AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

Coronavirus (COVID-19)

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These panel members represent expertise in occupational medicine, internal medicine, pulmonary medicine, and infectious disease. As required for quality guidelines – Institute of Medicine's (IOM's) Standards for Developing Trustworthy Clinical Practice Guidelines and Appraisal of Guidelines for Research and Evaluation (AGREE) – a detailed application process captured conflicts of interest. The above Panel has none to declare relevant to this guideline.

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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 April 22, 2020. The total depth and breadth of quality literature for the treatment of COVID-19 is quite limited. We intend to continue to monitor the literature and update as needed.*

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") [1]. Because it is new, little information is currently available about the virus.

The epidemic 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 epidemic and pandemic [2] for several reasons, including the number of undiagnosed, mild, or asymptomatic patients spreading the virus [3]; animals' susceptibility and involvement; and the spread of cases in a region prior to the recognition of COVID-19 within that area [4].

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 [5, 6]. When a virus mutates or changes, studies must be performed to determine the new strain's virulence, or 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 [7] and in many countries, including the United States [8].

Virus Characteristics

Contagiousness

COVID-19's SARS-CoV-2 virus appears to be much more contagious than the prior coronaviruses. There are increasing concerns that the virus is not only spread by hand-to-eye contact and respiratory droplets, but also by respiratory aerosols. Aerosols can remain suspended in the air for a longer time and well beyond the commonly quoted 6-foot physical distancing guideline [9].

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 [10], which is far higher than typical influenza transmission rate of ~1.3 [11]. The severity of COVID-19 is estimated to be approximately 10-fold higher than that of typical seasonal influenza [12]. More precise estimates of transmission rates will only become known with time. Future studies will need to 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 [13]. The total viable viral counts decline with time [9]. 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. [13].

Incubation

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 5 days [14], with infrequent cases of up to 14 days and some rare reports of up to 27 days [8, 15]. The few cases with unusually long incubation times may represent an initial non-exposure event followed by a subsequent true exposure that caused the disease, resulting in an artificially long incubation time.

Clinical Presentation

There are at least four distinct types or clinical presentations of COVID-19's SARS-CoV-2 virus infections:

1. Asymptomatic or nonspecific infection
2. Upper respiratory tract infection (URI), which also may include gastrointestinal symptoms
3. Lower respiratory tract infection, including pneumonia
4. 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 [16-18]:

- Fever (low or high grade) (80-88%)
- Dry cough [8, 21] (63-69%)
- Loss of appetite (39-84% [22])
- 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% [22])

- Nasal congestion (4-5%)
- Abdominal pain (4%)
- Conjunctivitis (pink eye) [19] (1%)
- Hemoptysis (1%)
- Rhinorrhea (runny nose)
- Anosmia and dysgeusia (loss of smell and taste) (85% moderate/severe or anosmic) [20]

There also have been reports of urticaria, stroke-like neurological symptoms, and cardiovascular symptoms and signs on initial presentation.

Because the symptoms for most patients are typical of respiratory tract infections, they can be difficult to distinguish from other diseases [23, 24]. 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 [25]. 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 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 [3, 25, 26]. Children tend to be asymptomatic or have milder symptoms, which suggests a mechanism that may accelerate disease transmission throughout the population [25]. Presymptomatic spread has been estimated to account for 44% of secondary cases during a period of community case finding and quarantining [3].

Mortality

The mortality rate is more recently being estimated at 1–2%, which is approximately 10 to 20 times the mortality rate for typical seasonal influenza (~0.1%), and some estimates are suggesting the mortality rate may be 0.1-0.5% when including the minimally symptomatic and asymptomatic cases. The mortality rate is highly related to age. For example, the 1.3% fatality rate for patients in their 50s increases to 15% for patients in their 80s. The mortality rate for males is 57–64% higher than that for females. Nursing home residence is a particularly potent risk [27-31]. 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 [32-35]; however, approximately 1% of fatalities occur in previously healthy patients [36]. 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.

Employer Considerations

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

Employee Contact

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

For employees returning from personal or work-related travel overseas or to other areas with high risk, the safest course of action is to self-quarantine and work from home for a minimum of 2 weeks[4] and avoid direct contact with other workers [15]. 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 and use a face covering or mask when going out of the home. Wearing a surgical-type mask when ill may help to reduce the spread of the virus from the wearer's sneezes or coughs. It is also recommended that healthy individuals wear a face covering or mask when going out in the community, as there is evidence of COVID-19's SARS-CoV-2 virus spreading by asymptomatic and presymptomatic individuals [37, 38]. Any questions about potential COVID-19 infections should be directed to the local health department, which (provided they are not overwhelmed) 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.

Employees in contact with someone exposed to COVID-19

Risk assessment includes whether the person was in close contact with someone exposed to the virus, the duration of that contact, whether they were using any personal protective equipment, and the type of personal protective equipment used (e.g., cloth face covering vs. respirator) [39]. 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, it may be most conservative to follow the same protocol as if the person was returning from an overseas country or an area with a high risk of infection.

One option is to consider having 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, and consistent mask-wearing instead of being quarantined for 14 days [40].

[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.

Guidance for Businesses

General Principles

- Work from home when feasible to help improve social distancing.
- Improve social distancing at work (e.g., increase distances between workers, install temporary barriers, use masks, institute another shift to reduce population densities, close cafeterias and offer individual prepackaged meals).
- 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, provide masks and gloves).
- Protect the vulnerable (older adults, those with underlying conditions resulting in immunocompromise, and pregnant women).
- Identify and remove newly infected persons.
- Keep employees and workplaces safe and sanitary.
- Have appropriate governance policies in place.

Recommended Planning

- Inform and seek authorization for your plan from your organization's leadership.
- Develop your plan in conjunction with occupational health and safety professionals, government regulations, and public health authorities.
- Sick employees (including those with minimal symptoms) should stay home.
- Eliminate all close contact with anyone with infectious symptoms [41]. If there is believed to be COVID-19's SARS-CoV-2 virus transmission in your area or someone has traveled to a region with potential infections, 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 [25].
- Stop all non-essential travel to any cities/countries with outbreaks or community spread in progress (see map to help with other risk considerations: https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6) [42]. Companies should assess their risk tolerance regarding cessation of all non-essential travel; this is especially true for travel either to, or through, any country/region/city reporting cases.
- 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.
- Train staff on how to disinfect workplaces and provide them with personal protective equipment (PPE). Appropriate PPE for cleaning an office contaminated by the virus typically is thought to include an N95 mask or other device to sufficiently filter the virus.
- Clean commonly touched worksite surfaces frequently (e.g., hourly), including machine controls, door handles, bathroom doors, faucet handles, lunch tabletops, etc. Consider propping open bathroom and other doors to reduce handling. Avoid shared equipment

when possible (e.g., keyboards), and clean common surfaces between shifts or between worker usage.

- Clean surfaces with an EPA-approved agent that kills viruses (e.g., 62-71% ethanol, 0.5% hydrogen peroxide, 0.1% sodium hypochlorite) for at least 1 minute [13]. It is important to allow sufficient time for sanitizing agents to work, and directions should be carefully followed.
- Encourage frequent handwashing [43].
- 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) [44].
- 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 [45]. 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. 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.
- 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.
- Return-to-work guidelines vary widely and are changing quickly. Some changes have been necessitated to ensure enough workers are available to perform critical functions. CDC has advised that essential service workers (e.g., healthcare providers, power plant workers) can return to work after a positive or presumed positive COVID-19 diagnosis with the following stipulations:
    - at least 7 days have passed from the onset of symptoms;
    - there have been 3 days without fever; and
    - respiratory symptoms have improved (but they do not need to have resolved).
- Emphasis should be placed on mitigating employees being at work during peak viral shedding, but then safely cycling back to the job as soon as feasible.
- Report any suspected case to the local health department.
- If there is a confirmed case in your workplace, attempt to maintain confidentiality but identify the most common contacts with that person. Using business risk tolerance procedures, identify whether any further action(s) are required other than increased monitoring (see above).
- When antibody testing becomes available, assess the antibody status of critical and susceptible populations (under medical direction to ensure proper implementation,

interpretation, and management). These populations include employees on oil drilling platforms, commercial maritime, 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.

More details regarding business concerns are available from the CDC [46].

Disability and Return-to-Work Considerations

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

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 [47, 48]. 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 [49]. Lung diffusion abnormalities can take up to 5 years to resolve in ARDS cases [49, 50]. 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 [48-52]. 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 [48, 51, 53, 54]. Cardiac problems are common with COVID-19, with cardiomyopathy, arrhythmia, and direct cardiac muscle injury affecting approximately 30%, 20%, and 10% of patients, respectively [55].

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. [48-52]. The potential for a minority of patients to be permanently totally impaired cannot be excluded [52].

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 [56] and 6th Edition [57].

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 [23, 24, 58]:

- Lymphopenia (a fairly unique and characteristic finding)
- Elevated liver enzymes
- Elevated lactate dehydrogenase (LDH)
- 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 creatinine
- Elevated blood urea nitrogen
- Hypoxemia

Diagnostic Testing

COVID-19 diagnostic testing has centered around polymerase chain reaction (PCR)-based techniques to identify the virus from nasopharyngeal and/or oropharyngeal swabs [59]. Antibody testing is under development and in early deployment. 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 [60, 61]:

- 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 [62].

These samples and techniques are based on PCR techniques, which may or may not reflect active virus shedding. These tests indicate the RNA debris of coronavirus and reflect non-viable virus remnants.

Importantly, the risks of false-negative and false-positive test results change as an epidemic progresses. For example, as an epidemic progresses and disease becomes more common, individuals who present with symptoms are increasingly most likely to represent false negatives. Thus, once an epidemic disease becomes pervasive, 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.

It is anticipated that immune status testing (IgG, IgM) will eventually be the most important test for both short-term diagnostic confirmation and longer-term assessment of population-based risk assessments, such as herd immunity. Theoretically, this testing may also help designate workers who may more safely interact with the public. 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 [63, 64]. Once these problems are addressed, it is anticipated that antibody testing will become widespread if not universal in many workplaces and other populations of concern (e.g., nursing homes).

Immune status 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).

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 [23, 65]. 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 [65].

Computerized tomograms are commonly performed [66, 67] and show patchy infiltrates and ground glass opacities [68-72]. 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 [24].

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. The U.S. Food and Drug Administration (FDA) has provided emergency approval for the use of both chloroquine and hydroxychloroquine [73], which have shown some evidence of efficacy against COVID-19 and are being investigated as possible treatments [74-96]. The FDA has also 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 [97]. No other medications are currently approved for the treatment of COVID-19, although other anti-viral drugs are also under investigation (e.g., remdesivir, lopinavir, ritonavir). A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19 did not improve outcomes [98]. The FDA has provided unprecedented flexibility to accelerate the development of new drugs and testing [99].

If individuals develop more severe symptoms or have complications (e.g., ARDS or respiratory failure), they are primarily treated with anti-cytokine storm agents, mechanical ventilation (including prone ventilation), other respiratory support measures, and DVT prophylaxis [100]. Evaluations should include exclusion of other causes (e.g., influenza). The use of glucocorticosteroids is controversial and is generally not advised without other indications [101]. Although multiple agents addressing the cytokine storm are under investigation, most of the publications are centered around interleukin-6 (IL-6). Genentech has FDA approval for a randomized, double-blind, placebo-controlled phase 3 trial of Actemra (tocilizumab, a humanized IL-6 receptor antagonist) in collaboration with the US Biomedical Advanced Research and Development Authority (BARDA). Actemra will be given intravenously plus standard of care in hospitalized adults with severe COVID-19 pneumonia, compared to placebo plus standard of care, with primary and secondary endpoints of clinical status, mortality, mechanical ventilation, and intensive care unit (ICU) variables. 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 [102]. Both 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 [95], although they are typically prescribed when at least some viral replication is still ongoing.

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

1. Hydroxychloroquine or chloroquine (HCQ/CQ)
2. HCQ/CQ plus azithromycin
3. Other anti-viral medication, including pharmaceuticals (e.g., lopinavir, remdesivir, ritonavir)

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

1. Oxygen supplementation
2. Prone positioning (due to shunting)
3. Interleukin-6 inhibition
4. Mechanical ventilation, prone
5. Extracorporeal membrane oxygenation (ECMO)

Because 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), the prevention of severe outcomes should be the primary treatment emphasis [103, 104].

Currently, there is no vaccine for COVID-19 [41]. Vaccine development has begun, but the World Health Organization has estimated it will require 12-18+ months.

Hydroxychloroquine for Treatment of COVID-19

Recommended.

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

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

Indications:	Moderate to severely affected patients with COVID-19. For severely affected patients, azithromycin may be added [77]; however, electrocardiogram monitoring (ECG) is advised when adjunctive therapy with agents prolonging the QT interval is considered (see Harms). The FDA advises against outpatient use due to cardiac concerns. 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 [95]. Use in mild cases could be justified, especially if administered early in the course for a patient with multiple co-morbidities (e.g., pre-diabetes, diabetes, cardiovascular disease, COPD). However, without a sound rationale and when the medication is effectively rationed, use in mild cases appears difficult to support.
Benefits:	Reduced need for a ventilator or ICU stay. Earlier clearance of pneumonia on CT scan [95].
Harms:	Negligible for most patients undergoing short-course use. One RCT reported one patient with rash and one patient with headache, the latter of which is a common symptom of the infection [95]. There are concerns about the potential for prolonged corrected QT intervals, and thus arrhythmias [105, 106]. ECG monitoring is particularly indicated for patients 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 azithromycin. Renal insufficiency also may increase toxicity risks.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect, prolongation of QT interval.
Frequency/Dose/Duration:	Multiple regimens have been used. There is a mechanistic rationale for the concomitant use of zinc to inhibit viral replication. The following are common regimens, the first of which was used in the one quality RCT: • Hydroxychloroquine 200mg BID x 5 days [95] • Hydroxychloroquine 200mg TID x 10 days [77] • Hydroxychloroquine 200mg TID x 10 days plus azithromycin 500mg x 1 day then 250mg QD x 4 days [77] • Hydroxychloroquine 400mg BID x 1 day, then 200mg BID for 4 days [76]. • Hydroxychloroquine 400mg BID x 1 day, then 400mg QD for 4 day. • Hydroxychloroquine 600mg BID x 1 day, then 400mg QD for 4 day.

Because the half-life of these medications is long, a loading dose for the first day or two may be preferable. Concomitant treatment with azithromycin for more severe cases has been reported in non-randomized studies as showing efficacy [77] [107].

Rationale:

One moderate-quality RCT showed reduced pneumonia on CT scan compared with placebo [95]. Another nonrandomized trial also showed efficacy for hydroxychloroquine, as well as suggesting synergy with azithromycin [77]; these authors reported similar results in a subsequent, larger case series of 80 cases [107]. One moderate-quality study found minimally faster improvements in symptoms, lymphopenia, and C-reactive protein; however, the average administration began at 16–17 days in the treatment course, which was likely after viral replication had largely ceased. Thus, the primary outcome of viral clearance rate did not exceed that of standard care [108]. There are many in vitro studies suggesting antiviral activity [75, 76, 82, 86, 88, 96, 109-111]. 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 human trials; such studies have sometimes failed to support treatment in human trials for other diseases [112, 113]. Because there is quality evidence for the efficacy of chloroquines (especially hydroxychloroquine) for the treatment of COVID-19, the medications are low cost, and adverse effects are minor for short courses of treatment, these medications are recommended. Based on the available limited evidence, earlier treatment appears to be important for efficacy compared with treatment in an ICU.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits 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 0 articles in PubMed, 55 in Scopus, 0 in CINAHL, 1 in Cochrane Library, 1175 in Google Scholar, and 4 from other sources[†]. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 4 from other sources. Of the 8 articles considered for inclusion, 4 randomized trials, 1 non-randomized trial, 2 case series and 1 systematic review met the inclusion 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

Recommended.

Chloroquine is recommended for the treatment of selected patients with COVID-19, primarily based on the evidence for hydroxychloroquine.

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

Indications:	This recommendation is primarily based on the evidence for hydroxychloroquine. Moderate to severely affected patients with COVID-19. For severely affected patients, azithromycin may be added [77], but ECG monitoring should be particularly considered when adjunctive therapy with agents prolonging the QT interval is considered (see Harms). The FDA advises against outpatient use due to cardiac concerns. 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 [95]. Use in mild cases could be justified, especially if administered early in the course for a patient with multiple co-morbidities (e.g., pre-diabetes, diabetes, cardiovascular disease, COPD). However, without a sound rationale and when the medication is effectively rationed, use in mild cases appears difficult to support.
Benefits:	Reduced need for a ventilator or ICU stay. Earlier clearance of pneumonia on CT scan [95].
Harms:	Negligible for most patients undergoing short-course use. One RCT reported one patient with rash and one patient with headache, the latter of which is a common symptom of the infection [95]. There are concerns about the potential for prolonged corrected QT intervals, and thus arrhythmias. ECG monitoring is particularly indicated in those 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 azithromycin. Renal insufficiency also may increase toxicity risks.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect, prolongation of QT interval.
Frequency/Dose/Duration:	Multiple regimens have been used. There is a mechanistic rationale for the concomitant use of zinc to inhibit viral replication. The following are common regimens, mostly from various national guidelines: • Chloroquine phosphate 500mg BID x 5 days • Chloroquine 600mg QD at diagnosis, then 300mg in 12 hours, then 300mg BID for 5 days • Chloroquine 600mg QD x 1 day, then 300mg BID for 5 days Because the half-life of these medications is long, a loading dose for the first day or two may be preferable. Concomitant treatment with azithromycin for more severe cases has been reported in non-randomized studies using hydroxychloroquine as showing efficacy [77] [107].

Rationale:

There are no quality studies of chloroquine. One moderate-quality RCT of hydroxychloroquine showed reduced pneumonia on CT scan compared with placebo [95]. Another nonrandomized trial also showed efficacy for hydroxychloroquine, as well as suggesting synergy with azithromycin [77]; these authors reported similar results in a subsequent, larger case series of 80 cases [107]. 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 [88]. There are many in vitro studies suggesting antiviral activity, which is similar to hydroxychloroquine [76], thus producing comparable rationale [75, 76, 81, 82, 88, 110, 111]. 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 human trials; such studies have sometimes failed to support treatment in human trials for other diseases [112, 113]. Because there is quality evidence for the efficacy of chloroquines (especially hydroxychloroquine) for the treatment of COVID-19, the medications are low cost, and adverse effects are minor for short courses of treatment, these medications are recommended. Based on the available limited evidence, earlier treatment appears to be important for efficacy compared with treatment in an ICU.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits 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 0 articles in PubMed, 55 in Scopus, 0 in CINAHL, 1 in Cochrane Library, 1175 in Google Scholar, and 4 from other sources[†]. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 4 from other sources. Of the 8 articles considered for inclusion, 4 randomized trials, 1 non-randomized trial, 2 case series and 1 systematic review met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits 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 49 articles in PubMed, 177 in Scopus, 0 in CINAHL, 1 in Cochrane Library, 4,042 in Google Scholar, and 2 from other sources[†]. We considered for inclusion 4 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 2 from other sources. Of the 8 articles considered for inclusion, 0 randomized

trials, 5 in vitro studies, and 1 systematic review met the inclusion 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 widespread prophylaxis against COVID-19.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – **Low**

Rationale: There are no quality trials reported, although several are underway. There is rationale that prophylactic use may have short-term efficacy based on suggestive evidence of prophylactic effects in vitro studies [76]. 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, current prophylactic use may make some sense, such as in a nursing home where the virus is circulating or in selected healthcare workers with particularly high risks. 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.

Evidence for the Use of Hydroxychloroquine and Chloroquine

Tang 2020 (score=7.0) [108]

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 200 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, possiblyl through anti-inflammatory effects."
Comments:	Open-label, 16–17 days after onset, likely after most or all of the viral replication stage. 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, but stopped prematurely) [114]

Category:	Hydroxychloroquine
Study Type:	RCT
Conflict of Interest:	Sponsored by the Government of the Amazonas State, Farmanguinhos (Fiocruz), SUFRAMA, CAPES, FAPEAM, and federal funds granted by a coalition of Brazilian senators. Members of a data and safety monitoring board were included as authors.
Sample Size:	N = 81 hospitalized patients with COVID-19 infection, respiratory rate higher than 24 rpm, heart rate higher than 125 bpm (with no fever), peripheral oxygen saturation lower than 90% in ambient air, and/or mean arterial pressure lower than 65 mmHg
Age/Sex:	Mean age: 51.1 years; 61 males, 20 females
Comparison:	High dose of chloroquine (CQ): 600 mg twice daily for 10 days, 12 g total (n=41) vs. Low dose CQ: 450 mg for 5 days, twice daily only on first day, 2.7 g total (n=40). Both groups could receive treatment with orally or via nasogastric tubes
Follow-up:	Follow-up at day 13
Results:	The higher-dosage CQ group presented more QTc>500 ms (18.9%) compared to the lower-dosage group. The higher-dosage group also had a trend towards higher lethality (39%). The fatality rate until day 13 (27%, 95% CI [17.9-38.2%]) was similar to historical data from similar patients not using CQ (95% CI [14.5-19.2%])
Conclusion:	"In conclusion, high CQ dosage scheme (12g), given for 10 days, was not sufficiently safe to warrant continuation of that particular study arm. We therefore strongly recommend that this dosage is no longer used anywhere for the treatment of severe COVID-19, especially because in the real world older patients using cardiotoxic drugs should be the rule."
Comments:	The trial was stopped due to cardiovascular risks. 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) [80]

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 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:	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%).

Gautret 2020 (score=NA) [77]

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.

Chen J 2020 (score=NA) [95]

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) [115, 116]

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 contagiosity in most cases."

Comments: Abstract and results table only.

Gautret 2020 (score=NA) [107]

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) [106]

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.

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 [117-120].

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

Indications:	Adjunctive use with hydroxychloroquine in severely affected patients with COVID-19. For severely affected patients, azithromycin may be added [77], 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 [95].
Benefits:	Theoretical reduced need for a ventilator or ICU stay.
Harms:	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.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect, prolongation of QT interval.
Frequency/Dose/Duration:	The regimen used for treatment of COVID is azithromycin 500mg on day 1 and then 250 mg/day for 4 days [77, 107].
Rationale:	There are no quality studies of azithromycin. One nonrandomized trial suggested improved efficacy when hydroxychloroquine was combined with azithromycin [77]; these authors reported similar results in a subsequent, larger case series of 80 cases [107]. There is low-quality evidence for adjunctive use of azithromycin but almost no other anti-viral 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.

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. There is one non-randomized controlled trial suggesting acceleration of viral clearance compared with lopinavir/ritonavir [121]. Although there is no quality evidence of efficacy, this non-randomized trial suggests efficacy and thus this medication may be helpful in the treatment of patients with COVID-19.

Evidence for the Use of Favipiravir

Cai 2020 (score=N/A) [86]

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

Not Recommended.

Lopinavir/ritonavir is not recommended for the treatment of COVID-19.

Strength of Evidence – **Not Recommended, Evidence (C)**
Level of Confidence – **Low**

Rationale: Lopinavir/ritonavir are anti-retroviral protease inhibitors that have been used to treat HIV and have been trialed in one open-label RCT, which showed a lack of efficacy compared with standard care [98]. This RCT treated severe patients; thus, it is unclear if the medications 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 [121]. However, because there are other medications with evidence of efficacy, lopinavir/ritonavir are not recommended for the treatment of COVID-19 patients.

Evidence for the Use of Lopinavir/Ritonavir

Cao 2020 (score=7.5) [77]

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.

Remdesivir for the Treatment of COVID-19

Recommended.

Remdesivir is selectively recommended for treatment of COVID-19. Further investigation is needed with reporting from the compassionate use and randomized trials for the treatment of COVID-19.

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

Indications:	Severe COVID-19 patients, with <94% O_2 saturation or need for O_2 supplementation; creatinine clearance >30 mL/min; ALT and AST <5 times upper limit of normal.
Benefits:	Possible improved survival.
Harms:	Increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effect.
Frequency/Dose/Duration:	Remdesivir 200mg IV on day 1, then 100mg QD for 9 additional days. [122].
Rationale:	There are no quality studies of remdesivir. There is one case series suggesting a fairly low death rate (13%) [122]. This medication is being used for the treatment of COVID-19 through RCTs and for compassionate use. There is evidence that remdesivir inhibits viral replication in vitro studies [86]. It is possible that remdesivir is more effective if administered in the viral replication stage. Nevertheless, select use of remdesivir is recommended in severely affected patients.

Evidence for the Use of Remdesivir

Grein 2020 (score=NA) [122]

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 and Sarilumab) for the Treatment of COVID-19

Recommended.

Interleukin-6 inhibitors are recommended for the treatment of selected patients with COVID-19.

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

Indications:	Severely affected patients with COVID-19 with cytokine storm manifestations, including ARDS, were assessed in a retrospective case series [123]. Patients had respiratory failure, shock, and/or other organ failure [123].
Benefits:	Improved oxygenation, reduced temperature, and reduced CRP [123]. Data also suggest improved survival because the hospital discharge rate of 90% was significantly above expectations.
Harms:	Potential infection risks.
Indications for Discontinuation:	Completion of a course, intolerance, adverse effects.
Frequency/Dose/Duration:	Tocilizumab 400mg IV. A small minority received a second treatment.
Rationale:	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, especially tocilizumab, are recommended.

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

Xu 2020 (score=N/A) [87]

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
Results:	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.
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 [124]. 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, O_2 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 [97].
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 [125, 126], although many trials are underway [127]. However, they were reportedly successful in one case series [128] and have been successfully used for other diagnoses, including Ebola [127, 129]. 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.

Glucocorticosteroids for the Treatment of COVID-19

Not Recommended.

Glucocorticosteroids are not recommended for the treatment of COVID-19 [130-132]. There are other indications for use that may occur in the context of treatment of COVID-19 (e.g., asthma, COPD).

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – **Low**

Rationale:	There are no quality trials of glucocorticosteroids for the treatment of COVID-19. Glucocorticosteroids have moderate adverse effects, may increase the risk of other infections in hospitalized patients, and are thus not indicated.

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