctive azithromycin. Comparative trials also suggest earlier viral clearance using adjunctive treatment with azithromycin [204, 205].

There are many in vitro studies suggesting antiviral activity, which is similar to hydroxychloroquine [156], thus producing comparable rationale [155, 156, 161, 162, 168, 207, 208]. Still, although in vitro studies generally show efficacy for a medication to be effective in humans, that is not necessarily a definitive measure of efficacy in humans; such studies have sometimes failed to support treatment in human trials for other diseases [209, 210].

In contrast with the bulk of RCTs, comparative trials, and pre/post interventional studies of HCQ, there are multiple large-scale, non-randomized case series that have uniformly suggested a lack of efficacy of HCQ [198, 211-213]. (One of these studies has been retracted [216].) In all cases, the HCQ-treated patients are shown to have been more ill with many measures of multiple organ systems than those not treated with HCQ. While these studies have typically attempted to adjust for various patient severity measure(s), whether such adjustments are adequate and can completely adjust for the severity is unknown. Thus, the RCT evidence is the highest level of evidence to address efficacy [214], and large-scale RCT results are expected later in 2020.

The largest trial of HCQ purportedly has found a lack of efficacy of HCQ among hospitalized patients [248]. Thus, based on reports of this large trial, this is a provisional recommendation against use of CQ in hospitalized patients. To date, there are no quality data regarding potential (in)efficacy of CQ for those within the first 1-2 days of symptoms to attempt to abort the trajectory towards hospitalization.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to April 2020 using the following terms: Chloroquine; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 2 articles in PubMed, 387 in Scopus, 2 in CINAHL, 7 in Cochrane Library, 2,037 in Google Scholar, and 2 from other sources[†]. We considered for inclusion 1 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from

Cochrane Library, 1 from Google Scholar, and 2 from other sources. Of the 5 articles considered for inclusion, 2 randomized trials, 1 retrospective analysis and 2 systematic reviews met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens, then the remaining articles are not reviewed due to a lack of relevancy.

Hydroxychloroquine or Chloroquine for Widespread Prophylaxis Against COVID-19

Not Recommended.

Hydroxychloroquine and chloroquine are not recommended for use for widespread prophylaxis against COVID-19.

Strength of Evidence – Not Recommended, Insufficient Evidence (I)

Level of Confidence – Low

Rationale:

One high-quality trial of hydroxychloroquine (without zinc) for postexposure prophylaxis suggested no statistically significant benefit (11.8% vs. 14.3%, 17.5% reduction, $p=0.35$), although there was a 17% reduction of risk [4] and thus underpowering is possible.

There is rationale that prophylactic use may have short-term efficacy based on suggestive evidence of prophylactic effects in vitro studies [156]. The weaknesses of prophylaxis include that: 1) subsequent waves of this epidemic are possible if not probable; 2) the number of patients with large numbers of virions being exposed to the chloroquines markedly increases the risks of resistance, which may mean subsequent epidemic waves will be more difficult to treat (assuming efficacy is confirmed in additional studies); and 3) it is unknown if a subsequent epidemic wave may be less or more virulent. In some instances, prophylactic use may make more sense, such as in a nursing home where the virus is circulating or in selected workers with particularly high risks, especially as adverse effects are minimal and/or not serious. However, for most situations, the potential development of immunity is likely preferable, as rescue therapy with one of the chloroquines for more severe cases currently appears possible, if needed.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to April 2020 using the following terms: hydroxychloroquine; prophylaxis; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization,

randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 0 articles in PubMed, 23 in Scopus, 0 in CINAHL, 1 in Cochrane Library, 1,237 in Google Scholar, and 1 from other sources[†]. We considered for inclusion 0 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 2 articles considered for inclusion, 1 randomized trial and 1 systematic review met the inclusion criteria. There were no exclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to April 2020 using the following terms: chloroquine; prophylaxis; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 0 articles in PubMed, 66 in Scopus, 0 in CINAHL, 2 in Cochrane Library, 1,310 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 0 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 0 randomized trials and 1 systematic review met the inclusion criteria. There were no exclusion criteria.

[†]The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Evidence for the Use of Hydroxychloroquine and Chloroquine

Boulware 2020 (score=9.0) [4]

Category:	Hydroxychloroquine Prophylaxis
Study Type:	RCT
Conflict of Interest:	Sponsored by several entities including David Baszucki and Jan Ellison Baszucki, the Alliance of Minnesota Chinese Organizations, the Minnesota Chinese Chamber of Commerce, and the University of Minnesota. COI: One or more of the authors have received or will receive benefits for personal or professional use.
Sample Size:	N = 821 asymptomatic participants with household or occupational exposure to an individual with positive COVID-19 at a distance of less than 6 feet for over 10 minutes while not wearing PPE

Age/Sex:	Mean age not reported; median age: 40 years; 397 males, 424 females
Comparison:	Hydroxychloroquine (800g once, then 600mg in 6-8 hours, then 600mg QDx 4 days) (n=414) vs. placebo (n=407)
Follow-up:	Follow-up at 14 days
Results:	Incidence of new illness compatible with COVID-19 was not significantly different between hydroxychloroquine and placebo groups (11.8% vs. 14.3%, 95% CI [-7.0, 2.2], p=0.35). Side effects of nausea and diarrhea were higher in the HCQ group (40.1% vs. 16.8%)
Conclusion:	“After high-risk or moderate-risk exposure to Covid-19, hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure.”
Comments:	Largely healthy, younger population; largely healthcare workers (66%). There was one high-quality trial of hydroxychloroquine (without zinc) for postexposure prophylaxis that suggested no statistically significant benefit (11.8% vs. 14.3%, 17.5% reduction, p=0.35), although there was a 17% reduction of risk and thus underpowering is possible. The addition of zinc may be important for efficacy, yet it was not included. There was no antibody testing; thus, the number of total infections is unclear.

Tang 2020 (score=7.0) [201, 202]

Category:	Hydroxychloroquine
Study Type:	RCT
Conflict of Interest:	Sponsored by the Emergent Projects of National Science and Technology, National Science Foundation of China, National Key Research and Development Program of China, Shanghai Municipal Key Clinical Specialty, National Innovative Research Team of High-level Local Universities, National Major Scientific and Technological Special Project for Significant New Drugs Development, Key Projects in the National Science and Technology Pillar Program. No COI.
Sample Size:	N = 150 patients with confirmed SARS-CoV-2 ongoing infection
Age/Sex:	Mean age: 46.1 years; 82 males, 68 females
Comparison:	HCQ: received 1200 mg hydroxychloroquine for 3 days then 800 mg per day for 2–3 weeks plus standard of care (n=75) vs. Standard Care: received standard of care only from national clinical practice guidelines for COVID-19 in China (n=75).
Follow-up:	Follow-up at days 7, 14, 21 and 28
Results:	Negative conversion rate of SARS-CoV-2 was 85.4% for the HCQ group compared to 81.3% in the standard care group (HR=0.846, 95% CI 0.58-1.234, p=0.341).
Conclusion:	“The administration of HCQ did not result in a higher negative conversion rate but more alleviation of clinical symptoms than (standard care) alone in patients hospitalized with COVID-19 without receiving antiviral treatment, possibly through anti-inflammatory effects.”
Comments:	Open-label, HCQ given 16–17 days after onset, likely after most or all of the viral replication stage already completed. Most patients given multiple anti-viral agents. Data suggest minimally faster improvement in symptoms, lymphopenia, and CRP, but no acceleration of viral clearance with HCQ above standard care which had rapid clearance.

Borba 2020 (score=7.5) [199]

Category:	Chloroquine
Study Type:	RCT
Conflict of Interest:	Sponsored by the Government of the Amazonas State, Farmanguinhos (Fiocruz), Superintendência da Zona Franca de Manaus, Coordination for the Improvement of Higher Education Personnel, Fundação de Amparo à Pesquisa do Estado do Amazonas, and the Brazilian Senate. Author Pacheco received grants from the National Council for Scientific and Technological Development and the Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro during the study. Author Naveca received grants from the National Council for Scientific and Technological Development and the Coordination for the Improvement of Higher Education Personnel during the study.
Sample Size:	N = 81 adult patients who were hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Age/Sex:	Mean age: 51.1 years; 60 males, 21 females
Comparison:	High-dose chloroquine diphosphate (CQ) vs. low-dose CQ. High-dose CQ: Patients received 600 mg CQ twice daily for 10 days (n = 41). Low-dose CQ: Patients received 450 mg CQ twice daily on day 1 and then once daily for 4 days (n = 40)
Follow-up:	Follow-up daily for 13 days
Results:	Overall lethality rate = 27.2%. Lethality up until day 13 was 39.0% in the high-dosage group and 15.0% in the low-dosage group. Lethality was associated with the high-dosage group (OR = 3.6, 95% CI [1.2, 10.6]). After controlling for age, the association was no longer significant (OR = 2.8 [0.9, 8.5]). Patients receiving high-dosage CQ presented more instances of QTc interval greater than 500 milliseconds when compared to the low-dosage group (18.9 % vs. 11.1%)
Conclusion:	“The preliminary findings of this study suggest that the higher CQ dosage should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir.”
Comments:	The trial was stopped due to cardiovascular risks in very high dose group. Severe ARDS patients had RR>24 and/or HR>125 and/or O ₂ <90% and/or shock. Differences at baseline. A very high CQ dose was used both daily (1.2g/d) and cumulatively (12 g) while combined with azithromycin. Data suggest excessive doses of CQ combined with azithromycin are associated with irregular heart rhythms.

Chen Z 2020 (score=5.5) [160]

Category:	Hydroxychloroquine
Study Type:	RCT
Conflict of Interest:	Sponsored by the Epidemiological Study of COVID-19 Pneumonia to Science and Technology Department of Hubei Province. No COI.
Sample Size:	N = 62 patients with COVID-19 in Renmin Hospital of Wuhan University, RT-PCR positive for SARS-CoV-2, CT showing pneumonia, and SaO ₂ /SPO ₂ ratio > 93% or PaO ₂ /FIO ₂ ratio > 300 mmHg
Age/Sex:	Mean age: 44.7 years; 29 males, 33 females
Comparison:	All participants received standard treatment of oxygen therapy, antiviral agents, antibacterial agents, and immunoglobins with or without

Follow-up:	corticosteroids. Treatment group received an additional 5-day hydroxychloroquine (HCQ) (400 mg/day) supply (n=31) vs. the control group, who did not receive an additional 5-day HCQ supply (n=31) Follow-up at 5 days after enrollment
Results:	Pneumonia improved in 67.7% of patients (29% moderately, 38.7% significantly improved). A larger proportion of improved pneumonia patients occurred in the HCQ group (80.6%) compared with the control group (54.8%). The HCQ group's mean body temperature recovery time was significantly shorter compared to controls (2.2 vs. 3.2 days, respectively, p<0.05). Mean cough remission time was significantly reduced in the HCQ group compared to controls (p<0.05). In the control group, 4 patients progressed to severe illness, whereas 0 did in the treatment group. 2 participants developed adverse effects from HCQ (one had a rash, the other had a headache).
Conclusion:	"Despite our small number of cases, the potential of HCQ in the treatment of COVID-19 has been partially confirmed. Considering that there is no better option at present, it is a promising practice to apply HCQ to COVID-19 under reasonable management. However, large-scale clinical and basic research is still needed to clarify its specific mechanism and to continuously optimize the treatment plan."
Comments:	Included hospitalized patients only. 100% follow-up and no deaths. Modest baseline differences in fever and days of cough may weakly favor HCQ. CT scans included all four objective measures of improvements. Data suggest HCQ hastened clinical recovery (cough, fever) and reduced pneumonia. More exacerbations were found on CT in the placebo group (29% vs. 6.5%) and more significant improvements were found on CT with HCQ (61% vs. 16%).

[Huang 2020](#) (score=3.5) [215]

Category:	Chloroquine
Study Type:	RCT
Comments:	Very small sample sizes and sparse methods reported. Data suggest trends towards earlier improvements on CT and earlier hospital discharge in the CQ group.

[Gautret 2020](#) (score=NA) [157]

Category:	Hydroxychloroquine
Study Type:	Non-randomized clinical trial
Conflict of Interest:	Sponsored by the French Government through the Investments for the Future program by the National Agency for Research. No COI.
Sample Size:	N = 42 patients with confirmed COVID-19 diagnosis
Age/Sex:	Mean age: 45.1 years; 15 males, 27 females
Comparison:	Participants were non-randomized. Cases were those who accepted 600mg (200 mg three times per day) of hydroxychloroquine daily for 10 days. Azithromycin was added depending on clinical presentation (n=26) vs. controls who refused the hydroxychloroquine treatment (n=16)
Follow-up:	Follow-up at 14 days
Results:	At day 6 post-inclusion, 70% of the hydroxychloroquine group and 12.5% of the control group were virologically cured (p=0.001). Of the cases, 100% treated with hydroxychloroquine and azithromycin were virologically

cured compared with 57.1% of those treated with hydroxychloroquine alone ($p < 0.001$) at day 6 post-inclusion.

Conclusion: “Despite its small sample size our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.”

Comments: Non-randomized comparative trial. Small sample size. Most treated early in course. Data show that hydroxychloroquine (HCQ) was superior to standard treatment for the viral load clearance. HCQ cleared nasopharyngeal carriage of SARS-CoV-2 in most COVID-19 patients in 3-6 days. A significant difference was observed between the HCQ patients and controls on day 3. Azithromycin as adjunct to HCQ was suggested to be synergistic by day 3.

Lover 2020 (score=NA) [203]

Category: Hydroxychloroquine

Study Type: Secondary analysis of Gautret 2020

Conflict of Interest: Sponsored by the French Government through the Investments for the Future program by the National Agency for Research. No COI.

Sample Size: N = 42 patients with confirmed COVID-19 diagnosis

Age/Sex: Mean age: 45.1 years; 15 males, 27 females

Comparison: Participants were non-randomized. Cases were those who accepted 600mg (200 mg three times per day) of hydroxychloroquine daily for 10 days. Azithromycin was added depending on clinical presentation (n=26) vs. controls who refused the hydroxychloroquine treatment (n=16)

Follow-up: Follow-up at 14 days

Results: Binary regressions used to calculate relative risk for clearance of viremia. HCQ-treated patients vs control showed significant risk ratio of 3.84 (95 % CI 1.02 - 14.42, $p = 0.047$). Analysis of HCQ and HCQ+AZ outcome not possible due to quasi-separation

Conclusion: “Results, especially in consideration of the loss to followup of six patients, do not provide sufficient evidence to support HCQ monotherapy for the treatment of COVID-19.”

Comments: Secondary analysis of Gautret 2020 study. Authors concluded against HCQ for monotherapy for clearance of viremia.

Chen J 2020 (score=NA) [175]

Category: Hydroxychloroquine

Study Type: RCT

Conflict of Interest: N/A

Comments: Only the abstract was available in English. Multiple co-interventions. Abstract suggests that late administration of hydroxychloroquine made no difference in the already fast rates of viral clearance.

Raoult 2020 (score=NA) [204, 205]

Category: Hydroxychloroquine

Study Type: Case Series

Conflict of Interest: No mention of COI or sponsorship.

Sample Size: N = 1,061 patients with PCR-positive COVID-19 infection, treated at IHU Méditerranée Infection

Age/Sex: Mean age: 43.6 years; 492 males; 569 females

Comparison:	Given a combination of hydroxychloroquine (HCQ) and azithromycin (AZ) for at least 3 days; no dosage amount was specified
Follow-up:	Follow-up for at least 9 days
Results:	Good clinical outcomes and virological cure obtained by 973 patients (91.7%) within 10 days. 47 patients had prolonged viral carriage after treatment (day 3) but viral culture negative at day 10. Poor outcome observed for 46 patients (4.3%), with 5 patients dying (0.47%). Poor clinical outcomes were associated with old age (OR=1.11), initial higher severity (OR = 10.05), and low HCQ serum concentrations. Mortality was lower in patients who received HCQ-AZ treatment compared to those treated with other regimens in the IHU ($p < 0.01$).
Conclusion:	“The HCQ-AZ combination, when started immediately after diagnosis, is a safe and efficient treatment for COVID-19, with a mortality rate of 0.5%, in elderly patients. It avoids worsening and clears virus persistence and contagiousity in most cases.”
Comments:	Abstract and results table only.

[Gautret 2020](#) (score=NA) [217]

Category:	Hydroxychloroquine
Study Type:	Case Series
Conflict of Interest:	Sponsored by the Institut Hospitalo-Universitaire (IHU) Méditerranée Infection, the National Research Agency, and the Région Provence Alpes Côte d’ Azur and European funding Feder Primi. No mention of COI.
Sample Size:	N = 80 patients with SARS-CoV-2
Age/Sex:	Mean age: 52 years; 43 males, 37 females
Comparison:	All patients received 200 mg oral hydroxychloroquine sulfate 3 times per day for 10 days, as well as 500 mg azithromycin on day 1 then 250 mg per day for the next 4 days
Follow-up:	Follow-up at 6 days
Results:	In all, 81.3% of patients were discharged with low NEWS scores. 15% of patients required oxygen therapy and 3 patients were transferred to the ICU. Negative viral loads by PCR Ct value and culture were 83% at day 7 compared to 93% at day 8.
Conclusion:	“We believe there is urgency to evaluate the effectiveness of this potentially-life saving therapeutic strategy at a larger scale, both to treat and cure patients at an early stage before irreversible severe respiratory complications take hold and to decrease duration of carriage and avoid the spread of the disease. Furthermore, the cost of treatment is negligible.”
Comments:	Case series. Data suggest favorable outcomes.

[Magagnoli 2020](#) (Score=NA) [198]

Category:	Hydroxychloroquine
Study Type:	Case Series
Conflict of Interest:	Sponsored by the National Institutes of Health, DuPont Guerry, III, Professorship, and University of Virginia Strategic Investment Fund. No COI.
Sample Size:	N = 385 hospitalized patients with SARS-CoV-2 infection
Age/Sex:	Mean age not reported. Median age for treatment groups: HC = 70 years, HC+AZ = 68 years, No HC = 69 years; 368 males, 17 females

Comparison:	Hydroxychloroquine (n=97) vs. Hydroxychloroquine and Azithromycin (n=113) vs. No Hydroxychloroquine (n=158)
Follow-up:	Follow-up through 5 weeks, until hospital discharge or death
Results:	Rates of death: HC = 27.8%, HC+AZ = 22.1%, No HC = 11.4%. Rates of ventilation: 13.3%, 6.9%, and 14.1%. Risk of death from any cause higher in HC group compared to no HC group, adjusted hazard ratio (HR) = 2.61 (p = 0.03), but was not statistically different than HC+AZ group, HR = 1.14 (p = 0.72). Risk of ventilation similar in HC was similar to no HC group, HR = 1.43 (p = 0.48). Risk was similar for HC+AZ group compared to no HC group as well, HR = 0.43 (p = 0.09)
Conclusion:	“In this study, we found no evidence that use of hydroxychloroquine, either with or without azithromycin, reduced the risk of mechanical ventilation in patients hospitalized with Covid-19.”
Comments:	Case series. Many major baseline differences in the groups (respiratory, O2 saturation, cardiovascular, metabolic, renal, albumin) all of which associated with higher fatality risks in the medicated groups and preclude initial assessment of potential suggestion of efficacy.

Molina 2020 (score=NA) [218]

Category:	Hydroxychloroquine
Study Type:	Case Series
Conflict of Interest:	No COI. No mention of sponsorship.
Sample Size:	N = 11 hospitalized with COVID-19
Age/Sex:	Mean age: 58.7 years; 7 males, 4 females
Comparison:	All patients received hydroxychloroquine (600 mg/day) for 10 days and azithromycin (500 mg on day 1 and 250 mg on days 2 to 5)
Follow-up:	Follow-up at days 3, 4, 5, 6 and 7
Results:	Within 5 days one patient died and two were transferred to the ICU. Mean through blood concentration of hydroxychloroquine = 678 ng/mL at days 3-7 after initial treatment. 8 of 10 patients tested positive for SARS-CoV2 RNA via nasopharyngeal swabs at days 5 and 6. “In summary, despite a reported antiviral activity of chloroquine against COVID-19 in vitro, we found no evidence of a strong antiviral activity or clinical benefit of the combination of hydroxychloroquine and azithromycin for the treatment of our hospitalized patients with severe COVID-19.”
Conclusion:	
Comments:	Very small case series

Carlucci 2020 (score=NA) [196]

Category:	Hydroxychloroquine
Study Type:	Retrospective pre-post intervention analysis
Conflict of Interest:	No mention of COI or sponsorship.
Sample Size:	N = 932 patients with positive COVID-19
Age/Sex:	Mean age: 62.4 years; 584 males, 348 females
Comparison:	Hydroxychloroquine (400 mg followed by 200 mg twice daily for 5 days) and azithromycin (500 mg once daily) alone (n=521) vs. hydroxychloroquine (400 mg followed by 200 mg twice daily for 5 days) and azithromycin (500 mg once daily) and zinc sulfate (220 mg capsule with 50 mg elemental zinc twice daily for 5 days) (n=411)

Follow-up: No follow-up

Results: Univariate analysis showed additional zinc treatment was not associated with a decrease in hospital stay length, duration of mechanical ventilation, maximum or average oxygen flow rate, or average fraction of inspired oxygen. After adjusting the model, zinc was associated with an increased frequency of discharge to home (odds ratio = 1.52, 95% CI [1.12, 2.09]) and a reduction in mortality or transfer to hospice (OR = 0.449, 95% CI [0.271, 0.744]).

Conclusion: “This study provides the first *in vivo* evidence that zinc sulfate in combination with hydroxychloroquine may play a role in therapeutic management for COVID-19.”

Comments: Change to include zinc associated with 44% lower need for mechanical ventilation, 46% lower need for ICU, and 51% lower mortality or discharge to hospice. The primary data weakness would be for the potential for another intervention to have produced those results.

[Geleris 2020](#) (score=NA) [212]

Category: Hydroxychloroquine

Study Type: Case Series

Conflict of Interest: Sponsored by the National Institutes of Health. No mention of COI.

Sample Size: N = 1,376 patients with COVID-19

Age/Sex: Mean age not reported; greatest proportion of participants were between ages 60 and 79 years; 851 males, 595 females

Comparison: Hydroxychloroquine 600 mg twice on day 1, 400 mg daily for median of 5 days (n=811) vs. no hydroxychloroquine given (n=565)

Follow-up: Follow-up up to 30 days

Results: No significant association between hydroxychloroquine use and intubation or death (hazard ratio = 1.04, 95% CI [0.82, 1.32])

Conclusion: “In this observational study involving patients with COVID-19 who have been admitted to the hospital, hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death. Randomized, controlled trials of hydroxychloroquine in patients with COVID-19 are needed.”

Comments: Consecutive case series. Those treated with HCQ had higher body mass index; had more hypertension; were on steroids, AZT, remdesivir, or other antibiotics; had lower PaO₂-FIO₂; had higher inflammatory markers; and had lower lymphocytes. Symptom duration before treatment was not reported. Unable to address efficacy of HCQ.

[Mehra 2020](#) (score=NA) [216] **STUDY RETRACTED**

Category: Hydroxychloroquine, Chloroquine

Study Type: Retrospective Analysis

Conflict of Interest: COI, one or more authors have received or will receive benefits for personal or professional use. Sponsored by William Harvey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women’s Hospital.

Sample Size: N = 96,032 patients with positive test for SARS-CoV-2

Age/Sex: Mean age: 53.8 years; 51606 males, 44426 females

Comparison: Chloroquine alone (n=1,868) vs. Chloroquine with a macrolide (n=3,783) vs. Hydroxychloroquine alone (n=3,016) vs. Hydroxychloroquine with a

	macrolide (n=6,221) vs. Control – received none of the other treatments (n=81,144)
Follow-up:	No follow-up
Results:	Mortality of each group compared to control group (9.3%): hydroxychloroquine – 18%, hazard ratio = 1.335, 95% CI [1.223, 1.457]), hydroxychloroquine with macrolide – 23.8%, 1.447, [1.368, 1.531]), chloroquine – 16.4%, 1.365, [1.218, 1.531], chloroquine with macrolide – 22.2%, 1.368, [1.273, 1.469]), each treatment was associated with increased risk of in-hospital mortality. De-novo ventricular arrhythmia during hospitalization compared to control (0.3%): hydroxychloroquine – 6.1%, 2.369, [1.935, 2.90]), hydroxychloroquine with macrolide – 8.1%, 5.106, [4.106, 5.983]), chloroquine – 4.3%, 3.561, [2.76, 4.596], chloroquine with macrolide – 6.5%, 4.011, [3.344, 4.812]), each treatment was associated with increased risk of de-novo ventricular arrhythmia during hospitalization
Conclusion:	“We were unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19.”
Comments:	Large database case series. Multiple variables were worse in the CQ, CQ/macrolide, HCQ, HCQ/macrolide treated groups to the non-treated/control groups (control group had the best measures/function of: CAD, CHF, DM, HTN, current smoking, O ₂ saturation and sepsis-related organ failure assessment). Data were unable to address efficacy of medications. THIS STUDY WAS RETRACTED

Rosenberg 2020 (score=NA) [211]

Category:	Hydroxychloroquine
Study Type:	Retrospective Study
Conflict of Interest:	No specified sponsorship. Author Dufort’s spouse has a Gilead Foundation-Focus HIV/HCV testing research grant.
Sample Size:	N = 1,438 participants with laboratory-confirmed COVID-19
Age/Sex:	Mean age not reported; median age: 60 years; 858 males, 580 females
Comparison:	Hydroxychloroquine (HCQ) and azithromycin (AZ) (n=735) vs. HCQ (n=271) vs. AZ (n=211) vs. Neither HCQ nor AZ (n=221)
Follow-up:	Followed up to 6 weeks since hospital admission
Results:	Probability of mortality: HCQ and AZ = 25.7% (95% CI [18.2, 22.4]), HCQ = 19.9% ([15.2, 24.7]), AZ = 10.0% ([5.9, 14.0]), Neither HCQ or AZ = 12.7% ([8.3, 17.1]). No significant difference in mortality in HCQ and AZ group (hazard ratio = 1.35, [0.76, 2.4]), HCQ group (1.08, [0.63, 1.85]), and AZ group (0.56, [0.26, 1.21]) when compared to neither HCQ or AZ group.
Conclusion:	“Among patients hospitalized...with COVID-19, treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, as not significantly associated with differences in in-hospital mortality. However, the interpretation of these findings may be limited by the observational design.”
Comments:	Large, longitudinal case series. Those treated with medications were more likely to be male, older, obese, lung-diseased, diabetic, heart-diseased, with elevated AST or ALT, have higher respiratory rate, have lower O ₂ saturation, and have abnormal chest imaging. Timing of medications

regarding symptom onset was not provided. Data were unable to determine efficacy of medications.

Azithromycin for Treatment of COVID-19

Recommended.

Azithromycin is recommended for the adjunctive treatment of selected patients with more severe COVID-19. Azithromycin has been suggested to inhibit the growth of both the Zika and Ebola viruses, as well as prevent severe lower respiratory tract infections [219-222].

Strength of Evidence – Recommended, Insufficient Evidence (I)

Level of Confidence – Low

<i>Indications:</i>	Adjunctive use with hydroxychloroquine in severely affected patients with COVID-19. For severely affected patients, azithromycin may be added [157], but ECG monitoring should be particularly considered when adjunctive therapy with agents prolonging the QT interval is considered, including azithromycin plus HCQ/CQ (see Harms). Evidence suggests better efficacy if administered earlier in the clinical course when viral replication is occurring. There is no quality evidence of efficacy after ARDS is established [175].
<i>Benefits:</i>	Theoretical reduced need for a ventilator or ICU stay.
<i>Harms:</i>	Negligible for most patients undergoing short-course use. There are concerns about the potential for prolonged corrected QT intervals when used in combination therapy, and thus arrhythmias. ECG monitoring is particularly indicated in those undergoing adjunctive treatment with HCQ/CQ with underlying cardiovascular disease, history of prolonged QT, unexplained syncope, family history of premature sudden cardiac death, electrolyte abnormalities, renal insufficiency, and use of other drugs reported to prolong QT intervals, including when there is planned adjunctive use with hydroxychloroquine/chloroquine.
<i>Indications for Discontinuation:</i>	Completion of a course, intolerance, adverse effect, prolongation of QT interval.
<i>Frequency/Dose/Duration:</i>	The regimen used for treatment of COVID is azithromycin 500mg on day 1 and then 250 mg/day for 4 days [157, 217].
<i>Rationale:</i>	There are no quality studies of azithromycin. One nonrandomized trial suggested improved efficacy when hydroxychloroquine was combined with azithromycin [157]; these authors reported similar results in a subsequent, larger case series of 80 cases [217]. There is low-quality evidence for adjunctive use of azithromycin but almost no other antiviral treatment option, these medications are low cost, and adverse effects are minor for short courses of treatment; thus, these medications are recommended. Based on the available limited evidence, earlier treatment appears to be important for efficacy compared with treatment in an ICU.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to April 2020 using the following terms: azithromycin; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials,

randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 0 articles in PubMed, 72 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 1,646 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria. There were no exclusion criteria.

[†] The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Favipiravir for the Treatment of COVID-19

No Recommendation.

There is no recommendation for or against the use of favipiravir for COVID-19.

Strength of Evidence – No Recommendation, Insufficient Evidence (I) *Level of Confidence – Low*

Rationale:

Favipiravir, a guanine analogue to inhibit RNA-dependent RNA polymerase, has been used to treat influenza. One RCT comparing favipiravir with arbidol found no significant differences in the main clinical outcome measure, although fever and cough resolved more quickly in the favipiravir group [224]. There is one non-randomized controlled trial suggesting acceleration of viral clearance compared with lopinavir-ritonavir [223]. Although there is no quality evidence of efficacy, these studies suggest there may be potential efficacy and thus, while needing further quality data, this medication may be helpful in the treatment of patients with COVID-19.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to April 2020 using the following terms: Favipiravir; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 1 article in PubMed, 70 in Scopus, 0 in CINAHL, 86 in Cochrane Library, 1678 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 1 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 4 articles considered for

inclusion, 1 randomized trial, 1 non-randomized trial, and 2 systematic review met the inclusion criteria. There were no exclusion criteria.

† The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Evidence for the Use of Favipiravir

Chen 2020 (score=5.0) [224]

Category:	Favipiravir
Study Type:	RCT
Conflict of Interest:	Sponsored by the National Key Research and Development Program of China. No mention of COI.
Sample Size:	N = 236 patients with COVID-19
Age/Sex:	No mean of mean age; 110 males, 126 females.
Comparison:	Favipiravir vs. arbidol. Favipiravir: 1600 mg twice first day, then 600mg twice daily for 6 days, plus standard care (n=120). Arbidol: 200 mg three times daily for 7 days, plus standard care
Follow-up:	Follow-up daily for 10 days
Results:	The clinical recovery rate on day 7 did not differ significantly between the Favipiravir group and Arbidol group (p = 0.1396). Favipiravir led to shorter latencies to relief for both pyrexia (p < 0.0001) and cough (p < 0.0001).
Conclusion:	“Among patients with COVID-19, Favipiravir, compared to Arbidol did not significantly improve the clinically recovery rate at Day 7. Favipiravir significantly improved the latency to relief for pyrexia and cough.”
Comments:	Open-label. No significant difference in the main outcome of clinical recovery; however, faster relief of fever and cough occurred in the favipiravir group.

Cai 2020 (score=N/A) [223]

Category:	Favipiravir
Study Type:	Open-label nonrandomized control study
Conflict of Interest:	Sponsored by National Science and Technology Major Project, Sanming Project of Medicine in Shenzhen, Shenzhen Science and Technology Research and Development Project, China Postdoctoral Science Foundation, Guangdong Special Fund for Science and Technology Innovation Strategy. No COI.
Sample Size:	N = 80 patients with positive respiratory or blood samples for novel coronavirus (>7 days)
Age/Sex:	Mean age: 47.0 years; 35 males, 45 females
Comparison:	FPV Group: received oral 1600 mg favipiravir (200 mg tablets) twice daily on day 1, 600 mg twice daily on days 2-14 (n=35) vs. LPV/RTV Group: received lopinavir/ritonavir 400 mg/100mg twice daily for 14 days (n=45). All patients received IFN-alpha-1-beta-60µg twice daily by aerosol inhalation
Follow-up:	Follow-up at 4, 9, and 14 days

Results:	Median time of viral clearance was 4 days in FPV group compared to 11 days in LPV/RTV group (p<0.001). Improvement on chest CT was greater in the FPV group compared to the LPV/RTV group (91.4% vs. 62.2%, p=0.004).
Conclusion:	“In this open-label nonrandomized control study, FPV showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance; if causal, these results should be important information for establishing standard treatment guidelines to combat the SARS-CoV-2 infection. “
Comments:	Nonrandomized controlled trial, with enrollments based on date of presentation. Comparable baseline data. Data suggest favipiravir was associated with faster resolution of pneumonia on CT and viral clearance compared with lopinavir/ritonavir.

Lopinavir-Ritonavir for the Treatment of COVID-19

Recommended.

Lopinavir-ritonavir is recommended in combination therapy [225], but is not recommended as solitary treatment of COVID-19 [77].

Strength of Evidence – Recommended, Evidence (C) (Combination therapy)

Level of Confidence – Low

Strength of Evidence – Not Recommended, Evidence (C) (Stand-alone treatment)

Level of Confidence – Low

<i>Indications:</i>	Adjunctive use with ribavirin and interferon beta-1b in moderately and severely affected patients with COVID-19 [225]. Evidence suggests better efficacy if administered within 7 days of symptom onset; after 7 days, data suggest no differences between this combination therapy and lopinavir-ritonavir [225].
<i>Benefits:</i>	Faster symptom resolution, viral clearance, and hospital discharge. Reduced need for a ventilator or ICU stay.
<i>Harms:</i>	Nausea, diarrhea, hepatitis.
<i>Indications for Discontinuation:</i>	Completion of a course, intolerance, adverse effect, prolongation of QT interval.
<i>Frequency/Dose/Duration:</i>	The regimen used for the treatment of COVID-19 is lopinavir 400mg, ritonavir 100mg every 12hrs, ribavirin 400mg every 12hrs, plus 3 doses of 8M IU interferon beta-1b on alternate days [225].
<i>Rationale:</i>	One open-label RCT found combination therapy of lopinavir 400mg, ritonavir 100mg every 12hrs, ribavirin 400mg every 12hrs, plus 3 doses of 8M IU interferon beta-1b on alternate days to be superior to lopinavir-ritonavir [225].

Lopinavir-ritonavir as sole antiviral treatment has been trialed in one open-label RCT, which showed a lack of efficacy compared with standard care [178], while another double-blind RCT also suggested lack of efficacy, although it may have been underpowered [226]. One RCT treated severe patients and the other treated mild/moderately severe patients at an average of 4-5 days duration. It is unclear if lopinavir-ritonavir would be effective if provided earlier in the clinical

course. These medications have also been suggested to be inferior to favipiravir in a non-randomized comparative trial [223].

Based on the one moderate-quality RCT showing evidence of efficacy, the regimen of triple-combination therapy using lopinavir, ritonavir, ribavirin, and interferon beta-1b is recommended [225]. However, the combination of only lopinavir-ritonavir is not recommended for the treatment of COVID-19 patients.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to April 2020 using the following terms: Lopinavir, rotinavir; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 19 articles in PubMed, 429 in Scopus, 4 in CINAHL, 11 in Cochrane Library, 1936 in Google Scholar, and 2 from other sources[†]. We considered for inclusion 1 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 2 from other sources. Of the 7 articles considered for inclusion, 3 randomized trials, 3 cohort studies, and 2 systematic reviews met the inclusion criteria. There were no exclusion criteria.

[†]The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Evidence for the Use of Lopinavir-Ritonavir

[Cao 2020](#) (score=7.5) [178]

- Category:** Lopinavir-Ritonavir
- Study Type:** RCT
- Conflict of Interest:** Sponsored by Major Projects of National Science and Technology on New Drug Creation and Development and others. COI: One or more of the authors have received or will receive benefits for personal or professional use.
- Sample Size:** N = 199 hospitalized adult patients with confirmed SARS-CoV-2 infection (COVID-19)
- Age/Sex:** Mean age: 58.0 years; 120 males, 79 females
- Comparison:** Lopinavir-Ritonavir: received 400 mg and 100 mg oral lopinavir-ritonavir twice daily plus standard care for 14 days (n=99) vs. standard care. Standard Care: received supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO) as needed for 14 days (n=100)
- Follow-up:** Follow-up at 7, 14, and 28 days

Results: Time to clinical improvement was 16 days for lopinavir-ritonavir (HR=1.31, 95% CI [0.95, 1.85], p=0.09). Lopinavir-ritonavir treatment within 12 days of onset symptoms did not reduce time to clinical improvement (HR=1.25, 95% CI [0.77,2.05]). Lopinavir-ritonavir group showed a 19.2% 28-day mortality compared to 25% in standard care group (95% CI [-17.3, -5.7]). Of the lopinavir-ritonavir group, 13.8% stopped treatment due to adverse events.

Conclusion: “In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir-ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit.”

Comments: RCT of severe COVID-19 patients with pneumonia. Data suggest lopinavir-ritonavir provided no benefit in addition to standard care.

[Li 2020](#) (score=7.5) [226]

Category: Lopinavir/Ritonavir

Study Type: RCT

Conflict of Interest: Supported by Chinese 13th Five-Year National Science and technology major project and Infectious Disease Specialty of Guangzhou High-level Clinical Key Specialty. No COI.

Sample Size: N = 44 patients with confirmed COVID-19 diagnosis

Age/Sex: Mean age: 49.4 years; 21 males, 23 females

Comparison: Lopinavir (200mg) boosted by ritonavir (50mg) LPV/r (oral, q12h, 500 mg each time for 7-14 days) (n=21) vs. Arbidol (100mg) (oral, 200mg TID for 7-14 days)(n =16) vs control (n =7) were they received no medication for 21 days.

Follow-up: Follow at 7, 14 and 21 days

Results: Mean time (days) to positive-to-negative conversion of SARS-CoV-2 nucleic acid: LPV/r group = 8.5, Arbidol = 7, Control = 4 (p =0.751). Positive-to-negative conversion at 7 days: LPV/r group, the arbidol group and the control group were 42.9% (9/21), 62.5% (10/16) and 71.4% (5/7) (p =0.942). At 14 days of treatment, the positive-to-negative conversion was 76.2% (16/21), 87.5% (14/16) and 71.4% (5/7) for the LPV/r group, the arbidol group and the control group (p =0.681).

Conclusion: “In conclusion, our study found LPV/r or arbidol monotherapy seems little benefit for improving the clinical outcome of mild/moderate COVID-19, and LPV/r might lead to more adverse events.”

Comments: Modest sample size with underenrollment due to the epidemic being brought under control. Small placebo group (n=7). Some trends in baseline differences. Study emphasized viral clearance. Clinical efficacy unclear, largely due to under-enrollment. No evidence of efficacy.

[Hung 2020](#) (score=6.0) [225]

Category: Lopinavir/Ritonavir

Study Type: Open-label randomized trial

Conflict of Interest: Sponsored by the Shaw-Foundation, Richard and Carol Yu, May Tam Mak Mei Yin, and Sanming Project of Medicine. No COI.

Sample Size: N = 127 patients with virologically confirmed COVID-19

Age/Sex: Mean age: 51.3 years; 68 males, 59 females

Comparison: Combination of lopinavir (400 mg) and ritonavir (100 mg) every 12 hours, Ribavirin (400 mg) every 12 hours, Three doses of 8 million international units of interferon beta-1b on alternate days (n=86) vs. Control of lopinavir (400 mg) and ritonavir (100 mg) every 12 hours (n=41). Both treatments were given for 14 days.

Follow-up: Follow-up daily for 7 days

Results: Combination group had shorter median time to negative nasopharyngeal swab compared to control group (7 days vs. 12 days, hazard ratio = 4.37, 95% CI [1.86, 10.24], p=0.001)

Conclusion: “Triple antiviral therapy with interferon beta-1b, lopinavir–ritonavir, and ribavirin were safe and superior to lopinavir–ritonavir alone in shortening virus shedding, alleviating symptoms, and facilitating discharge of patients with mild to moderate COVID-19.”

Comments: Data suggest early administration of combination therapy (lopinavir-ritonavir, ribavirin, and β -interferon) was significantly superior to control group (lopinavir-ritonavir) in shortening median time to negative nasopharyngeal swab (7 days versus 12 days, $p=0.001$). Viral shedding and symptom alleviation with shortened LOS occurred in combination group. Subgroup analysis showed no difference if treated >7 days compared with <7 days.

[Deng 2020](#) (score=NA) [227]

Category: Lopinavir/Ritonavir

Study Type: Cohort

Conflict of Interest: No COI or sponsorship.

Sample Size: N = 33 patients with COVID-19 without invasive ventilation

Age/Sex: Mean age: 44.6 years; 17 males, 16 females

Comparison: Oral arbidol (200 mg every 8 hours) and lopinavir/ritonavir (400 mg/100 mg every 12 hours) (LPV/r) combination until RT-PCR was negative for coronavirus three times (n=16) vs. oral LPV/r only (400 mg/100 mg every 12 hours) until RT-PCR was negative for coronavirus three times (n=17)

Follow-up: Follow-up at days 7 and 14

Results: SARS-CoV-2 not detected in 12/16 (75%) combination group patients via nasopharyngeal specimens after 7 days compared to 6/17 (35%) in monotherapy group ($p < 0.05$). After 14 days, these numbers changed to 15/16 (94%) for combination group and 9/17 (53%) for monotherapy group ($p < 0.05$). After 7 days, chest CT scans showed improvement for 11/16 (69%) in combination group compared to 5/17 (29%) in monotherapy group ($p < 0.05$)

Conclusion: “In patients with COVID-19, the apparent favorable clinical response with arbidol and LPV/r supports further LPV/r only.”

Comments: Small sample size.

[Yan 2020](#) (score=NA) [228]

Category: Lopinavir/Ritonavir

Study Type: Cohort

Conflict of Interest: No COI or sponsorship.

Sample Size: N = 120 patients with SAR-CoV-2 infection

Age/Sex: Mean age not reported, median age: 52 years; 48 males, 72 females

Comparison: Lopinavir/ritonavir (LPV/r) treatment (400 mg/100 mg orally twice daily) given for 10 or more days (n=78) vs. No LPV/r treatment (n=42)

Follow-up: Follow-up throughout 56 days

Results: Lack of LPV/r treatment was an independent risk factor for prolonged SARS-CoV-2 RNA shedding via logistic regression (OR = 2.42, 95% CI [1.1, 5.35], $p = 0.029$). Median duration of viral shedding: LPV/r group = 22 days, no LPV/r group = 28.5 days ($p = 0.02$)

Conclusion: “In summary, older age and lack of LPV/r treatment contributed to prolonged SARS-CoV-2 RNA shedding. Earlier administration of LPV/r treatment can shorten the duration of SARS-CoV-2 RNA shedding.”

Comments: Efficacy unclear.

[Ye 2020](#) (score=NA) [229]

Category:	Lopinavir/Ritonavir
Study Type:	Cohort
Conflict of Interest:	No COI. Sponsored by the Zhejiang Natural Science Foundation, Medical Science and Technology Project of Zhejiang Province, and the Ruian Science and Technology Bureau.
Sample Size:	N = 47 patients with COVID-19 infection
Age/Sex:	No mean age given, age range 5-68 years; 22 males, 25 females
Comparison:	Lopinavir/ritonavir (LPV/r) treatment (400/100 mg twice daily or 800/200 mg once daily) with adjuvant medicine (n=42) vs. No LPV/r treatment with adjuvant medicine (n=5)
Follow-up:	Follow-up daily for 10 days
Results:	Body temperature of LPV/r group was not significantly different than control group ($p > 0.05$). In those with body temperature of 37.5° C at admission, those in LPV/r group returned to a normal body temperature in a shorter time period compared to control (4.8 days vs. 7.3 days, $p = 0.0364$). Number of days for nCoV-RNA negative result: LPV/r group = 7.8 days, control group = 12.0 days ($p = 0.0219$)
Conclusion:	“We prove that the combination treatment of LPV/r and routine adjuvant medicine against pneumonia could produce much better efficacy on patients with COVID-19 infection compared to treatment with adjuvant medicine alone. Hence, we suggest to widely apply the combination treatment in treatment patients with COVID-19 infection.”
Comments:	Modest sample size. Efficacy unclear.

Remdesivir for the Treatment of COVID-19

Recommended.

Remdesivir is recommended for the supervised treatment of selected patients with COVID-19.

Strength of Evidence – Recommended, Evidence (C)

Level of Confidence – Low

<i>Indications:</i>	Severe COVID-19 patients, with <94% O ₂ saturation or need for O ₂ supplementation, mechanical ventilation, or extracorporeal membrane oxygenation [153]. Generally, patient should have creatinine clearance >30 mL/min; ALT and AST <5 times upper limit of normal.
<i>Benefits:</i>	Reportedly shortened ICU stay by 31% and possible improved survival.
<i>Harms:</i>	Increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension. However, the largest RCT did not report significantly increased adverse events in any category [1].
<i>Indications for Discontinuation:</i>	Completion of a course, intolerance, adverse effect.
<i>Frequency/Dose/Duration:</i>	Remdesivir 200mg IV on day 1, then 100mg QD for 9 additional days [1, 230].
<i>Rationale:</i>	<p>There is one high-quality RCT of remdesivir suggesting a lack of clinical efficacy, although it also suggests non-significant trends toward earlier clinical improvements [231]. A larger, moderate-quality NIH trial showed modest efficacy, including 31% shorter ICU stays and earlier clinical improvements. Neither RCT was able to show statistically improved survival, although the NIH trial trended toward improved survival [1]. There is one case series suggesting a fairly low death rate (13%) [230]. There is evidence that remdesivir inhibits viral replication in vitro studies [166]. It is possible that remdesivir is more effective if administered in the viral replication stage.</p> <p>Remdesivir is invasive (IV), has minimal adverse effects, is high cost, has evidence of efficacy (particularly for the treatment of hospitalized patients requiring oxygen), and thus is recommended.</p>
<i>Evidence:</i>	<p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to April 2020 using the following terms: remdesivir; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 6 articles in PubMed, 392 in Scopus, 0 in CINAHL, 6 in Cochrane Library, 1,905 in Google Scholar, and 2 from other sources[†]. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 3 articles considered for inclusion, 2 randomized trials, 1 case series and 0 systematic reviews met the inclusion criteria. There were no exclusion criteria.</p>

[†] The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature

appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Evidence for the Use of Remdesivir

Wang 2020 (score=8.5) [231]

Category:	Remdesivir
Study Type:	RCT
Conflict of Interest:	Sponsored by the Chinese Academy of Medical Sciences Emergency Project of COVID-19, National Key Research and Development Program of China and the Beijing Science and Technology Project. Gilead provided the remdesivir. Author Hayden has been a non-compensated consultant to Gilead Sciences.
Sample Size:	N = 237 hospitalized patients with laboratory-confirmed SARS-CoV-2 infection
Age/Sex:	Mean age: 65.1 years; 140 males, 97 females
Comparison:	Intravenous remdesivir (200 mg on day 1, then 100 mg on days 2-10 in single daily infusions) (n=158) vs. Placebo (same frequency and dosage) (n=79)
Follow-up:	Follow-up through 28 days
Results:	Remdesivir group did not have a significantly different time to clinical improvement versus placebo group (hazard ratio = 1.23, 95% CI [0.87, 1.75])
Conclusion:	“In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in tie to clinical improvement in those treated earlier requires confirmation in larger studies.”
Comments:	Tachypnea (>24) higher in placebo at baseline (14% v 23%). Data suggest no statistically significant benefits but trends towards earlier clinical improvement.

Beigel 2020 (ACCT-1 Trial) (score=7.5) [1]

Category:	Remdesivir
Study Type:	RCT
Conflict of Interest:	Sponsored by the National Institute of Allergy and Infectious Disease, National Institutes of Health, the National Cancer Institute, the Department of Defense, Defense Health Program, and by governments of Japan, Mexico, Denmark, and Singapore, the Seoul National University Hospital, and the United Kingdom Medical Research Council. Remdesivir provided by Gilead Sciences. Original draft was prepared by an employee of Gilead Sciences and several authors are affiliated with the sponsor.
Sample Size:	N = 1,063 hospitalized patients with COVID-19 and evidence of lower respiratory tract involvement
Age/Sex:	Mean age: 58.9 years; 684 males, 379 females
Comparison:	Remdesivir 10-day course consisting of 200 mg intravenously on day 1, then 100 mg daily for 9 days (n=541) vs. Placebo (n=522)
Follow-up:	Follow-up through 29 days

Results: Those in the remdesivir group had shorter time to recovery compared to the placebo group (median time: 11 days vs. 15 days, rate ratio = 1.32, 95% CI [1.12, 1.55], p < 0.001)

Conclusion: “Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection.”

Comments: Some unblinding in Europe possible as matching placebo not available. High rate of incomplete treatments in both study arms. Data suggest modest efficacy to shorten ICU stay and clinical recovery. Data do not show differences among those who received high-flow oxygen of noninvasive mechanical ventilation, mechanical ventilation or ECMO. Thus, the primary benefits appear to be among those less severely ill but receiving oxygen. Study likely underpowered to detect differences in survival.

Grein 2020 (score=NA) [230]

Category: Remdesivir

Study Type: Case Series

Conflict of Interest: Sponsored by Gilead Sciences. Original draft was prepared by an employee of Gilead Sciences and several authors are affiliated with the sponsor.

Sample Size: N = 61 patients hospitalized due to SARS-CoV-2 infection, with oxygen saturation of 94% or less while breathing ambient air or receiving oxygen support

Age/Sex: Age and sex data only available for 57 patients. Mean age not reported – median age: 60 years; 40 males, 13 females

Comparison: Remdesivir on compassionate-use basis, 10-day course consisting of 200 mg intravenously on day 1, then 100 mg daily for 9 days

Follow-up: Follow-up up to 44 days, median follow-up time was 18 days

Results: Improvement in oxygen-support class was seen in 36 patients (68%). 17 patients of 30 (57%) who received mechanical ventilation were extubated. 25 (47%) were discharged while 7 died (13%). Mortality: 18% in those receiving invasive ventilation, 5% in those not receiving invasive ventilation

Conclusion: “In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy.”

Comments: Case series. Data suggest 68% had clinical improvement and 13% death rate among severe COVID-19 patients.

Interleukin-6 (IL-6) Receptor Antagonists (Tocilizumab, Sarilumab, and Siltuximab) for the Treatment of COVID-19

Recommended.

Interleukin-6 inhibitors (sarilumab, siltuximab, and tocilizumab) are recommended for the treatment of selected patients with COVID-19.

Strength of Evidence – Recommended, Insufficient Evidence (I) **Level of Confidence – Low**

<i>Indications:</i>	Most commonly used in clinical trials for COVID. May be used off-label, as these agents are not FDA-approved for treatment of COVID-19. Severely affected patients with COVID-19 with cytokine storm manifestations, including ARDS, were assessed in a retrospective case series [232]. Patients had respiratory failure, shock, and/or other organ failure [232].
<i>Benefits:</i>	Improved oxygenation, reduced temperature, and reduced CRP [232]. Data also suggest potential improved survival as in one report, the hospital discharge rate of 90% was significantly above expectations.
<i>Harms:</i>	Potential infection risks.
<i>Indications for Discontinuation:</i>	Completion of a course, intolerance, adverse effects.
<i>Frequency/Dose/Duration:</i>	Per trial protocols.
<i>Rationale:</i>	One case series suggested significant survival and oxygenation benefits. Because there are so few treatments directed at the cytokine storm, the fatality rate is >60%, and the available data are supportive, IL-6 inhibitors are recommended.
<i>Evidence:</i>	<p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to April 2020 using the following terms: Interleukin-6 (IL-6) Receptor Antagonists, Tocilizumab, Sarilumab; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 2 articles in PubMed, 112 in Scopus, 0 in CINAHL, 2 in Cochrane Library, 93 in Google Scholar, and 1 from other sources[†]. We considered for inclusion 0 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 1 from other sources. Of the 5 articles considered for inclusion, 0 randomized trials, 1 case series and 4 systematic reviews met the inclusion criteria. There were no exclusion criteria.</p> <p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to April 2020 using the following terms: Siltuximab; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic,</p>

systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 0 articles in PubMed, 2 in Scopus, 0 in CINAHL, 2 in Cochrane Library, 140 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 0 randomized trials and 1 systematic review met the inclusion criteria. There were no exclusion criteria.

[†] The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Evidence for the Use of Interleukin-6 (IL-6) Receptor Antagonists

[Xu 2020](#) (score=N/A) [232]

Category:	Tocilizumab
Study Type:	Case Series
Conflict of Interest:	No COI. Sponsored by the Department of Science and Technology of Anhui Province and the Health Commission of Anhui Province and the China National Center for Biotechnology Development 175.
Sample Size:	N = 21 patients diagnosed with several or critical COVID-19 based on criteria of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia
Age/Sex:	Mean age: 56.8 years; 18 males, 3 females
Comparison:	All patients received lopinavir, methylprednisolone, other symptom relievers and oxygen therapy, and tocilizumab. Tocilizumab was 400 mg once via IV drip.
Follow-up:	Follow-up at days 1, 2, 3, 4, and 5 All patients' body temperatures returned to normal after the first day of tocilizumab and remained stable. 15 patients had lowered oxygen intake. Another patient was taken off a ventilator after the first day of tocilizumab. Another patient regained consciousness on day 5 after tracheal extubation. On day 5, only 2 of 19 patients had abnormal values of white blood cell count values. In 10 out of 19 patients, the percentage of lymphocytes returned to normal while CRP returned to normal for 16 patients.
Results:	
Conclusion:	"In summary, tocilizumab effectively improves clinical symptoms and represses the deterioration of severe COVID-19 patients. Therefore, tocilizumab is an effective treatment in severe patients of COVID-19, which provided a new therapeutic strategy for this fatal infectious disease."
Comments:	Case series. Survival of >90% is far above expected rates, provided evidence is suggestive of efficacy.

Convalescent COVID-19 Antibodies

Recommended.

Convalescent antibodies are recommended for the treatment of selected patients with COVID-19.

Strength of Evidence – Recommended, Insufficient Evidence (I)
Level of Confidence – Low

Indications: Timing of convalescent antibodies is in the viral replication stage [233]. There are three pathways for administration: 1) clinical trials, 2) expanded use, and 3) single-patient emergency Investigational New Drug. Severely affected patients with COVID-19. FDA requirements include laboratory confirmation and severe disease (dyspnea, respiratory rate >30, O₂ saturation ≤93%, or lung infiltrates >50% within 24-48 hrs) or life-threatening disease (respiratory failure, septic shock, and/or multiorgan failure or dysfunction) and informed consent [177].

Benefits: Expected reduced need for a ventilator, ICU stay.

Harms: Allergic reactions, thrombotic events.

Indications for Discontinuation: Completion of a course, intolerance, adverse effect.

Frequency/Dose/Duration: N/A

Rationale: There are no quality trials of convalescent antibodies [234, 235], although many trials are underway [236]. However, they were reportedly successful in one case series [179] and have been successfully used for other diagnoses, including Ebola [236, 237]. Because the alternative is typically a fatality rate of at least 50–60%, convalescent antibodies are recommended for severe cases in the viral replication stage.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to April 2020 using the following terms: Convalescent COVID-19 Antibodies, convalescent plasma, antibodies; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 18 articles in PubMed, 57 in Scopus, 10 in CINAHL, 13 in Cochrane Library, 740 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 1 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 0 randomized trials, 1 case series, and 3 systematic reviews met the inclusion criteria. There were no exclusion criteria.

[†] The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy. The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains

no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Evidence for the Use of Convalescent COVID-19 Antibodies

[Duan 2020](#) (score=NA) [238]

Study Type:	Case Series
Conflict of Interest:	No mention of COI. Sponsored by the Ministry of Science and Technology China “Preparation of specific plasma and specific globulin from patients with a recovery period of COVID-19 infection” and Shanghai Guangci Translational Medicine Development Foundation.
Sample Size:	N = 10 patients with severe COVID-19 infection
Age/Sex:	Mean age: 53.4 years; 6 males, 4 females
Comparison:	All patients received single dose of 200 mL convalescent plasma (CP), derived from recently recovered donors with neutralizing antibody titers above 1:640, also received maximal supportive care and antiviral agents (n=10)
Follow-up:	Follow-up at 3 and 7 days
Results:	Level of neutralizing antibodies increased to 1:640 in five cases. Clinical symptoms improved with increase of oxyhemoglobin saturation within 3 days. Viral load undetectable in seven patients with previous viremia
Conclusion:	“This study showed CP therapy was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases.”
Comments:	Small case series. Efficacy unclear.

Glucocorticosteroids for the Treatment of COVID-19

Recommended.

Glucocorticosteroids are provisionally recommended for the treatment of COVID-19 [239-241]. There are other indications for use that may occur in the context of treatment of COVID-19 (e.g., asthma, COPD) (pending publication of UK trial data [244, 245]).

Strength of Evidence – Recommended, Insufficient Evidence (I) ⁷

Level of Confidence – Low

<i>Indications:</i>	Hospitalized patients with moderate or severe COVID-19. Especially effective reportedly for those critically ill on ventilators or requiring supplemental oxygen. The single trial reports no efficacy among those without either of those two parameters, although the available press release suggests there may be a trend towards efficacy among those otherwise hospitalized (p=0.14).
<i>Benefits:</i>	Reduced mortality by 20% if requiring supplemental oxygen, and 35% if ventilated.
<i>Harms:</i>	Hyperglycemia, risk of secondary infection, higher blood pressure.
<i>Indications for Discontinuation:</i>	Completion of a course, intolerance, adverse effect.
<i>Frequency/Dose/Duration:</i>	Reportedly used Dexamethasone 6 mg QD x 10 days.
<i>Rationale:</i>	There are no as-yet published quality trials of glucocorticosteroids for the treatment of COVID-19. However, a large placebo-controlled UK trial (n>11,500) has reported reductions in fatalities by 35% among those on a ventilator and 20% among those requiring only supplemental oxygen [244, 245]. As glucocorticosteroids have moderate adverse effects, low costs, and have been reported to have efficacy in reducing mortality, this is a provisional recommendation pending publication of the final data.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to April 2020 using the following terms: glucocorticoids, glucocorticoid steroid, prednisone, dexamethasone, hydrocortisone; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 0 articles in PubMed, 51 in Scopus, 0 in CINAHL, 1 in Cochrane Library, 1,133 in Google Scholar, and 2 from other sources [†] . We considered for inclusion 0 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 2 from other sources. Of the 5 articles considered for inclusion, 0 randomized trials, 2 cohort studies, and 3 systematic reviews met the inclusion criteria. There were no exclusion criteria.

[†] The results for databases are sorted by relevancy based on customized search term algorithms. Algorithms for each database determine relevancy.

⁷ Provisional recommendation pending publication of UK trial data [152, 153].

The first 100 articles are reviewed in each search, and if relevant literature appears in the first 100 articles, we review an additional 100 articles. If relevant articles appear in these additional 100 articles, we then review another 100. We continue this pattern of review until we review a batch of 100 articles that contains no relevant literature. When this happens then the remaining articles are not reviewed due to a lack of relevancy.

Evidence for the Use of Glucocorticoid Steroids

[Lu 2020](#) (score=NA) [242]

Category:	Glucocorticoid Steroids
Study Type:	Cohort
Conflict of Interest:	Sponsored by the National Key R&D Program of China, the National Natural Science Foundation of China, the “Double First-Class” University Project, the China Postdoctoral Science Foundation, the Science Foundation of Jiangsu Commission of Health, and the Emergency Project for the Prevention and Control of the Novel Coronavirus Outbreak in Suzhou. No mention of COI.
Sample Size:	N = 244 patients in intensive care wards with SARS-CoV2 infection
Age/Sex:	Mean age: 62.1 years; 128 males, 116 females
Comparison:	Steroid group – given antiviral therapy and adjunct corticosteroid treatment, hydrocortisone (dosage range: 100-800 mg/day) (n=151) vs. Non-steroid group – given just antiviral therapy (n=93)
Follow-up:	Follow-up was at 28 days after admission
Results:	Adjunct steroid therapy independent from 28-day mortality – multivariate adjusted logistic regression and individual propensity score (adjusted OR = 1.05, 95% CI [-1.92, 2.01]) and case-control analysis propensity score-matched (31 pairs, log-rank test p = 0.17). Increased steroid dosage significantly associated with elevated mortality risk with adjustment for administration duration (p = 0.003) – every ten-milligram increase in hydrocortisone-equivalent dosage associated with 4% additional mortality risk (adjusted HR = 1.04, 95% CI [1.01, 1.07])
Conclusion:	“Our findings indicated that limited effect of corticosteroid therapy could pose to overall survival and prudent dose within effective limits may be recommended for critically ill patients under certain circumstances.”
Comments:	

[Wang 2020](#) (score=NA) [243]

Category:	Glucocorticoid Steroids
Study Type:	Cohort
Conflict of Interest:	No COI. Sponsored by the Natural Science Foundation of China.
Sample Size:	N = 46 hospitalized patients with 2019-nCoV pneumonia
Age/Sex:	Mean age: 54 years; 26 males, 20 females
Comparison:	Intravenous methylprednisolone 1-2 mg/kg/d for 5-7 days (n=26) vs. No steroid treatment (n=20)
Follow-up:	Follow-up daily for 11 days
Results:	Average number of days for body temperature to return to normal range significantly shorter in patients given steroid compared to those with no steroid treatment (2.06 days vs. 5.29 days, p = 0.01). Patients not given steroids were on

	supplemental oxygen therapy for a significantly longer time compared to those on steroids (13.5 days vs. 8.2 days, $p < 0.001$)
Conclusion:	“Our data indicate that in patients with severe COVID-19 pneumonia, early, low-dose and short-term application of corticosteroid was associated with a faster improvement of clinical symptoms and absorption of lung focus.”
Comments:	Modest-sized longitudinal case series. Efficacy unclear.

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