

Coronavirus (COVID-19)

Last Updated: March 29, 2021

Prior versions: April 8, 2020; April 24, 2020; May 8, 2020; June 12, 2020; June 17, 2020; August 19, 2020; December 14, 2020.

The March 29, 2021 update includes the following major changes:

- New guidance on rehabilitation (pulmonary, cardiac, cognitive, musculoskeletal, debility) for severe and/or chronic COVID-19 cases
- Vaccination information, including travel advice for vaccinated individuals, success against common virus variants, and adverse effects
- New recommendation on the Johnson & Johnson COVID-19 vaccine
- Upgraded recommendation for baricitinib from insufficient evidence (I) to evidence (B)
- Upgraded recommendation for bamlanivimab from insufficient evidence (I) to evidence
- Upgraded recommendation for interferon beta-1b from insufficient evidence (I) to evidence (B)
- Upgraded recommendation for low-molecular-weight heparin from insufficient evidence (I) to evidence (C)
- Downgraded recommendation for convalescent antibodies to No Recommendation (I)
- Review of evidence for ivermectin (insufficient evidence, with no recommendation)
- Review of masking efficacy
- Updates from the CDC on physical distance in K-12 classrooms

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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.

Α	Strong evidence-base: Two or more high-quality studies.*		
В	Moderate evidence-base : At least one high-quality study or multiple moderate-quality studies [†] relevant to the topic and the working population.		
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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.[‡] Each criterion receives a score of 0, 0.5, or 1. See <u>Table B in the Methodology</u> 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://www.mdguidelines.com/wp-content/uploads/2019/08/Methodology-2017-Update.pdf for our full methodology.

^{*} 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.

[†] 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.

[‡] 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 **March 29, 2021.**

This guideline has previously undergone extensive peer reviews. However, the total depth and breadth of quality literature for the treatment of COVID-19, although growing, remains fairly 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, continue to be published prior to peer review. Some vaccination phase 3 trials have not been published; thus, reliance for those is necessarily on press releases and other non-peer-reviewed sources. 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 publication of randomized controlled trial data and/or 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 variously named "coronavirus disease 2019" (abbreviated "COVID-19") [1].

The pandemic began in Wuhan, China in November 2019, then expanded markedly throughout the Wuhan region. Based on prior research and experience with coronavirus infections, the origin of this pandemic is thought to be traced to bats near Wuhan, China; speculation is that pangolins may have been an intermediate species between bats and humans [2, 3]. COVID-19's SARS-CoV-2 virus can now be found in humans on all continents around the world [4, 5]. There is indirect and strongly disputed evidence suggesting that the epidemic may have begun earlier than November, including increased hospital traffic, web searches for potential COVID-related symptoms in Wuhan beginning in August 2019, and other information that suggested a potential laboratory shutdown in October 2019 [6-10]. Regardless, the Chinese New Year likely accelerated the spread of the virus through global travel and hastened the development of a pandemic.

Quarantines were implemented early in pandemic. However, they were likely ineffective at preventing the pandemic [11] for several reasons, including delayed global implementation of quarantining, travel bans, droplet/aerosol precautions, and other public health measures; early emphasis on contact instead of respiratory spread; the number of undiagnosed, mild, or asymptomatic patients spreading the virus [12, 13]; and the spread of cases in a region prior to the recognition of COVID-19 within that area [14]. An added complication in preventing the elimination of the virus from the global human population is the susceptibility of animals,

although the importance of this potential factor is still poorly documented; it is not believed to be a significant contributor to the pandemic spread beyond China.

Public health management of this pandemic has varied across countries, states, and jurisdictions. Because there was no quality evidence to support any of these measures early in the pandemic, expert opinion was used for their implementation. The initial guidance focused on handwashing and restricting travel to China (January 2020, which subsequently expanded to include other countries), varying degrees of closure for businesses and schools (March 2020), recommendations for personal masking (March-April 2020), and public masking orders (April-July 2020). Some states began to reopen most, if not all businesses, starting in May-June 2020. Typically, a combination of approaches has been used, including the quarantine of affected individuals, contact tracing, isolation, stay-at-home orders, physical distancing, mask use, and the closure of non-essential businesses [15].

The pandemic subsided markedly in the summer of 2020 in northern latitudes. However, as fall/winter 2020–21 began, the pandemic predictably surged in northern, cold climates where conditions of lower temperatures, lower humidity, less intense ultraviolet (UV) irradiation, and higher indoor population densities combined to cause record levels of cases in nearly all jurisdictions [16-18]. Additionally, controversy regarding the efficacy and sustainability of various public health measures, especially the (re)closure of businesses and schools, has intensified as the case rates plummeted in 2021. Quality data are weak; some countries (e.g., Japan, South Korea) have instituted less stringent measures with seemingly somewhat comparable or better results [19-29]. Worldwide, the pandemic continues to provide numerous challenges, especially in countries with lagging immunization rates, including surges, hotspot outbreaks, 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; resurgences of cases with loosening of restrictions; and increasing business/economic concerns.

Termination of the COVID-19 pandemic (or at least this phase of it) is now in sight in the United States. Termination is primarily credited to the rapidly increasing rates of vaccination, residual immunity due to prior infections in the population, and falling infection rates. Attention is now turning to issues such as vaccine hesitancy, whether to immunize children, the duration of vaccine-related immunity, and virus variants.

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 [30, 31]. When a virus mutates or changes, studies must be performed to determine the new strain's virulence (i.e., its ability to infect humans).

Virus Characteristics

Contagiousness

COVID-19's SARS-CoV-2 virus appears to be more contagious than the prior coronaviruses. Initially, the virus was thought to be primarily spread through direct contact. That belief has changed markedly and the virus is now thought to be spread by respiratory droplets (defined as >100 µm in size), with weaker but increasing evidence for microdroplets/aerosols (defined as <0.5 µm), and less so via direct hand-to-mucous membrane contact. Consensus now is that droplets are the primary method of spread [32]. Although respiratory aerosol spread was initially controversial, a committee of the National Academy of Sciences and others found limited evidence that the virus is also spread by respiratory aerosols [33-41]; other evidence of at least some spread by aerosols is rapidly accruing [42]. Currently, droplet spread continues to be viewed as the major mode of transmission [38, 41, 43-51]. 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 [51]. Whether, and to what extent, an infectious dose can be generated and present beyond 6-foot distances has yet to be clearly demonstrated [52-58].

The contagiousness and virulence of the SARS-CoV-2 virus appear 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 [59], which is far higher than typical influenza transmission rate of ~1.3 [60]. While the prior Centers for Disease Control and Prevention (CDC) estimate for the United States was 2.5 [13], recent estimates for the 50 US states range from 0.91 to 1.54 [61]. From a population standpoint, however, each case does not appear to be equally infectious. One analysis of 1,038 confirmed SARS CoV-2 infections in Hong Kong between January and April 2020 revealed that 80% of the infections were caused by just 19% of the initial cases; the majority of patients failed to infect anyone else. Most transmission occurred from household contacts, followed closely by external social events [62]. Beyond the transmission rates, the CDC previously estimated that >10 times more cases are missed than are recorded based on seroprevalence studies [63], suggesting a far higher degree of contagiousness; this underestimate may be even greater depending on the rate of false-negative results from seroprevalence tests. Serial seroprevalence studies across all states have shown evidence of prior infection ranging from 1% to 23% [64]. The most recent CDC estimates from February-December 2020 indicate that only 52.6% of hospitalized cases, 23.8% of symptomatic cases, and 21.7% of all COVID-19 infections are reported [65], in which case there have been 83.1 million total infections. Estimates for reaching herd immunity may have large degrees of error if they do not incorporate these underestimates of infections.

More precise estimates of transmission rates will become known with time, particularly as testing rates escalate, although false-negative rates are reportedly 20-67% [32]. Collectively, although global next-generation sequencing results indicate that SARS-CoV-2 genomes are relatively stable (mutating on average 2 times per month), dynamic mutations can be selected in symptomatic individuals [66]. There have been 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) [67].

It is now estimated that 40–45% of infections develop due to exposure to asymptomatic or presymptomatic cases [68]. Yet, the proportion who remain persistently asymptomatic is unclear [69-88]. Among 59,073 contacts of 5,706 COVID-19 index patients, 11.8% had COVID-19 compared with 1.9% of non-household contacts [89], showing the importance of close contacts. The viral load needed to infect a contact remains unclear.

The virus's survivability on surfaces varies depending on the material; it has been estimated with experimental methods to survive up to 9 days [90], although those experimental methods are limited by not including environmental settling rates, inactivation by UV light, or diffusion. Furthermore, a thin nanofilm of liquid from droplets has been reported to extend the viral survival on surfaces [91]. The total viable viral counts decline with time [51]. 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 [90]. Survival on human skin has been measured at 9.04 hours, which is much longer than the measured survival of influenza virus on skin (1.82 hours) [92]. 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. Many studies show detection of viral RNA that is likely inadequate for and/or incapable of transmitting an infection.

Preliminary experimental and epidemiological-ecological data suggest spread may be optimal in indoor and/or cooler climate conditions [16, 93-96], and prior data on the SARS coronavirus are corroborative [97]. 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 [98]. The ecological data indicate that there were slower rates of infection with higher temperatures in Delhi, India, and Pakistan [16, 96], although there was no correlation with humidity [16]. The data from Pakistan also suggest an inverse relationship between COVID infection rates and UV light, although the UV data appear to be highly correlated with the heat indices [96]. Other data suggest lower infections with higher humidity [18]. This suggests highly variable disease transmission risks based on seasonality and in indoor compared with outdoor environments. Taken together, these data were projected by this guideline in spring 2020 to project a surge in COVID cases in northern latitudes in fall 2020 [94]; further, it could be predicted that even in the absence of vaccination, the pandemic would taper down by summer 2021. Similarly, disease surges in Florida and Texas in August 2020 are explicable by these conditions, avoidance of time in the humid outdoors, and the use of air conditioning. Less dramatic epidemic surges were predicted to occur during winter 2020-21 in the deep South, assuming that the viral epidemic did not tail off and/or sufficient numbers of individuals did not become immune (i.e., herd immunity) through infection or vaccination 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 5–6 days [13, 99, 100], with 97.5% of cases occurring by 11.5 days after exposure and infrequent cases of up to 14 days [5, 32, 101]. The time between symptom onset in an individual and symptom onset in a second person infected by that individual also averages 6 days [13]. Viral shedding may antedate symptoms by 1–2 days, and viral titers are highest in the earliest phases of infection.

The duration of infectious viral shedding is controversial, primarily due to the ability to measure virus and/or virus particles in body fluids for long periods after the acute infection with sensitive techniques, such as polymerase chain reaction (PCR) [102, 103]. Yet, it is less clear whether these particles are infectious, and there are far fewer studies of viral shedding that relied on viral culture suggesting active virus. Even those few studies with viral culture results may not yield enough virus particles that are sufficient to provide an infectious dose [103].

A pooled study of 79 studies with 1,858 patients reported that pharyngeal virus shedding peaks prior to the onset of symptoms, averages 17 days, and lasts up to 83 days [104, 105]. The mean durations of viral shedding were 14 days in the lower respiratory tract, 16 days in stool, and 16 days in serum. Although replication-competent virus has not been isolated 3 weeks after symptom onset, recovered patients can continue to have SARS-CoV-2 RNA detected in their upper respiratory specimens for up to 12 weeks [106-108]. Further study of 285 "persistently positive" persons, which included 126 persons who had developed recurrent symptoms, found no secondary infections among 790 contacts attributable to contact with these case patients. Efforts to isolate replication-competent virus from 108 of these case patients were unsuccessful, suggesting a lack of viable virus [106]. No study detected live virus beyond the ninth day [104]. These findings contrast with those of MERS and SARS, which peaked after symptom onset and lasted for shorter durations.

There are some case reports of re-infections [109-111], which include a few cases with a different genomic COVID-19 strain [112-114]. However, whether these cases represent true reinfection or reactivation is unclear [109, 115, 116]. In a few cases, the purported second apparent infection was more severe [117]; in others, it was less severe or even asymptomatic [118].

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 [13]:

- 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 <u>Treatment section</u> 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 [32, 119-122]:

- Fever (low or high grade; 80–88%)
- Dry cough (63–69%) [5, 123]
- Loss of appetite (39–84%) [124]
- 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%) [124]
- Nasal congestion (4–5%)
- Abdominal pain (4%)
- Conjunctivitis (pink eye; 1%) [125]
- Hemoptysis (1%)
- Rhinorrhea (runny nose)
- Anosmia and dysgeusia (loss of smell and taste; 85% moderate/severe or anosmic)
 [126]

Severity of disease may be related to the inoculation dose [127]. The wearing of masks has been theorized to increase the proportion of asymptomatic cases by lowering that inoculation dose [127, 128].

Cardiovascular symptoms and signs may also be noted on initial presentation [129-134]. Immunothrombotic dysregulation associated with COVID-19 pneumonia has been described [135]. Coagulopathy associated with antiphospholipid antibodies and multiple infarcts have been reported [136, 137]. Seizures have been reported as a presenting disorder [138]. Young and old patients have presented with large-vessel strokes as an initial manifestation of COVID-19 infection [138, 139]. Among ICU patients, 31–59% of patients incurred venous or arterial thromboembolic event(s) [140, 141], compared with 10–25% of patients hospitalized for other

reasons [141, 142]. Recovering competitive athletes also have been found to have cardiac abnormalities on magnetic resonance imaging (MRI) [143].

Dermatological abnormalities such as urticaria, vasculitides, and pityriasis rosea have been described [144-147]. The most common dermatological presentations have been polymorphic and erythematous, chilblain-like, and urticarial lesions [148]. Various neurological and psychiatric presentations including stroke-like symptoms, altered mental status, dementia-like syndromes, and new or recurrent affective disorders have been reported [149-156]. Although 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 [157]. Acute kidney injury is thought to be triggered by a 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 [158], along with the isolation of viral RNA from urine [159]. Most (71%) of those who die from COVID-19 have findings consistent with disseminated intravascular coagulation [160].

Because the symptoms for most patients are typical of nonspecific respiratory tract infections, they can be difficult to distinguish from other diseases [161, 162]. 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 [163]. This appears to be most common at days 4–7 after symptom onset. 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 hallmarks of COVID-19 infection on thoracic imaging have been bilateral and peripheral ground-glass and consolidative pulmonary opacities [164].

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 [12, 163, 165]. The CDC estimates that 40–45% of transmission occurs prior to symptom onset and that the infectiousness is comparable between asymptomatic and symptomatic individuals [12, 13]. Children tend to be asymptomatic or have milder symptoms, which suggests a mechanism that may accelerate disease transmission throughout the population [163], although this is not proven. It is also possible that the immune system of most children effectively detects the virus with resultant lower average viral loads and thus contagion; however, nasopharyngeal viral loads are not well correlated, whereas saliva viral loads have been correlated with severity [166, 167]. Regardless, one-third of hospitalized children require ICU stays [168]. A pediatric multisystem inflammatory syndrome also has been reported in children who presented with persistent fever and features of Kawasaki disease or toxic shock. 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 [169].

Mortality

The mortality rate for COVID-19 has changed considerably over the course of the epidemic, being much lower more recently [170]. The mortality of COVID-19 was estimated to be approximately 10-fold higher than that of typical seasonal influenza [171]. Subsequently, severity estimates have been reported as low enough to be comparable with prior influenza epidemics [87, 172-174], with a range of infection fatality rates of 0.03–0.5% and corrected rates of 0.02–0.4% [175]. More recently, the CDC estimated the overall *symptomatic* case fatality ratio is 0.004, or 1 in 250 [13]. Using the CDC estimate of 83.1 million infections and the overall COVID mortality of 503,587 [176], the overall case fatality rate over the duration of the pandemic in the United States would be approximately 1 in 165. Mortality can be predicted based on risk factors and clinical findings on presentation [177].

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 [13]. The mortality rate for males is 57–64% higher than that for females. Nursing home residence is a particularly potent fatality risk [178-182]. 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 [41, 183-188]; however, approximately 1% of fatalities occur in previously healthy patients [189]. Genetic susceptibility (i.e., 3p21.31 gene cluster) has been reported in a large genome-wide association study, along with a 45% increased risk among those with type A blood [190]. 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 airborne respiratory and secondarily on 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. Physical distancing methods
- 4. Personal protective equipment (e.g., respirators, masks, gloves, face shields)
- 5. Ventilation issues
- 6. Disinfection practices and contact spread measures
- 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. This is particularly true given that the current vaccination rates vary more than 100-fold

across the globe [191], and it can be anticipated that differences by northern/southern hemisphere and other environmental issues (i.e., heat, humidity, UV, use of air conditioning) will persist. McKinsey suggested risks for a given jurisdiction should be related to four metrics assessing the strength of test, trace, and quarantine efforts (adapted from [192]):

- 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*: It is recommended to check for current guidance from the Centers for Disease Control and Prevention.)

Employee Issues

COVID-19 Vaccination

Employers are recommended to strongly encourage vaccination of their entire workforce at the earliest date (see also <u>Vaccination recommendations</u>). The CDC has produced many publications to support these efforts [193, 194]. States are implementing markedly different vaccination prioritizations (e.g., CDC/ACIP prioritizations based on susceptibilities and select workforces [195] vs. age-based only) with different administration strategies (mass vaccination sites vs. pharmacy-based vs. healthcare-based vs. combinations), and at considerably different success rates (which range by more than 2-fold) [196]. Communication to employees regarding their eligibility is recommended. Encouraging household member vaccination also is recommended, as it helps protect the workforce. Other considerations include facilitation of vaccination appointments for workers (e.g., computers at the worksite to access scheduling platforms) and hosting on-site vaccination clinics.

Until there is evidence herd immunity has been achieved, the CDC recommends that masking be continued [197]. If there is a possible or confirmed COVID exposure to a fully vaccinated worker who is between 2 weeks after and not more than 90 days after their second immunization, quarantining is no longer required [198].

COVID-19 surveillance

Employers are recommended to have implemented a surveillance system that continues to include education and screening to avoid having workers with potential asymptomatic, 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 at least until herd immunity is largely achieved) include daily/periodic electronic questionnaires with or without temperature measurements. Electronic questionnaires are likely to be more effective than temperature measurements because 69% of seriously ill individuals are afebrile [199]; temperature measurements are also likely to miss all subclinical and many symptomatic cases [13]. 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. Testing daily or every few days has been increasingly used in some workplaces and among mission-critical workers. However, testing without experienced medical judgment is ill-advised because the false-negative rates are reportedly 20-67% [32]; thus, cases with high indices of clinical suspicion should typically be treated as presumptive cases [32]. 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 [200]. If there is believed to be SARS-CoV-2 virus transmission in the area (currently true of essentially all US urban and many rural areas, although the rates are now decreasing markedly), 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, and potentially severe, COVID-19 infection [163], 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 wear a mask in public settings.

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 including volunteers, 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 [201]. Current guidance includes the following [201, 202]:

- A symptom-based strategy should be used for PCR or antigen-confirmed symptomatic workers, who are recommended to be excluded from work until there has been at least 1 day since resolution of fever (without use of medication), other symptoms have improved, and at least 10 days since the symptoms first appeared.
 For those with severe illness and/or immunocompromised state, there should be at least 20 days since symptom onset, and consultation with an infectious disease expert is advised.
- A time-based strategy should be used for PCR- or antigen-confirmed but asymptomatic employees, who are recommended to be excluded from work for 10 days following the positive test result.
- A test-based strategy is no longer recommended as the basis of a return to the workplace, other than to discontinue isolation or other precautions earlier than would occur under the symptom-based strategy above. This strategy requires negative PCR or antigen tests on at least 2 consecutive respiratory specimens collected at least 24 hours apart.

Readers are advised to refer to current CDC guidance, as this changes frequently [203]. It is also advisable for a healthcare employer to consider factors including staffing needs, 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 [201, 202]. 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 in conjunction with local health department guidance, including isolating at home (if able). A symptom-based approach recommends recording temperatures twice daily until at least 24 hours have passed without fever or treatment with any fever-reducing medications. In order to leave isolation, it is advised that a minimum of 10 days have passed since the onset of symptoms, with then at least 1 day of no fever and improvement in other symptoms. A testing-based approach requires two negative PCR (or antigen) viral tests obtained at least 24 hours apart if there is a need for a shorter waiting time. Otherwise, testing to return to work is not recommended as viral particles (which may not be infectious) can persist for 90 days after acute infection. 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. Coordination with the local health department's contact tracing efforts is generally essential, and the employer is frequently able to augment and assist with those efforts.

Employees in contact with an infected coworker

If a fully vaccinated worker who is between 2 weeks after the second immunization and 90 days after immunization is exposed to a known/suspected case, quarantine is no longer advised by the CDC [198]. Otherwise, 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 for 15 cumulative minutes over 24 hours starting from 2 days before symptoms onset [204, 205]. 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) [206]. The employer should 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 higherrisk exposures with greater business considerations (e.g., mission-critical workers), the most conservative approach is to have employees who could be in the incubation stage selfquarantine and work from home for at least 10 days; they may then be released with monitoring of symptoms until day 14 after the possible exposure. If there is an absence of symptoms, another option is to quarantine for 7 days; with a negative test on day 5 or later, the person may be released on day 8 with ongoing monitoring until day 14 [207, 208]. The CDC has changed their quarantine recommendations for exposed but asymptomatic workers to 10 days, or 7 days with a negative PCR test after a minimum of 5 days.

In certain manpower shortage situations, medical centers, and critical services, COVID-19 exposed workers are being allowed to work while asymptomatic with self-surveillance for symptoms, physical distancing, disinfection of workspaces, and consistent mask-wearing instead of being quarantined [209]. This option is controversial and not without considerable risks because 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 [199, 210]:

- 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 immunemodulating medications; undergoing cancer treatment)
- Smoking, current or former
- Obesity, especially severe [183]
- Diabetes mellitus
- Chronic kidney disease, especially those undergoing dialysis
- Liver disease
- Hypertension
- Current cancer
- Neurological diseases, including stroke and dementia

Generally, the risks of severe illness associated with the above conditions are greater as the severity of the conditions increase. The presence of multiple conditions increases the risk of severe disease [211].

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 all, but especially high-risk, individuals behind barriers.
- Institute physical distancing [212].
- Reduce public-facing work.
- Use personal protective equipment (PPE) to protect from exposure.
- Use masks; evidence that masks prevent transmission is accruing [212-221].
 Randomized controlled trials have not shown differences between the effectiveness of masks and respirators for preventing influenza [222-225]; however, some studies have been critiqued for power and unclear effects of outside influenza vaccination. A longitudinal pre/post interventional study reported 67% lower COVID tests among healthcare workers after masking compared with before masking [226].
- Use respirators, especially for higher exposure risks and for those with higher risks of severe disease. Evidence has suggested a surgical mask is equally effective as an N95 respirator for prevention of influenza.
- Consider placing high-risk individuals closer to ventilation that provides fresh air.
- Regularly disinfect surfaces.

Some educational videos help to demonstrate significant reductions in droplets with the use of a mask [227]. Other training videos help illustrate potential transmission by contact spread and donning/doffing masks [228]. A recent study compared face mask efficacy for filtering expelled droplets during speech. A fitted N95 respirator was the most efficient, but 3-layer surgical masks, cotton-polypropylene-cotton 3-layer masks, 2-layer polypropylene apron masks, and 2-layer cotton pleated-style masks were nearly as effective at reducing relative droplet transmission through the mask [229]. A low-cost, low-tech method to assess facemask efficacy has been reported [229].

Travel Issues

Travel risks include those associated with travel to and from a site, as well as business conducted at those sites [230]. Risks differ considerably by mode of transportation, geographic locations, current state of the epidemic in any given locale, and vaccination rates. Businesses need to weigh the value of the travel against the risks associated with that travel.

Fully vaccinated employees may reasonably travel. For non-vaccinated employees, travel valuations should include costs associated with any potential illness and any post-trip quarantine period. Caution is advised for non-essential travel by non-vaccinated employees to locales with outbreaks or community spread in progress [230], which currently includes much of the United States (see map to help with other risk considerations: https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ec f6) [231]. International trips are currently significantly affected as many countries are limiting travel from countries with outbreaks, although this is anticipated to change rapidly with the acquisition of herd immunity. Air travel may be safer than some other forms of travel [232], although the primary risks of air travel are more likely to be exposure risks at the destination, which may be challenging to control in non-vaccinated individuals by methods other than masking. As risks are now subsiding, travel to lower-risk locales is increasingly acceptable, although the destination country or region may not permit visits from countries or regions with high rates of viral transmission and/or may be slow to adapt to the rapidly changing risks. Mask or respirator use during air travel is advised, at least until herd immunity and lack of high community spread has been shown.

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

For non-vaccinated employees returning from personal or work-related travel to areas with community-based COVID-19 spread, the safest course of action is to self-quarantine while working from home for 2 weeks§ and avoiding direct contact with other workers [101], especially for travel from 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, wear a mask in public, and/or when needed, to be given an appropriate type of mask before entering the building). The person should also avoid all contact with other people.

Physical Distancing Methods

Physical distancing is believed to be one of the most effective control measures, particularly because it does not rely on training and compliance (e.g., as effective masking requires) [233]. The following are some physical distancing options to consider, especially for non-vaccinated personnel when there is ongoing community spread:

- Work from home when feasible to help improve physical distancing.
- Consider rotating workers between home and work settings to reduce workplace population densities while facilitating functions that are best performed at work.
- Improve physical distancing at work (e.g., increase distances between workers and workstations to a minimum of 6 feet, install temporary barriers, mark 6-foot distances on the floor between co-workers).

[§] 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.

- Consider either physical spacing in cafeterias, closing cafeterias and offering individual prepackaged meals, using disposable packaging and utensils to avoid the potential for contamination before cleaning, and/or having workers eat their own food at their workstations.
- Where there are two options for walking through a workplace, set up one-way walkways.
- Reorganize shifts to spatially and temporally spread workers.
- Route shifts of workers to enter through one entrance and exit through a different one.
- Provide protection for those who interact with the general public (e.g., install temporary barriers to prevent respiratory transmission, install barriers to ensure physical distancing of 6+ feet).
- Consider discouraging carpooling and mass transit; encourage the use of masks if using
 either of those options (although a face mask in public places is now a requirement in
 many cities and states).
- 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 (respirators, masks, gloves, and eye protection/face shields [212, 234-238]) have been recommended to be used until there is further evidence that herd immunity has been achieved, but they are lower on the list of controls. Detailed tables are available from the World Health Organization [234, 235]. Currently, at least 16 states either never had or no longer have a statewide masking mandate [239] and thus far are without evidence of a resurgence of COVID cases. Regardless, resurgence is still possible, if not likely, at some point with a virus variant. Evidence suggests that PPE helped to slow the spread of the COVID-19 virus. The following options continue to be recommended, at least until herd immunity is shown:

- Healthy individuals should wear a face covering or mask when interacting with the public or other workers, as evidence suggests efficacy in preventing viral transmission [215]. Results from a natural experiment on the effects of state government mandates for face mask use in public places were accrued between April 8 and May 15, 2020. Mandating public face mask use was associated with declining daily COVID-19 infection rates, which decreased by 0.9% in the first 1–5 days after the mandate, and by 2% at 21 or more days after the mandate [240]. See also the section on Masking, below.
- There is strong evidence that the SARS-CoV-2 virus may be spread by asymptomatic and presymptomatic individuals [241, 242]. Infection risk from these individuals is also reduced by wearing masks.
- In terms of the kinds of masks/respirators recommended, the fitted N95 respirator is the most efficient at reducing relative droplet transmission through the mask. However, a 3-layer surgical mask, a cotton-polypropylene-cotton 3-layer mask, a 2-layer polypropylene apron mask, and a 2-layer cotton pleated style mask were nearly as effective [229]. Single-layer, non-cotton clothing (e.g., gaiters and some bandanas) are least effective and should be discouraged if better options for masking are available. A

- randomized controlled trial (RCT) in Denmark suggested minimal efficacy of a mask added to other public health measures [243].
- Use of N95 respirators with exhalation valves is generally not recommended due to theoretical exposure to other individuals.
- Use face shields, especially where there is potential for human-related splashes or droplet exposures, and with aerosol-generating procedures. However, a face shield should be combined with a mask as a face shield has not been shown to be sufficiently protective.
- Follow OSHA guidance regarding requirements for fit testing of respirators and to assure proper use, donning, and doffing [244, 245].
- Appropriate PPE for cleaning and disinfecting a workspace contaminated by the virus is thought to normally be a face mask and gloves. If there are increased concerns about aerosols (e.g., an infected worker was in the room, especially with bronchoscopy, suctioning, sputum induction), an option may be to leave the room overnight before cleaning and disinfecting it; otherwise, an N95 respirator would ideally be recommended (P100 is not an appropriate mask for these purposes).

Reuse, Extended Use, and Reprocessing of Respirators

The pandemic initially caused demands on all types of PPE far beyond manufacturing capacities, which has been subsequently alleviated. Differences in management by sector (i.e., healthcare vs. general) was proposed. Accordingly, protocols were developed for reuse, extended use, and reprocessing of respirators [246, 247], including the following:

- It has been recommended that reuse, extended use, and reprocessing of respirators be reserved for situations where their use is indispensable.
- Nevertheless, respirators should be discarded after procedures at high risk of contamination (e.g., aerosol-generating), when contaminated, when defective, or when no longer functioning properly.
- Extended use of respirators typically involves up to 6–8 hours of use time. The respirator should still be able to make a tight seal and the mask should not be wet or damaged [246].
- Extended use has been advised over reuse as reuse also involves handling of a
 potentially contaminated respirator. This is facilitated by co-location of COVID19 patients.
 - Extended-use risks include contamination by touching the respirator, dermatitis, respiratory fatigue, impaired work capacity, increased O₂ debt, earlier exhaustion at light workloads, elevated CO₂ levels, and increased non-compliance with best practices [246].
- The CDC's reuse protocol involves supplying each worker with the number of N95 respirators that they need for an upcoming week's work, then reusing a respirator up to 7 days later [247].
 - A face shield is recommended to reduce the probability of respirator contamination.
 - Storage in a paper bag is advised.

- Paper bags should be clearly marked.
- Handwashing and handling should be done with care to avoid contamination, especially during doffing.
- Reprocessing systems involve sterilization with the following: saturated steam,
 UV light, gas plasma, and vaporized hydrogen peroxide. Reprocessing should
 follow protocols, be carefully monitored, and be matched to the type of
 respirator, which can differ due to factors such as the process degrading the
 efficiency of the respirator.

Ventilation Issues

Ventilation issues (general and local supply of fresh air) have been markedly underutilized as potential COVID controls [248-252]. This issue also has potentially major implications for the future reduction in other epidemics, such as influenza or resurgences of COVID-19. Consultation with an HVAC expert may be helpful. Area ventilation can provide a relatively safe zone for workers. The following general ventilation measures can be used to dilute viral concentrations:

- Identify the number of air exchanges per hour (ACH) in the room.
- Increase ACH in work areas. The number of necessary ACH depends upon occupancy of the area and the purposes for which the area is used (e.g., more ACH in healthcare or crowded areas than in sparsely populated warehouses).
- Assure homogeneity of airflow to avoid "dead spots" and short-circuiting from air supply to exhaust.
- Run the ventilation system as many hours as possible.
- Increase the proportion of fresh (rather than recirculated) air.
- Filter and/or disinfect the air.
- Use effective filters in the HVAC system. HEPA filters are optimal, but some ventilation systems cannot effectively overcome their added resistance. A minimum filtration efficiency rated at least MERV 13 should be used [253, 254].
- Air disinfection, such as ultraviolet germicidal irradiation, can be placed within the central HVAC system [251, 254]. Use portable air cleaners and local exhaust.
- Local standalone HEPA filtration in high-risk areas may be potentially helpful for risk mitigation.
- Fans and other airflow and/or filtration devices may be used to control the direction of airflow from clean to potentially contaminated areas. Where possible, consider using portable air purification systems for small work areas.

Disinfection Practices and Contact Spread Measures

Ventilation and other control measures addressing droplets and microdroplets are far more important than disinfection of surfaces for COVID-19 [255]. Disinfection of surfaces may have some limited role in reducing spread. The following disinfection practices may be helpful:

• Train staff on how to disinfect workplaces.

- Disinfect commonly touched worksite surfaces daily. Consider cleaning commonly used select surfaces handled by non-gloved workers between shifts (e.g., machine controls).
- 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.
- Disinfect 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, and 0.1% sodium hypochlorite for at least 1 minute [90], although some agents will require longer contact times. It is important to allow sufficient time for disinfecting agents to work, and directions should be carefully followed. The CDC has a list of disinfecting agents and the EPA has a list of products active against human coronavirus, with recommendations for the duration of contact time [256].
- Encourage frequent hand hygiene (handwashing or use of alcohol-based hand disinfectants) with appropriate techniques [257].
- Provide ample hand sanitizer and hand-sanitizer stations throughout the worksite.

Policies and Procedures

The following are potential policies and procedures to consider:

- Inform and seek support and 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 the 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.
- Consider instituting required daily electronic symptom trackers with an automated management system for all employees to report symptoms of COVID-19 infection, including fever, cough, shortness of breath, myalgias, abdominal discomfort, and diarrhea. Responses should be monitored daily by the medical department or health and safety [258-261].
- If daily symptom tracking is not instituted, 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 now widely available, but the sensitivity and specificity vary greatly between kits (see <u>Diagnostic Testing</u>). Their usefulness is limited in areas where the prevalence of disease is around 1 to 3%; 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, 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. These guidelines assume lack of herd immunity and/or ongoing community-based spread. Further guidance is available from the CDC [253].

Restaurants

- Provide physical 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. Other options are electronic access and use of QR codes.
- Clean and disinfect chairs and tables after each customer use (see <u>Disinfection</u> Practices).
- 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.
- 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 physical 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 physical distancing.
- Encourage customers to use personal respiratory protection and provide PPE to customers where feasible.

Hospitality

- Eliminate handling of luggage and other customer items.
- Valet services should be provided by lower-risk employees if possible.
- 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.
- Towel service and other laundry should ideally be handled by low-risk employees.
- Disinfect equipment between patrons.
- 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 and disinfection 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.
- Evaluate ventilation measures (see above)

Food Production Facilities

Meat and poultry processing facilities have been hot spots of virus infection due to structural and socioeconomic challenges. 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 [262]. 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 [253].

Schools

Schools have high human population densities. However, extensive data show that children have the lowest risk of symptomatic, severe, and/or fatal COVID-19 disease across the lifespan, with the risks appearing to be lowest in the youngest school-age children [120, 263, 264]. Data to explain these observations are sparse; theories include that children have relative lymphocytosis, superior immunity to coronaviruses, and an ACE2 receptor (to which the virus binds to gain entry) that is inadequately developed in their airways [265, 266]. Initial reports that children do not become infected appear increasingly dubious [267]; however, that they are resilient to symptomatic and/or severe disease is not in question.

Schools in most countries were at least temporarily closed in spring 2020 in response to the pandemic. However, students' learning by distance-based methods has been reportedly suboptimal and sometimes poor. The burden of the inability to educate students using traditional methods also disproportionately falls on the poor and immigrant populations, which have fewer skills and resources to educate and/or guide their children's learning [268-272]. For example, increases in computer search intensity for school-centered resources in higher socioeconomic US regions were double those of lower socioeconomic status regions in April 2020 compared with 2015–2020 [270]. A 5-month global shutdown of schools has been estimated to have had an adverse worldwide impact, with a loss of \$10 trillion of lifecycle earning for the 1 billion affected students because of lower levels of learning, lost months, or dropping out of school [273]. Schools also play important roles in students' social development and mental health [274-276].

Restarting of schools has been controversial and widely divergent strategies have been deployed. Nearly all reports have suggested few problems with most re-openings in Belgium, Denmark, Finland, France, Japan, Norway, Germany, Quebec, Singapore, South Korea, and Sweden; these reports have also included some opening without physical distancing, masking, alternate school schedules, or other mitigations [277]. The main contrary example is Israel, where school-based transmission to teachers was briefly problematic [278, 279]. However, this exception may have been due to very hot weather, which led many to stop wearing masks and close windows. The many successful countries also have had generally lower rates of transmission when the schools (re)opened; thus, the implications and safety of schools reopening may not be readily applied to many US states or other geographic regions with ongoing significant community spread. Alternatively, areas having had sufficient community spread may have attained some degree of herd immunity.

The CDC has developed sets of guidance for schools [280-285], which include decision logic for (re)opening schools [280]. Others have recommended a combination of ventilation and mask use [286, 287]. This ACOEM guideline primarily addresses the protection of teachers/staff (see also <u>Appendix A</u>). Student-related guidance has been recommended by the CDC to be summarized in policies and briefly includes the following: (1) wearing face protection, (2) physical distancing, (3) washing hands and other personal hygiene measures, (4) cohorting of

students, (5) regular cleaning and disinfection, and (6) removing those students infected with COVID [288]. Regardless of community transmission levels, the CDC recommends that all elementary school students can remain 3 feet apart in classrooms where mask use is universal; middle and high school students can also remain at least 3 feet apart in classrooms where mask use is universal and in communities where transmission is low, moderate, or substantial. Where community transmission is high, middle and high school students should be at least 6 feet apart if cohorting is not possible. Face shields have not been recommended for children [288], and face shields without masks have not been shown to be sufficiently preventive. However, in situations where compliance is an issue, face shields may be a reasonable alternative, although use with a mask (especially a clear mask) may be an option. Face shields are suggested for teachers, particularly for teachers of younger age groups where development depends on social queuing.

Cloth face coverings are recommended and are classified as "may be considered" for other more dispersed seating arrangements, as well as for during recess, music classes, physical education (vigorous exercise is not advised if in a confined space), mealtime, among children under 2 years of age, and for students who are deaf, are hard of hearing, and/or use lip-reading in communicating. Universal symptom screening of students is not recommended, although preclusion of attendance if symptoms develop is advised [288]. It is advised to identify an isolation room for those who develop COVID-like symptoms at school [282]. While CDC guidance for teachers is limited, the CDC does not recommend universal testing of students and staff [282]. Yet, many schools have instituted such testing protocols. A universal testing or sampling strategy may be helpful in identifying asymptomatic students and staff with COVID-19, allowing isolation of COVID-19-positive individuals to prevent transmission; such an approach could also guide school administration in monitoring the number of cases to inform decision making.

Teachers may be protected using methods that are somewhat similar to other adults. These methods should be administratively coordinated, and policies and procedures should be developed and enforced. Teachers should undergo daily symptom screening when working (e.g., electronic survey). As with all individuals, those with symptoms consistent with COVID-19 should be tested, although there is risk of false-negative results. Symptomatic, presumptively positive teachers should be isolated for 10 days. Contact tracing of positive cases should be performed, and contacts should be quarantined for up to 14 days. Symptomatic contacts should be tested.

The administrative options for students discussed previously (e.g., cohorting, physical distancing, masking) should reduce teachers' risk of disease. Other options for protecting teachers include universal masking, N95 respirators for those with comorbidities (if available), face shields, physical distancing between the teacher and students, shielding around the teacher's desk, and fully remote teaching for those with the highest degrees of risks/comorbidities.

Security and administrative personnel should follow similar protocols to those of the teachers. These include daily electronic symptoms screening, physical distancing, mask use, and glove use for security personnel. As the epidemic waxes and wanes, it is helpful to have pre-planned policies and procedures that may administratively and readily become more or less restrictive as determined by community rates of disease. For example, with greater COVID-19 incidence rates, learning could move to more distance-based teaching methods. Table 1 provides an example matrix for adaptive implementation and relaxation of restrictions in schools for the protection of teachers.

Table 1. Adaptive Matrix for Implementation and Relaxation of Restrictions in Schools*

	Green (no or minimal community spread; <5%)	Yellow (sporadic or low- level community spread; 5–10%)	Red (widespread, uncontrolled community spread; >10%)
Teacher age			
<40 years, no comorbidities**	No mask	Mask	Mask
40-65 years	No mask	Mask	Mask
>65 years	No mask	Mask	Respirator (N95 respirator if available; mask if unavailable). Consider co-use of face shield for multiple co-morbidities, or a face shield when also remote teaching.
Comorbidities*	No mask	Respirator (N95 respirator if available; mask if unavailable)	Respirator (N95 respirator if available). Consider co-use of face shield for multiple co-morbidities, or a face shield when also remote teaching.

^{*}These categories are expert opinion, as there currently is insufficient evidence for evidence-based guidance.

^{**} Comorbidities include heart disease, hypertension, diabetes mellitus, chronic renal disease, dialysis, liver disease, chronic obstructive pulmonary disease (COPD), smoking, and obesity [185-188].

Disability and Return-to-Work Considerations

Disability from COVID-19 will be better defined with studies over time. Extrapolation using recovery from other conditions, such as pneumonia and ARDS, may provide some preliminary estimates.

Preliminary reports suggest recovery duration is, unsurprisingly, at least partially correlated with measures of case severity. At least one symptom persisting for at least 60 days has been reported among hospitalized survivors, with the most prevalent symptoms being fatigue, dyspnea, joint pain, chest pain, cough, and anosmia [289]. However, persistent symptoms are reported in individuals with mild cases, and long-term symptoms have been reported [290]. There are many cases that require home healthcare after discharge [291].

Permanent disability is determined by the existence of some combination of fixed deficits when a healing plateau has been reached (see the <u>ACOEM Disability Prevention Guideline</u>). One of the greatest factors facilitating recovery is the interest and ability of the employer to reintegrate the employee into their workforce. Such integration often requires accommodations that hopefully can be reduced as time, recovery, and workarounds progress. While not yet demonstrated for COVID-19, employer support for recovery is critical for many other conditions.

Permanent disability is only appropriate for those with fixed, non-improving chronic impairments (see the <u>Rehabilitation section</u> below). Some of these cases have obvious permanent deficits from complications such as myocardial infarction and stroke. There is also increasing literature supporting the development of chronic symptoms associated with COVID, which is elsewhere termed "ongoing symptomatic," "post-COVID syndrome," and "long COVID" [292]. The term "post-acute sequalae of COVID" has also been used by the National Institutes of Health.

Factors contributing to disability beyond fixed but remediable deficits can include a lack of full implementation and utilization of evidence-based treatments, and lack of effort and compliance. Other factors may potentially involve advocagenic, psychological, and other influences.

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. One random sample (n=292) of affected individuals diagnosed as outpatients reported 65% had returned to normal health at a median of 16 days; no or few comorbidities and age statistically impacted those rates, with 74% among

those 18–34 years of age, 68% among those 35–49 years of age, and 53% among those 50 years and older returning to normal health [293]. 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 [294, 295]. 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 [296]. Lung diffusion abnormalities can take up to 5 years to resolve in ARDS cases [296, 297]. 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 [295-301]. 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 [295, 298, 302, 303]. Cardiac problems are common with COVID-19, with cardiomyopathy, arrhythmia, and direct cardiac muscle injury affecting approximately 30%, 20%, and 10% of patients, respectively [304]; they are contributing causes to fatality [304-306].

In general, for patients who are intubated and survive, recovery of the cardiorespiratory systems and endurance are estimated to take at least several months. Among recent COVID-ARDS survivors, 78% had evidence of cardiac involvement and 60% had evidence of ongoing myocardial inflammation on MRI [307]. 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 [295-299, 308]. There is also the potential for a minority of patients to be permanently totally impaired [299].

Cardiac, respiratory, and neurological disability measures include the following:

- 6-minute walk test
- Metabolic stress echocardiogram (including ECG)
- Full pulmonary function testing with impedance booth or washout testing
- High-resolution CT scan of the chest, especially for those with COVID-19 pneumonia
- Functional capacity testing (although there are some limits in interpretation)
- Neuropsychological testing

For individuals with less symptoms but high exertion requirements, a cardiac evaluation may be indicated.

An approach to evaluating COVID-19 worker's compensation claims has been published [309]. There is no specific impairment class for COVID-19 and surrogate diagnoses may be needed and/or used by analogy. Ratings for impairment can be found in the AMA Guides 5th Edition [310] and 6th Edition [311].

Vaccines

Development work has progressed at record speed on more than 270 COVID-19 vaccine candidates [200, 312-314]. These efforts have used at least four types of vaccine classes or approaches against this infection (virus, viral vector, nucleic acid, and protein-based) [313]. Although vaccine development was estimated to require 12–18+ months if successful, it has been achieved in approximately 9–10 months [315]. Several more of these COVID-19 vaccines are in advanced stages of development and have potential for approval (see Table 2). Few relevant efficacy data have been published in peer-reviewed publications. Safety data are largely reported from phase 2 trials; thus, some of the information is based on relatively small sample sizes. Reported rates of vaccine efficacy range from 62% to 95% [316]. After initiating vaccination programs, COVID-19 infections have declined markedly [317].

There is a helpful website (see https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/) updated weekly with multiple COVID-19 vaccine databases, including a vaccine pipeline tracker, clinical trials database, and living review [312, 316]. The CDC has also provided guidance regarding what is recommended for those who have been vaccinated [318].

The vaccines have very good to excellent rates of efficacy both in randomized trials and in early reports from community-based studies and surveillance systems, which underscores support for broad-scale vaccination programs. As the vaccinations are being widely implemented, the following questions require answering going forward, although they should not delay the expeditious and widespread implementation and completion of the vaccination programs:

- Duration of vaccine-induced immunity and whether there are differences between the types of immunizations
- Success of immunity, especially durability
- Whether duration of immunity differs in different subgroups, which may suggest the need for (earlier) re-vaccination
- Whether immunity is shorter-lived in vaccinated patients or in naturally infected patients
- Whether annual immunizations are needed
- The proportion of the population that requires immunization to prevent COVID-19 re-emergence
- Utility and/or adverse effects among those who have been infected with COVID-19
- Long-term adverse effects
- Whether the vaccine is safe in the elderly

- Whether children at risk of severe disease should be immunized
- Whether all children should be immunized

Adverse Effects

Both the Pfizer and Moderna vaccines have been associated with a low frequency of adverse effects. Even though vaccine reactions are rare, it is important to address them because they may generate fear, anxiety, and vaccine avoidance that is out of proportion with the actual prevalence of these outcomes. The earliest reports appeared in the January 6, 2021 MMWR [319], which described data collected from the December 14–23, 2020 period of vaccine administration of the Pfizer-BioNTech COVID-19 vaccine. Out of 1,893,360 first doses administered, there were 4,393 (0.2%) adverse events reported. After reviewing all cases, only 175 cases were considered to be consistent with a severe allergic reaction; of these, only 21 cases were deemed to represent anaphylaxis, for a rate of 11.1 per million doses administered. Nonallergic adverse events, mostly vasovagal or anxiety-related, were excluded from analyses. The median age of those with anaphylaxis was 40 years, and 90% were women. Typical symptoms included a diffuse erythematous rash, throat closure, hoarseness, swollen lips, difficulty swallowing, wheezing, cough, and nausea. Most (17/21; 81%) had a prior history of allergic reactions to drugs, medical products, foods, and insect stings, and 9.5% (2/21) had prior reactions to a vaccine. Most (19/21; 90.5%) were treated with epinephrine, and no deaths were reported. There was no geographical clustering of cases or associations with any specific vaccine lot. There were 83 cases of non-anaphylactic allergic reactions, with a similar age and sex distribution, and 56 (67%) also had a prior history of allergies or allergic reactions. Almost all reactions occurred in the first 30 minutes after vaccine administration.

A review subsequently published noted that confirmed allergic reactions to vaccines are usually not to the active ingredients, but rather due to reactions to excipients [320]. Reactions specifically focus on polyethylene glycol (PEG) and polysorbate, which have been added to multiple other vaccines, injected medications, chemotherapeutic agents, and biologicals to increase water solubility. These excipients are also found in multiple creams, ointments, lotions, and personal care products. Multiple existing vaccines contain polysorbate 80, including the AstraZeneca and Johnson & Johnson vaccines, and both the Pfizer and Moderna vaccines contain PEG2000. A recent study of the general population found that 5 to 9% of serum samples were positive for anti-PEG IgG [321]. Skin tests for polyethylene glycol are available, and other medications containing PEG3350 (methylprednisolone acetate), polysorbate 80 (triamcinolone acetonide, Refresh eye drops, Prevnar) or polysorbate 20 (hepatitis A vaccine, Twinrix) can be used for skin testing to document an allergy to one of these excipients. The authors proposed a risk stratification to determine who should undergo pre-vaccination skin testing or extended observation postvaccine, using the following patient-directed questions:

Do you have a history of a severe allergic reaction to any of the following:

- 1. An injectable medication (IV, IM, or SQ)
- 2. A prior vaccine
- 3. Another allergen, such as food, venom, or latex?

4. Polyethylene glycol (PEG), a polysorbate, or a paclitaxel-containing injectable or vaccine?

If the patient answers "yes" to question 4, he or she is higher risk and should be referred to an allergist before receiving the vaccine. Questions 1, 2, and 3 represent medium risk; the patient should be observed for 30 minutes after the vaccine. If the patient answers "no" to all four questions, then he or she is lower risk and should be observed for 15 minutes after the vaccine.

Delayed large local reactions to the Moderna vaccine occurring 8 to 12 days after vaccination have been described in 12 patients [322]. Of these, 10 were women, 8 had a prior history of allergy or allergic reactions, 9 described itching, 9 described pain, and 7 described fatigue or other systemic symptoms. Most were treated with antihistamines and topical steroids, and two received oral steroids. Reactions resolved by day 14 to 19. All then received the second vaccine dose, with only minor rash or itching reported; none were severe.

In addition, there have been reports of 36 cases of immune thrombocytopenic purpura (ITP) following the vaccination of 31 million people as of February 8, 2021, but no cases were associated with any one vaccine or vaccine lot. The majority of patients received platelet transfusions, IVIG, and/or steroids along with hospital care; there was one reported death. Importantly, ITP has been associated with other vaccines, including the MMR, DTaP, varicella, hepatitis B, and pneumonia vaccines [323], as well as following viral infections. For patients with a pre-existing history of ITP, the American Society of Hematology recommends that platelet counts be checked before receiving the vaccine; however, the presence of ITP is not a contraindication to receiving the vaccine.

Variant Concerns

The spike protein of the SARS CoV-2 virus is the focus of all currently available vaccines. This is the primary viral protein responsible for entry into host cells by attaching to the ACE2 cellular receptor present on multiple human tissues, including the lungs, heart and blood vessels, kidney, testis, and brain. The primary antibody response elicited by the virus in natural infections is directed against the spike protein. Hence, as the spike protein appears to be the preferred target of the natural immune response, it was naturally selected as the primary target for the vaccine response.

The first variant of the SARS CoV-2 spike protein, D614G, was detected in early March 2020, substituting a glycine for an aspartic acid in the carboxy terminal region of the S1 domain. Not present in any of the viral sequences in January and February 2020, it constituted 26% of viral sequences in March and 70% in May, attributed to enhanced ACE2 binding affinity and infectivity [324, 325].

The next set of more transmissible variants, all containing adaptations in the spike protein, were identified in the fall of 2020 and include B.1.1.7 (UK), B1.351 (South Africa), and P.1 (Brazil). The B.1.1.7, or UK variant, was first identified on September 20, 2020 In Kent, England.

It is thought to have arisen in a patient with an impaired immune system who was treated with antibodies from a recovered patient, and possibly also with remdesivir [326]. With this patient's specific scenario, the virus would theoretically have the opportunity to replicate multiple times, increasing the odds of random mutations, and under the pressure of antibodies targeted to the spike protein. Hence, those variants that survived could develop slightly different spike proteins that are not (as well) recognized by existing antibodies. This variant carries a N501Y mutation of asparagine to tyrosine in the S protein that increases its binding strength to the ACE2 cellular receptor, as well as a deletion at positions 69 and 70, which are both hypothesized to increase transmissibility. The deletion causes S-gene target failure in one PCR-based assay, the ThermoFisher TaqPath COVID-19 assay, producing a negative result for the S-gene target and still positive results for the other two targets.

By January 12, 2021, the B.1.1.7 variant had been detected in 12 U.S. states. Estimates are that this will become the dominant strain in the United States by the end of March 2021 [327]. There is some concern that this variant is more lethal than previous strains: the mortality hazard ratio associated with infection with B.1.1.7 compared with infection with previous variants was estimated at 1.64 (95% confidence interval 1.32 to 2.04) [328].

B.1.351 is another variant that independently emerged in South Africa; it was first detected in the US at the end of January 2021. It carries eight specific mutations in the spike protein, along with the N501Y variant carried in the UK strain. Preliminary results demonstrated that a higher titer of antibodies generated by the MRNA-1273 (Moderna) vaccine were required to neutralize the B.1.351 variant, although sera were still able to fully neutralize the virus. Specifically, geometric mean titers (GMT) of immunized human sera to neutralize the D614G variant were 1:1852, compared to GMT of 1:290 against the B.1.351 variant. What is not clear, however, is whether this translates to any reduction in protection against infection [329]. Similarly, sera from subjects immunized with the BNT162b2 (Pfizer) vaccine exhibited the same neutralization of a Y501 laboratory variant as the parent N501 version of the virus [330].

P-1 is a variant of SARS-CoV-2 that emerged in Manaus, Brazil, and was detected in the United States at the end of January 2021. This variant carries 20 unique mutations, including three identified in other variants in the receptor binding domain of spike protein (K417T, E484K, and N501Y). A separate study showed that serum samples from subjects immunized with the BNT162b2 (Pfizer) vaccine effectively neutralized engineered CoV-2 viruses carrying all the identified variant spike proteins, most at titers >1:40 [331].

It is important to note that all settings of natural and vaccine-induced immunity will exert selection pressures against the virus and drive the emergence of resistance mutations. One study cultured a SARS-CoV-2 recombinant virus in the presence of 18 different neutralizing monoclonal antibodies that were selected for different RBD mutations. In all cases, the antibody selected for the emergence of a resistant variant. This same study also demonstrated that antibodies elicited by either the Moderna (mRNA-1273) or Pfizer BioNTech (BNT162b2) vaccine were nearly identical and were effective against the dominant variant of SARS CoV-2 (D614G), with only a modest decrease in the ability of these antibodies to neutralize viral

variants [332]. This likely reflects the polyclonal nature of neutralizing antibodies elicited by the vaccines—that is, that the mRNA carried by these vaccines codes for a number of different proteins with many different antigenic epitopes. Antibody responses will correspond to multiple epitopes, including many sites that remain unchanged in different variants of the virus.

Although the intense scrutiny of the SARS CoV-2 virus has resulted in early identification of viral variants, their emergence should be considered a normal process in a pandemic. As host susceptibility to infection changes, the virus, under these selection pressures, will change accordingly. More variants will emerge. This may, or may not, have an effect on host susceptibility. Thus far, vaccine-elicited antibodies have been shown to remain active against spike protein variants. Most SARS CoV-2 specific CD4+ and CD8+ T-cell responses from both naturally infected and vaccinated subjects are equally effective against variant strains [333]. Lastly, it is expected that the vaccines will be altered going forward to address novel variants that have already emerged, as well as those yet to emerge.

Vaccines for the Prevention of COVID-19

Strongly Recommended.

Vaccination is strongly recommended for the prevention of COVID-19.

Strength of Evidence – Strongly Recommended, Evidence (A) Level of Confidence – High

Indications:

Indicated for nearly all adults. Particularly indicated for those with increased risk of severe COVID-19 disease (e.g., increased age, obesity, diabetes mellitus, COPD, cardiovascular disease, renal disease, immunosuppressed states). Earlier vaccination is indicated for adults with high numbers of close personal contacts as a means to terminate the pandemic sooner (e.g., healthcare workers, grocery workers, firefighters, police officers, EMS, assembly line workers, teachers). Because the pandemic is primarily affecting middle to older age groups, vaccination of young adults is of unclear benefit compared with natural immunity, particularly early in the vaccination period when vaccines should be reserved for higher-risk groups.

Common RCT exclusion criteria include pregnancy, immunodeficiency, immunosuppression, use of glucocorticoids 20+ mg/day in the past 6 months, and prior vaccine allergic reactions. Thus, efficacy and applicability for these populations are technically less clear. However, those with immunosuppressed states would be potentially high-impact populations to receive early vaccination. Safety in pregnancy is unknown and immunization in pregnant women is not generally recommended.

Benefits:

Markedly reduced risk of COVID-19 infection, as well as serious COVID-19 disease. Termination of the pandemic. Two 2-shot series of mRNA vaccines (Pfizer and Moderna) have ~95% efficacy, whereas the single shot (Janssen/Johnson & Johnson has ~67% efficacy [334].

Harms: Reported rates of adverse effects from a passive but large-scale

surveillance system (V-safe) include injection site pain

(Pfizer/Moderna; Pfizer dose #2; 73-78% after first dose and 79% after second dose), fatigue (22-25%/25-54%), headache 15-23%/20-43%), myalgia (15-23%/18-47%), chills (6-11%/8-31%), fever (6-11%/8-29%), injection site swelling (6-11%/9-13%), joint pain (5-10%/7-24%), and

nausea (4-9%/6-14%) [316, 335, 336].

Anaphylactoid reactions are quite rare (4.5 per million doses

administered [335]); those with severe food and/or medicine allergies

have been suggested to delay getting the vaccine.

Pfizer BioNTech/Fosun Pharma: Grade 3 adverse effects >2% were

fatigue 3.8% and headache 2.0% [316].

Indications for Discontinuation: N/A for single-administration series. A second immunization is not

recommended for those with significant and/or serious adverse effects with the first administration of a two-immunization series.

Frequency/Dose/Duration: N/A

Rationale: One trial has been reported and found 95.1% efficacy [337]. Other

available data are published in press releases and suggest strong efficacy of these vaccines. Adverse effects reported thus far are

relatively minor. There are no long-term safety data.

COVID-19 immunizations are minimally invasive (IV), thus far have minor reported adverse effects, are usually no-cost, have reported evidence of strong efficacy, and thus are strongly recommended.

Evidence for the Use of COVID-19 Vaccines

Polack 2020 (score=8.0) [337]

Category: Vaccine Study Type: RCT

Conflict of Interest: BioNTech, Pfizer. No conflicts of interest declared.

Sample Size: N = 43,548 participants aged ≥16 years Age/Sex: 42.2% >55 years old; 49% females

Comparison: Vaccine safety population (n=18,860) vs. placebo vaccine (n=18,846). Two

doses, 21 days apart.

Follow-up: Follow-up thus far for 2 months.

Results: COVID-19 disease rate of 8/21720 (0.03683%) vs. 162/21728 (0.7456%);

95.1% reduction in risk.

"A two-dose regimen of BNT162b2 conferred 95% protection against

Conclusion: Covid-19 in persons 16 years of age or older. Safety over a median of 2

months was similar to that of other viral vaccines."

Comments: Large sample size. Low adverse effects. Strong apparent efficacy, although

intermediate to long-term durability of efficacy is unknown.

Table 2. Advanced COVID-19 Vaccine Candidate Information*

Vaccine / Manufacturer	Type (Platform)	Participant Characteristics	IM Doses	Special Handling	Primary Outcomes	Adverse Events	Efficacy / Interim Analysis
AstraZeneca (University of Oxford)	Weakened adenovirus, non- replicating viral vector (ChAdOx1-S AZD 1222)	40,051 participants aged ≥18 years	2 doses, days 1 and 29	None; store at normal refrigeration temperatures for up to 6 months	 Incidence of COVID- 19 cases at days 43 to 365 Incidence of AEs, SAEs, MAAEs, and AESs at 28 days after doses and up to day 730 Incidence of solicited and local and systemic AEs up to days 8 and 36 	Nonquantified reports of injection site pain, rash, headaches, muscle soreness, and fevers. Nearly half reported neutropenia.	50% (with 95% CI, lower bound >30%)
Jannsen (Johnson & Johnson)	Non- replicating viral vector As26.COV2.S	60,000 participants aged ≥18 years	1 dose	None; safe to store at normal refrigeration temperatures	Incidence of moderate to severe/critical COVID-19 cases up to day 759	Mild adverse effects similar to those seen with other vaccines, including injection site pain, rash, headaches, muscle soreness, and fevers.	60% (with 95% CI, lower bound >30%)
Moderna/NIAID	LNP- encapsulated mRNA (mRNA- 1273)	30,000 participants aged >18 years	2 doses; days 1 and 29	Yes; requires storage at -20°C. May store at normal refrigeration temperatures up to 30 days.	 Incidence of COVID- 19 cases at days 43 to 759 Participants' AEs and MAAEs leading to withdrawal up to day 759 Participants with solicited local and systemic ARs up to day 8 and 36 and unsolicited AEs up to day 57 	Fatigue, 9.7%; myalgia, 8.9%; arthralgia, 5.2%; headache, 4.5%; injection site pain, 2.7%; erythema at injection site, 2.0%; headache, 2.0%; fever, <2.0%	Vaccine efficacy against COVID-19 was 94.1%; vaccine efficacy against severe COVID-19 was 100% (90 vs. 5 COVID cases; 11 vs. 0 severe COVID cases occurred)

Novavax	Recombinant	30,000	2 doses;	None; safe to	•	Incidence of COVID-	Reports include	Currently
	glycoprotein	participants	days 1	store at		19 cases at days 29	injection site pain,	unknown
	nanoparticle	aged ≥18 years	and 29	normal		to 750	rash, headaches,	
	(NVX-			refrigeration			muscle pain, fever,	
	CoV2373)			temperatures			nausea, and	
							vomiting.	
Pfizer	3 LNP-mRNA	43,998	2 doses,	Yes; requires	•	Incidence of COVID-	Influenza-like	95% meeting all
(BioNTech /	(mRNA BNT	participants	days 1	storage at		19 cases at days 29	symptoms, injection	primary efficacy
Fosun Pharma	162)	aged ≥12 years	and 22	−70°C. FDA-		to 730 (per 1000	site pain, rash,	endpoints (162
				approved		person-years of	fever, headaches,	vs. 8 COVID
				storage at		follow-up)	muscle soreness,	cases; 9 vs. 1
				usual	•	Incidence of AEs and	and nausea. Grade 3	severe COVID
				refrigerator		SAEs after doses and	adverse effects >2%	cases occurred)
				temperatures		up to day 202	were fatigue (3.8%)	
				for up to 2			and headache	
				weeks [338].			(2.0%).	

Abbreviations: AE, adverse event; AES, adverse event of special interest; AR, adverse reaction; CI, confidence interval; LNP, lipid nanoparticle; MAAE, medically attended adverse event; SAE, severe adverse event.

^{*}Adapted from Dal-Ré R, Caplan AL, Gluud C, Porcher R. Ethical and scientific considerations regarding the early approval and deployment of a COVID-19 vaccine. *Ann Intern Med.* 2020 Nov 20:M20-7357. doi: 10.7326/M20-7357. Epub ahead of print. PMID: 33216636; PMCID: PMC7713906. Data from clinical trials as of November 20, 2020. Data supplemented from London School of Hygiene & Tropical Medicine's COVID-19 Vaccine Tracker (https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape) [316].

Masks and Respirators

Masks are used to control respiratory exposures, are relatively easy to use, and do not require special fitting. Respirators have much higher performance standards, are more challenging to use, and require fit testing. Masks have been commonly used by the public to control COVID-19 exposure. Respirators have been selectively used to control COVID-19 viral exposures among higher-risk workers or individuals. Masking mandates have been used for control of COVID-19 both in the workplace and in jurisdictions (e.g., statewide) [15].

Masking for the Prevention of COVID-19 Transmission

Sometimes Recommended.

Masking in closed public spaces is recommended for the prevention of COVID-19 transmission when there are significant community-based COVID transmission rates. Masking may be selectively indicated when there are insufficient immunization rates but some ongoing community spread. Individual masking may be advisable for those at higher risk for complications and/or when there is not achievement of herd immunity. Masking may not be indicated when there is a lack of community spread and/or when there is sufficient immunity. In contrast with masks, N95 respirators may be indicated for select populations (e.g., high-exposure workers, workers with high personal risks).

Strength of Evidence – Recommended, Insufficient Evidence (I)

(When transmission is moderate or high)

Level of Confidence - Low

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

(When transmission is low and herd immunity is inferred to have been achieved)

Level of Confidence - Low

Indications:

Masking in closed public spaces is: (1) recommended when there are significant community-based COVID transmission rates; and (2) selectively indicated when there are insufficient immunization rates, yet some ongoing community spread.

Individual masking may be advisable for those at higher risk for complications and/or when there is not yet achievement of herd immunity. Three-ply masking is preferable to 2-ply masking, and ASTM-rated mask standards are available [339]. Single fabric layers are not advised unless there is no alternative [340-342].

Masking may not be indicated when there is a lack of community spread and/or when there is sufficient immunity. Sufficient immunity is challenging to determine as the numbers of cases reported may be underestimated by more than 5-fold, and antibody tests likely miss

some individuals with sufficient immune system protection yet nondetectable circulating antibodies.

N95 respirators may be indicated for either high-exposure workers (e.g., frontline healthcare personnel) and/or workers with high personal risks for a severe outcome [343, 344]. Respirators require at least a health questionnaire, potentially require a medical examination, and necessitate appropriate fit testing. Fit testing should include observation of appropriate donning and, relevant for COVID-19, doffing.

For populations using masks, education on how to obtain a good seal during use is believed to be quite important. Training in donning and doffing, as well as assessments for tolerance and appropriate use, may also be helpful. Guidance is available regarding how to obtain a tighter seal by tying a knot in the ear loops, flattening material near the face, and tucking the knot [345].

Reduced community spread and reduced risk of individual patient disease acquisition. However, once fully immunized, benefits are nearly entirely limited to unimmunized patients.

Dermatological problems, inconvenience, reduced communication. There is evidence that poor mask hygiene may be associated with increased risk of infections [346, 347].

Masking may not be indicated when there is a lack of community spread and/or when there is sufficient immunity.

In closed public spaces. Recent guidance has suggested double-masking, which infers there are increasing concerns about microdroplet and aerosol spread. However, there are few data to suggest the superiority of double-masking. N95 respirator use among those who are high risk and not yet immunized may be the most effective strategy, assuming mask availability (which currently is good). Contamination of masks may be an avoidable problem [348] and should be addressed by proper training (see Indications above). One community-based moderate-quality trial from Denmark found a lack of benefits from mask wearing in addition to other measures in the COVID epidemic [349]. One trial of mask use for COVID-19 assessing household transmission failed to find at least 50% reduction in risk and reported that most disease acquisition was thought to be

community-based [350].

Quality RCTs mostly involve influenza and influenza-like illness [219, 351-356] and show somewhat conflicting results regarding efficacy to reduce risks of infections, particularly with use of respirators; there are more negative [357-361] than positive trial results [362-364]. Equivalency has been reported between surgical mask use and N95 respirators [222, 225], although experimental evidence suggests superiority of respirators to reduce droplet and aerosols [340-342]. Weak evidence suggests masking may be effective and that N95 respirator use may be superior to mask use in healthcare settings [347, 365-367]. All of the epidemiological data have the benefits of being real-world data, but weaknesses include unclear compliance and masking techniques [368]. Respirators performed better than masks in

Benefits:

Harms:

Indications for Discontinuation:

Frequency/Dose/Duration:

Rationale:

simulation studies [369]; however, a simulation of SARS-CoV-2 found incomplete protection from masks and N95 respirators [370].

Data on filtering were as follows: N95 respirators, 99%; medical masks, 59%; 3-ply cotton, 51% vs. 47%; double-gaiter, 60%; face shield, 2% [343, 371]. Surgical and cloth mask efficacies vary widely [372].

Although quality data on the efficacy of masking are sparse and conflict, some data suggest efficacy. With few other options for control of a pandemic, the risk-benefit ratio favors masking during the active pandemic phase. Masking in closed public spaces is: (1) recommended when there are significant community-based COVID transmission rates; and (2) selectively indicated when there are insufficient immunization rates and some ongoing community spread. Individual masking may be advisable for those at higher risk for complications and/or when there is not achievement of herd immunity.

Masking may not be indicated when there is a lack of community spread and/or when there is sufficient immunity. Sufficient immunity is challenging to determine as the numbers of cases reported may be underestimated by more than 5-fold; furthermore, antibody tests may miss some individuals with sufficient immune system protection but non-detectable circulating antibodies.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to February 2020 using the following terms: Mask, bandana, scarf, reusable cloth mask, standard surgical mask, N-95, face shield; 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 237 articles in PubMed, 70 in Scopus, 71 in CINAHL, 117 in Cochrane Library, 2882 in Google Scholar, and 3 from other sources[†]. We considered for inclusion 29 from PubMed, 4 from Scopus, 2 from CINAHL, 1 from Cochrane Library, 44 from Google Scholar, and 3 from other sources. Of the 82 articles considered for inclusion, 23 randomized trials and 40 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:

Evidence for the Use of Masking

COVID-19 Mask Efficacy

<u>Schaller 2020</u> (score=6.0) [373]

Category: Mask Efficacy
Study Type: RCT, Experimental

Conflict of Interest: No mention of sponsorship. No COI.

Sample size: N = 35 participants showing exhibiting saccharin sensitivity and no comorbidities to smell

or taste

Results:

Comments:

Comparison:

Results:

Age/Sex: No mention of mean age or sex

Group 1: Participants were exposed to nebulized 45% sodium saccharin solution while wearing a Stryker Flyte Surgical Helmet accompanied by a 3D FT-10 Fit Test Hood (n = 20)

Comparison:

vs. Group 2: Participants were exposed to sterilized water while in the same sterile

surgical helmet system (SSHS) as Group 1 (n = 15)

Follow-up: No mention of follow-up.

Group 1 tested positive for tasting saccharin in 8/20 (40%) participants with SSHS fans turned on, and 20/20 (100%) positive tests with fans off. Group 2 had zero participants

test positive with fans turned on and 1/15 with fans off (p=0.000000024). Mean time to

taste was 123.5 seconds with fans on and 62.6 seconds with fans off (p=0.049). "SSHS do not protect against aerosol particulate and therefore are not efficacious in protection against COVID-19. The fan system employed may even increase risk to the

Conclusion: surgeon by drawing in particulates as well as delay recognition of intraoperative cues,

such as exhaust from diathermy, that point to respirator mask leak."

Pre-test-post-test randomized study evaluating surgical helmets to prevent COVID-19. Saccharin detection used for efficacy as is done with N-95 fit testing. Exposure is a 45% nebulized saccharin solution versus placebo (sterilized water). Small sample (N=35). Data

suggest lack of efficacy as 20/20 participants in the surgical helmet group had a + taste

test.

Bundgaard 2020 (score=5.0) [350]
Category: Mask Efficacy

Study Type: RCT

Conflict of Interest: Sponsored by The Sailing Foundations. No COI.

Sample size: N = 6024 participants without current/prior COVID-19 symptoms or diagnosis reported at

least 3 hours of daily outdoor exposure and no use of masks during daily work.

Age/Sex: Mean age and gender data only available for 4862 participants. Mean age: 47.2 years;

1746 males, 3116 females.

Group 1: Participants were provided 50 three-layer, 98% filtration surgical masks and instructed to a mask whenever outside for the following month (n = 2392) vs. Group 2:

Participants were not provided masks nor were they instructed to wear masks (control)

(n = 2470).

Follow-up: Follow-up every week for one month

42 participants (1.8%) in Group 1 tested positive for SARS-CoV-2 (primary outcome tested using antibody test) vs. 53 participants (2.1%) in Group 2. Percent difference between Group 1 and 2 was –0.3% (95% Cl of –1.2 to 0.4, p =0.38), hence no significant

difference. 95% CI implied a 46 % reduction up to 23% increase in infection for SARS-CoV-

2.

"The recommendation to wear surgical masks to supplement other public health

Conclusion: measures did not reduce the SARS-CoV-2 infection rate among wearers by more than

50% in a community with modest infection rates, some degree of social distancing, and

uncommon general mask use. The data were compatible with lesser degrees of self-

protection."

Randomized face mask use in the prevention of SARS COVID-19 DANMASK. Participants included those spending at least 3 hours outside of the home. Inconclusive results as

compliance to proper mask use low. Missing data, patient reported results, no blinding.

Influenza Mask Efficacy

Comments:

Age/Sex:

Conclusion:

Comments:

Suess 2012 (score=5.5) [359]

Category: Mask Efficacy

Study Type: RCT

Conflict of Interest: Sponsored by the German Federal Ministry of Health. No COI.

Sample size: N = 111 households with influenza positive index patients (84 households listed with 84

index cases and 218 household contacts).

2009/2010 index cases control/mask/mask & hygiene: 8/7/7 years respectively; 2009/2010 household contacts control/mask/mask & hygiene: 35/37/34 years; 2010/2011 index cases control/mask/mask & hygiene: 8/8/7 years; 2010/2011

No mention of mean age, median age reported for 84 households in several groups:

2010/2011 index cases control/mask/mask & hygiene: 8/8/7 years; 2010/2011 household contacts control/mask/mask & hygiene: 38/25/35 years; 156 males, 146

females.

Group 1 (2009/2010 and 2010/2011 sub-groups): Participants were part of the control arm and were not assigned masks nor hand rub (n = 49/n = 63 respective to sub-groups) vs. Group 2 (2009/2010 and 2010/2011 sub-groups): Participants were provided and

Comparison:

instructed how to properly use surgical face masks (n = 42/n = 53) vs. Group 3

(2009/2010 and 2010/2011 sub-groups): Participants were provided with both surgical masks and alcohol hand-rub (w/ instructions for proper hygiene) (n = 56/n = 39).

Follow-up: No mention of follow-up

Group 1 (2009/2010 and 2010/2011) reported 19/82 RT-PCR positive influenza cases (8

and 11 respective to sub-groups) (95% CI of 13-35) vs. Group 2 (2009/2010 and

Results: 2010/2011) with 6/69 (3 and 3) (95% CI of 3-19) vs. Group 3 at 10/67 (3 and 7) (95% CI of

5-27) (p = 0.18). The resulting total infection rate was 16%, and intention to treat findings

between Group 2 and 3 were insignificant.

"Results suggest that household transmission of influenza can be reduced by the use of NPI, such as facemasks and intensified hand hygiene, when implemented early and used

diligently. Concerns about acceptability and tolerability of the interventions should not

be a reason against their recommendation."

Cluster randomized influenza transmission in household trial. Data suggest household

transmission of influenza likely reduced by proper facemask use and meticulous hand

hygiene, but this reduction was not significant.

Canini 2010 (score=5.0) [357]

Category: Mask Efficacy

Study Type: RCT

Conflict of Interest:

Sponsored by grant from the Ministere de la Sante and la Direction des Hopitaux, as well

as funding from the Assistance Publique des Hopitaux de Paris. No COI.

N = 105 households (with 105 index cases and 306 total contacts) sampled from 3 French

Sample size: regions with sizes of 3-8 members and one index patient testing (rapid) positive for

influenza A.

Mean age: 26.8 years (Index cases with mean of 26.5 and household contacts with mean

Age/Sex: of 27 years); 207 males, 204 females (index cases with 55 males, 50 females; household

contacts with 152 males, 154 females)

Group 1: Participants received 30 three-layer age-appropriate (child/adults) surgical

masks (AEROKYN) for usage 5 days after index patient medical visit and instructions to

replace masks every 3 hours (n = 200) vs. Group 2: Received no masks/intervention over

7-day period from inclusion (n = 211).

Follow-up: Follow-up survey performed daily for 7-day period.

Group 1 reported ILI in 24/148 participants (16.2%) vs. Group 2 with 25/158 (15.8%); the

group differences were 0.40% (95% CI of -10% to 11%, p=1.00). The adjusted

Results: multivariate odd ratio (Group 1 vs. Group 2) was reported to be statistically insignificant

at 0.95 (95% CI of 1.53 to 8.73, p=0.90). Good adherence/compliance was observed in

the intervention group with reference to mask-wearing.

"This study should be interpreted with caution since the lack of statistical power

Conclusion: prevents us to draw formal conclusion regarding effectiveness of facemasks in the

context of a seasonal epidemic."

Cluster randomized influenza transmission in household trial. Data did not show efficacy

Comments: in facemask use for reduction of influenza transmission. However, compliance to proper

facemask use difficult to accurately assess.

Loeb 2009 (score=5.0) [225]

Comparison:

Category: Mask Efficacy

Study Type: RCT

Conflict of Interest: Sponsored by the Public Health Agency of Canada. No COI.

Sample size: N = 446 nurses working within the scope of 8 Ontario tertiary care hospitals who were

able to provide fit-test certification

Age/Sex: Mean age: 36.2 years; 26 males, 420 females

Group 1: Nurses were instructed/required to wear their currently used hospital brand of surgical masks alongside gloves and gowns while working with patients with febrile

Comparison: respiratory illness until the end of influenza season (n = 212) vs. Group 2: Nurses were

instructed/required to wear N95 respirators under same clothing and operating

conditions as Group 1 (n = 210).

Follow-up: Follow-up varied with an average of 97.6 days between groups

50 nurses (23%) in Group 1 were (laboratory) confirmed to have influenza (primary outcome) vs. Group 2 with 48 nurses (22.9%) w/ an absolute risk difference of –0.73%. 95% CI (difference) of –8.8% to 7.3 % (p=0.86). RT-PCR tests for influenza A and B yielded 5 confirmed cases in Group 1 vs. 1 in Group 2 (A) and 1 in Group 1 vs. 3 in Group 2 (B)

Results: 5 confirmed cases in Group 1 vs. 1 in Group 2 (A) and 1 in Group 1 vs. 3 in Group 2 (B).

Absolute risk differences were -1.88 (95% CI of -4.13 to 0.36, p=0.22) and 0.96 (95% CI of -0.89 to 2.81, p=0.37) respectively. Non-significant differences when tested using RT-

PCR for 5 other respiratory viruses (including Coronaviruses).

Conclusion: "Among nurses in Ontario tertiary care hospitals, use of a surgical mask compared with

an N95 respirator resulted in noninferior rates of laboratory-confirmed influenza." Randomized influenza trial comparing surgical masks to N-95 respirators but only using

these when providing patient care within the hospital. Data suggest comparable efficacy

between masks and N-95 respirators for preventing influenza acquisition (23.6% versus

22.9%), suggesting there is no added benefit of the N-95.

Aiello 2010 (score=5.0) [362]

Comments:

Category: Mask Efficacy

Study Type: Cluster Randomized Trial

Conflict of Interest: Sponsored by grant from the Centers for Disease Control and Prevention. NO COI.

Sample size: N = 1372 participants living in university residence halls who were above the age of 18

years and did not exhibit any skin alcohol-related allergies

Age/Sex: Mean age and sex data only available for 1297 participants. Mean age: 18.6 years; 436

males, 861 females

Group 1: Participants were instructed to use both a face mask and proper hand hygiene

(alcohol-based hand sanitizer, cough etiquette, etc.) for a 6-week period (although hand

hygiene was introduced to all groups) (n = 367) vs. Group 2: Participants were only instructed to actively use face marks for 6 weeks (n = 378) vs. Group 3: Participants were

instructed to actively use face masks for 6 weeks (n = 378) vs. Group 3: Participants were part of the control group and received no interventions during the 6-week period (n =

552).

Follow-up: Follow-up every week (via surveys) for 6 weeks.

In Group 1, 92 participants were shown to exhibit influenza-like illness (ILI; the primary outcome) vs. Group 2 with 99 and vs. Group 3 with 177. No significant differences were shown between the three groups surveyed symptoms (all p>0.05). After adjustments for

covariates, Group 1 showed statistically significant reductions from Group 3 for ILI for weeks 4-6 with rate ratios of 0.72 (95% CI of 0.53 to 0.98, p=0.03), 0.65 (95% CI of 0.43 to

0.98, p=0.04), and 0.58 (95% CI of 0.34 to 1.00, p=0.05). respectively.

"These findings suggest that face masks and hand hygiene may reduce respiratory illnesses in shared living settings and mitigate the impact of the influenza A (H1N1)

Conclusion: illnesses in shared living settings and mitigate the impact of the influenza A (H1N1)

pandemic."

Cluster randomization influenza trial. There was an observed significant reduction in influenza-like illness (ILI) in the mask and hand hygiene group compared to controls (35%)

versus 51%). Adjusting for vaccination, a face mask alone was also better than controls.

MacIntyre 2016 (score=5.0) [374]
Category: Mask Efficacy

Results:

Study Type: Cluster randomized trial

Sponsored by a UNSW Goldstar award. COI, Chandini Raina MacIntyre received grants

Conflict of Interest: and support from Pfizer, CSK, and Bio-CSL and Holly Seale received funds from CSK, bio-

CSL, and Saniofi Pasteur.

Sample size: N = 245 patients with influenza-like illness (ILI) who lived with at least 2 other people.

Age/Sex: Mean age: 40.0 years; 101 males, 144 females.

Mask Group: Patients wore a mask at home when in the same room as another person

Comparison: except when eating or sleeping for 7 days or until symptoms stopped (n=123) vs Control

Group: Patients did not receive any intervention (n=122).

Follow-up: Follow-up at 7 days.

Number of household members with clinical respiratory illness in mask vs control group: 4 vs 6 (relative risk (RR)=0.65), (p>0.05). Number of household members with ILI in mask

Results: vs control group: 1 vs 3 (RR=0.32), (p>0.05). Number of household members with

laboratory confirmed viral respiratory infection in mask vs control group: 1 vs 1

(RR=0.97), (p>0.05).

"The study indicates a potential benefit of medical masks for source control, but is limited by small sample size and low secondary attack rates. Larger trials are needed to

confirm efficacy of medical masks as source control."

Cluster randomized trial to determine whether medical mask use in influenza like illness individuals is protective for their respective contacts. Post hoc analysis showed a

protective effect in preventing clinical respiratory illness but not against influenza like

illness (ILI) nor laboratory confirmed viral infections of the respiratory tract.

Radonovich 2019 (score=4.5) [222]
Category: Mask Efficacy

Study Type: RCT

Conclusion:

Comments:

Sponsored by the US Centers for Disease Control and Prevention, Veterans Health

Administration, and the Biodefense Advanced Research and Development Agency. COI,

one or more of the authors have received or will receive benefits for personal or

professional use.

Sample size: N = 2862 healthcare personnel (HCP) who work within 6 feet of patients and work more

than 24 hours per week.

Age/Sex: Mean age: 43.0 years; 493 males, 2369 females.

N95 Group: participants wore an N95 respirator whenever within 6 feet of patients with respiratory illness for a 12-week period determined by the ALERT algorithm to be high in

respiratory illness and infection each year for 4 years (n=2512) vs Medical Mask Group:

followed the same protocol as the N95 group except with a medical mask (n=2668).

Volunteering participants were cluster randomized each year for 4 years.

Follow-up: Follow-up at 5 years.

Comparison:

Comments:

Comparison:

Results:

Conclusion:

Total number (percent difference) of laboratory confirmed influenza in the N95 vs Medical Mask Group: 207 vs 193 (1.0%), (p=0.18). Difference in incidence rate per 1000

Results: HCP-season for acute respiratory illness in N95 vs Medical Mask Group: -21.9 (p=0.1).

Difference in incidence rate per 1000 HCP-season for laboratory-detected respiratory

infections in N95 vs Medical Mask Group: -8.9 (p=0.47).

"Among outpatient HCP, N95 respirators vs medical masks as worn by participants in this

Conclusion: trial resulted in no significant difference in the incidence of laboratory-confirmed

influenza."

Influenza prevention trial comparing N-95 respirators to standard medical masks. Population of direct patient care givers working a minimum of 24 hours per week.

Aerosol generating procedures were recorded. Data suggest no difference between

groups for influenza prevention.

Cowling 2009 (score=4.5) [364]
Category: Mask Efficacy

Study Type: Cluster randomized trial

Conflict of Interest: Sponsored by Centers for Disease Control and Prevention. No COI.

N = 407 Indexed patients with at least 2 acute respiratory illness symptoms and a positive

Sample size: test for influenza A or B. N= 749 household contacts who have no symptoms in 259

households.

No mention of mean age; median age for indexed patients: 10.7 years; 201 males, 206

Age/Sex: females. No mention of mean age; median age for household contacts: 38.7 years; 306

males, 443 females.

Control Group: Households received healthy lifestyle advice (n=134) vs Hand Hygiene Group: Households received education on hand washing and used 221 mL Ivory liquid hand soap after using the bathroom, coughing, or sneezing and used alcohol rub of 80% ethanol, 1.45% glycerol, and 0.125% hydrogen peroxide every time they got home or

touched a contaminated surface for 7 days (n=136) vs Facemask plus Hand Hygiene Group: Households received the same hand washing as above in addition to wearing a

surgical mask when at home or around the indexed patients for 7 days (n=137).

Follow-up: Follow-up at 7 days

Secondary attack ratio for Control vs Hand Hygiene vs Facemask Plus Hand Hygiene Group by 7 days for reverse-transcription polymerase chain reaction (RT-PCR) confirmed: 10 (95% CI: 6,14) vs 5 (CI: 3,9) vs 7 (CI: 4,11), (p=0.22), for participants with at least 2 of the symptoms including a temperature of 37.8 °C or higher, cough, headache, sore

throat, or myalgia: 19 (CI: 14,24) vs 16 (CI: 12,21) vs 21 (CI: 16,27), (p=0.40), and for participants with a temperature of $37.8~^{\circ}$ C or higher and a cough or sore throat: 5 (CI:

2,8) vs 4 (CI: 2,6) vs 7 (CI: 4,11), (p=0.28).

"Hand hygiene and facemasks seemed to prevent household transmission of influenza virus when implemented within 36 hours of index patient symptom onset. These findings suggest that nonpharmaceutical interventions are important for mitigation of pandemic

and interpandemic influenza."

Cluster randomized influenza transmission prevention study in households. Data suggest

Comments: that hand hygiene and facemask use appear to prevent transmission of influenza if

implemented within 36 hours of index patient onset of symptoms.

Leung 2020 (score=NA) [375]

Category: Mask Efficacy

Study Type: Post-hoc analysis of Cowling 2009

Sponsored by General Research Fund of the University Grants Committee, the Health and

Conflict of Interest:

Medical Research Fund, and a commissioned grant of the Food and Health Bureau and

the Theme-based Research Scheme of the Research Grants Council of the Hong Kong SAR

Government. COI, B.J.C consults for Roche and Sanofi Pasteur.

Sample size: N = 246 patients who provided an exhaled breath sample.

Age/Sex: No mention of mean age; 102 males, 144 females.

Group 1: Patients did not wear a face mask for their first exhaled breath collection

Comparison: (n=246) vs Group 2: Patients wore a face mask during the exhaled breath sample

(n=124).

Follow-up: No follow-up.

Results:

Number (percent) of positive influenza virus detection with droplet particles for Group 1 vs Group 2: 6 (25%) vs 1 (4%), (p=0.04). Number (percent) of positive coronavirus detection with aerosol particles for Group 1 vs Group 2: 4 (40%) vs 0 (0%), (p=0.04). Median (interquartile range) of influenza viral load with droplet particles for Group 1 vs

Group 2: 0.3 (0.3, 1.1) vs 0.3 (0.3, 0.3), (p=0.01). Median (interquartile range) of coronavirus viral load with aerosol particles for Group 1 vs Group 2: 0.3 (0.3, 0.3) vs 0.3

(0.3, 0.3), (p=0.02)

Conclusion: "Our results indicate that surgical face masks could prevent transmission of human

coronaviruses and influenza viruses from symptomatic individuals."

Surgical face masks significantly reduced detection of influenza virus, the presence of RNA in respiratory droplets and coronavirus RNA in aerosols trending towards a

Comments: reduction of a reduction of RNA in respiratory droplets suggesting face masks could

prevent transmission of both influenza and coronavirus from symptomatic individuals.

Cowling 2008 (score=4.0) [363]

Category: Mask Efficacy

Study Type: Cluster randomized trial

Sponsored by the US centers for Disease Control and Prevention, the Research Fund for

Conflict of Interest: the Control of Infectious Disease, Food and Health Bureau, and the Area of Excellence

Scheme of Hong Kong University Grants Committee. No COI.

N = 198 participants reporting at least wo symptoms of influenza-like-illness (ILI) and

Sample size: living in household with at least two other individuals who did not reported ILI symptoms

in previous 14 days

Age/Sex: No mention of mean age; 90 males, 108 females.

Control: received education about the importance of healthy diet and lifestyle (n=127 households) vs. Face Mask: received same education as controls plus education about the potential efficacy of mask, and 50 surgical masks (n=35 households) vs. Hand

Comparison:

Hygiene: received same education as controls plus education about potential efficacy of proper hand hygiene in reducing transmission, and given alcohol hand sanitizer and

liquid soap, (n=36 households)

Follow-up: Follow-up at 36 hours and at days 3, 6, and 9

Secondary Attack Ratio (lab-confirmed) overall was 6.0% (95% CI [3.8, 9.0]). Compared to

Results: the control group the face mask group had an odds ratio (OR) of 1.16 (95% CI [0.31,

4.34]) and the hand hygiene group had an OR of 1.07 [0.29, 4.00].

Conclusion: "Hand hygiene and facemasks seemed to prevent household transmission of influenza

virus when implemented within 36 hours of index patient symptom onset. These findings

suggest that nonpharmaceutical interventions are important for mitigation of pandemic

and interpandemic influenza."

Cluster randomized influenza trial to prevent household transmission of influenza. High

dropout rate and low interventional adherence.

Simmerman 2011 (score=4.0) [358]
Category: Mask Efficacy

Study Type: RCT

Conflict of Interest: Sponsored by the US CDC. COI, Cowling has received funding from MedImmune Inc. **Sample size:** N = 465 pediatric patients with influenza-like illness at outpatient department

Age/Sex: No mention of mean age, age range 0-15 years; Gender data available for only 348 index

patients: 192 males, 156 females

Hand-washing education and given hand-washing kit with liquid hand soup (n=155) vs. Hand-washing education and given hand-washing kit, also given 50 standard paper

Comparison: surgical fact masks and 20 pediatric fact masks (n=155) vs. Controls received education

on nutrition, exercise, and smoking cessation (n=155)

Follow-up: Follow-up at 24 hours and at days 3, 7 and 21

Overall secondary attack rate (SAR) was 21.5%, of which 16.3% of secondary cases were

asymptomatic. Secondary influenza infection was not significantly different between handwashing group and control group (odds ratio [OR] = 1.2, p = 0.442). It was also not

Results: handwashing group and control group (odds ratio [OR] = 1.2, p = 0.442). It was also not significantly different between the handwashing and masking group and control group

(OR = 1.16, p = 0.525)

Conclusion: "Influenza transmission was not reduced by interventions to promote hand washing and

face mask use."

Randomized influenza prevention study comparing handwashing to handwashing and

facemask use. Data suggest influenza transmission did not decrease via handwashing and

facemask use perhaps due to transmission prior to the interventional start or poor

compliance.

Larson 2010 (score=3.5) [376]

Category: Mask Efficacy

Study Type: RCT

Randomized non-pharmaceutical intervention trial to prevent influenza and other URIs in

crowded urban households. There appears to be no datable added benefit from either

Comments: hand sanitizer or face masks in decreasing upper respiratory infections (URIs) versus

targeted education. However, facemasks were associated with decreased rates of

secondary transmission

Respiratory Disease Transmission Mask Efficacy

MacIntyre 2009 (score=5.0) [360]
Category: Mask Efficacy

Study Type: Cluster randomized trial

Conflict of Interest: Sponsored by the Office of Health Protection, Department of Health and Ageing,

Australia, 3M Australia, and Medical Research Council (UK). No mention of COI.

Sample size: N = 145 households with 2 or more healthy adults and a child with a fever or other

respiratory symptoms.

Age/Sex: No mention of age or gender distribution.

Surgical Mask Group: Adults wore a 3M surgical mask when in the same room as the sick child for 1-week (n=47) vs P2 Mask Group: adults wore a 3M flat-fold P2 mask when

Comparison:

in the same room as the sick shild for 1 week (n=46) vs Control Croun; adults did not

in the same room as the sick child for 1-week (n=46) vs Control Group: adults did not

wear a mask (n=52).

Follow-up: Follow-up at 1 and 2 weeks.

Proportion (percent) of individuals with influenza-like illness after 1 week in Surgical Mask vs P2 Mask vs Control Group: 21/94 (22.3%) vs 14/92 (15.2%) vs 16/100 (16.0%), (p=1) Total laboratory confirmed infection for Surgical Mask vs P2 Mask vs Control

Results: (p=1). Total laboratory confirmed infection for Surgical Mask vs P2 Mask vs Control

Group: 6 vs 8 vs 3, (p=0.12). The number of adults who tested positive for the same respiratory virus as the child for the Surgical Mask vs P2 Mask vs Control: 3 vs 5 vs 2,

(p>0.05).

"We concluded that household use of face masks is associated with low adherence and is ineffective for controlling seasonal respiratory disease. However, during a severe

pandemic when use of face masks might be greater, pandemic transmission in

households could be reduced."

Cluster randomized face mask trial for prevention of respiratory viral transmission in household contacts. Participants were parents of children seeking care for temperature >37.8 and either a cough or a sore throat. Three arms: 3M surgical masks, P-2 masks

(similar to US N-95 HEPA masks), controls, (no masks). Outcome was a diagnosis of viral

infection within one week of study enrollment. Data suggest no difference between

groups likely due to lack of mask compliance.

<u>Jacobs 2009</u> (score=4.0) [361]

Conclusion:

Comments:

Category: Mask Efficacy

Study Type: RCT

Conflict of Interest: No mention of sponsorship. No COI.

Sample size: N = 32 healthcare workers were recruited from 520-bed tertiary care hospitals

Age/Sex: Mean age: 35.46 years; 9 males, 23 females

Group 1: Wore face mask while on hospital property while working, disposable surgical

Comparison: mask MA-3 (n=17) vs. Group 2: No mask while on hospital property unless required to

do so by job duties (n=15)

Follow-up: Follow-up at end of study participation (range 0-210 days, average 43.3 days)

Results: Those in the mask group were more likely to experience headache during the study (p <

0.05). Only one person from each intervention group developed a cold.

Conclusion: "Face mask use in health care workers has not been demonstrated to provide benefit in

terms of cold symptoms or getting colds."

Randomized surgical face mask trial to prevent cases of the common cold. Small sample

Comments: (N=32), therefore interpretation of results is limited. Also, facemask use was not

controlled for outside of the hospital setting.

Alfelali 2020 (score=3.0) [377]

Category: Mask Efficacy

Study Type: RCT

Comments: Cluster randomized trial to prevent viral respiratory infections in Hajj pilgrims using

facemasks. Data suggest lack of efficacy likely due to lack of compliance.

Alfelali 2019 (score=2.0) [378]

Category: Mask Efficacy

Study Type: RCT

Comments: Open-label cluster randomized trial to prevent viral respiratory infections. High dropout

rate and low compliance.

Mask Type Comparison – Mask Efficacy

MacIntyre 2015 (score=5.0) [346]
Category: Mask Efficacy

Comparison:

Results:

Comments:

Study Type: Cluster randomized trial

Sponsored by the Australian Research Council. COI, Chandini Raina MacIntyre received

Conflict of Interest: grants and support from Pfizer, CSK, and Bio-CSL and Holly Seale received funds from

CSK, bio-CSL, and Saniofi Pasteur.

Sample size: N = 1607 healthcare workers (HCW) in high-risk wards of a hospital.

Age/Sex: Mean age: 35.7 years; 357 males, 1250 females.

Medical Mask Group: HCWs were supplied with 2 medical masks per day to wear for the duration of every shift for 4 weeks (n=580) vs Cloth Mask Group: HCWs were provided with 5 cloth masks total which were to be worn for the duration of every shift and

washed/rotated for 4 weeks (n=569) vs Control Group: HCWs wore a mask according to standard practice which could include some mask wearing and was documented for 4

weeks (n=458).

Follow-up: Follow-up daily for 4 weeks.

Percent of patients with influenza-like illness (ILI) for Medical Mask vs Cloth Mask Group: 0.17% vs 2.28% (relative risk (RR)=13.25), (p<0.05). Percent of patients with (ILI) for Medical Mask vs Cloth Mask Group: 2.28% vs 0.66% (RR=3.49), (p<0.05). There were

no significant differences for Medical Mask vs Cloth Mask vs Control Group in terms of

percent of patients with clinical respiratory illness: 4.83% vs 7.56% vs 6.99% or

laboratory confirmed viral infections: 3.28% vs 5.45% vs 3.94%.

"This study is the first RCT of cloth masks, and the results caution against the use of cloth masks. This is an important finding to inform occupational health and safety. Moisture retention, reuse of cloth masks and poor filtration may result in increased risk of infortion. Further research is peeded to inform the wides proad use of cloth masks.

Conclusion: of infection. Further research is needed to inform the widespread use of cloth masks

globally. However, as a precautionary measure, cloth masks should not be

recommended for HCWs, particularly in high-risk situations, and guidelines need to be

updated."

Cluster randomized trial comparing cloth masks to medical masks in healthcare workers (HCWs). Control arm was not a pure "no mask" group as some mask use occurred in the control arm. Data suggest penetration into the cloth masks was 97% versus the medical masks 44% as the rate of all influenza like illness (ILI) was significantly higher in the cloth

mask group (RR=13.0), compared to the medical mask group.

MacIntyre 2020 (score=NA) [379]
Category: Mask Efficacy

Study Type: Post Hoc Analysis of MacIntyre 2015

Conflict of Interest:

Sponsored by the National Health and Medical Research Council Principal Research

Fellowship. COI, Tham Chi Dung works for the Vietnam Ministry of Health.

Sample size: N = 607 healthcare workers (HCW) from the MacIntyre 2015 study who used two-

layered cloth masks.

Age/Sex: No mention of mean age; No mention of gender distribution.

Self-Washing Group: HCWs received 5 cloth masks to wear and rotate by washing with

Comparison: soap and water then hanging to dry for 4 weeks (n=467) vs Hospital Laundry Group: received 5 cloth masks to wear and rotate by washing in the hospital laundry machine

with detergent for 4 weeks (n=140)

Follow-up: Follow-up at 4 weeks.

Hazard ratio (95% CI) of infection for Self-washing vs Hospital Laundry group: 2.04 (1.03,

Results: 4.00), (p=0.04). There was no significant difference in infection rate for Self-washing vs

Hospital Laundry Group (p=0.5).

"Using self-reported method of washing, we showed double the risk of infection with

seasonal respiratory viruses if masks were self-washed by hand by HCWs. ... Cloth masks washed in the hospital laundry were as protective as medical masks. Both cloth and

Conclusion: washed in the hospital laundry were as protective as medical masks. Both cloth and medical masks were contaminated, but only cloth masks were reused in the study,

reiterating the importance of daily washing of reusable cloth masks using proper method. A well-washed cloth mask can be as protective as a medical mask."

A subgroup of the original participants was analyzed. Self-hand washing of cloth masks was associated with a twofold increase in seasonal respiratory viruses. Cloth masks

laundered in the hospital laundry according to procedure were determined to be as

effective as medical masks.

MacIntyre 2013 (score=4.0) [380]

Comments:

Conclusion:

Comparison:

Category: Mask Efficacy

Study Type: Cluster randomized trial

Conflict of Interest: Sponsored by the National Health and Medica Research Council of Australia # 630787.

No mention of COI.

Sample size: N = 1669 nurses and doctors who are full time in the emergency department or

respiratory ward

Age/Sex: Mean age: 33.10 years; 243 males, 1426 females.

Group 1: 3M Standard Tie-On Surgical Mask (n=572) vs. Group 2: 3M Health Care N95

Comparison: Particulate Respirator (n=516) vs. Group 3: targeted (intermittent) use of N95

respirators only while doing high risk procedures or barriers (n=581). All participants

wore masks during shifts for 4 weeks

Follow-up: Follow-up at 4 weeks

The clinical respiratory illness (CRI) was highest in Group 1 (98 /572; 17%) followed by

group 3 (61/516; 11.8%), and then by group 2 (42/581; 7.2%) (p<0.05). Bacterial

Results: respiratory tract colonization in those with CRI was highest in group 1, then group 2 and

then group 3 (14.7%, 10.1%, 6.2%, p=0.02)

"In summary, this study adds evidence in favor of N95 respirators as respiratory

protection for HCWs, and describes for the first time a differential rate of bacterial detection in the respiratory tract depending on level of respiratory protection."

Cluster randomized clinical trial for prevention of respiratory illness. Baseline

differences in numbers of influenza vaccinations among groups as the N-95 group had more vaccinations. Data suggest continuous use of N-95 respirators was associated with

significantly greater efficacy for the prevention of clinical respiratory illness (CRI) p <0.5, compared to targeted N-95 use or medical mask use. Medical mask use reported 17%

CRIs, targeted N-95 11.8% and continuous N-95 7.2%

MacIntyre 2011 (score=4.0) [381]
Category: Mask Efficacy

Study Type: Cluster randomized trial

Conflict of Interest: Sponsored by the Medical Research Council. COI, Macintyre received grants from

influenza manufacturers GSK and CSL biotherapies.

Sample size: N = 1441 health care workers from 15 emergency departments and respiratory wards

Age/Sex: Mean age: 33.6 years; 142 males, 1299 females.

Group 1: wore medical masks for every shift for 4 weeks (3M Medical mask, catalogue number 1820, St Paul, MN USA) (n=492) vs Group 2: wore N95 fit-tested mask for 4 weeks (3M flat-fold N95 respirator, catalogue number 9132) (n=488) vs Group 3: wore

N95 non-fit-tested mask for 4 weeks (3M flat-fold N95 respirator, catalogue number

9132) (n=461).

Follow-up: Follow-up at 4 weeks.

Results: Clinical respiratory illness (CRI) ranged between 3.9% to 6.7% (Medical mask 6.7%,

Reference group; N95 fit-tested 4.6%, OR=0.76, 95% CI(0.27-2.13); N95 3.3%, OR=0.48,

(0.24-0.98)). Influenza-like illness ranged between 0.3% to 0.6% (Medical mask 0.6%, Reference group; N95 fit-tested 0.2%, OR=0.35, (0.04-3.42); N95 0.3%, OR=0.67, (0.11-

4.03))

"In summary, our study adds evidence on the use of respiratory protection for healthcare workers, but highlights the needs for larger trials and comparison of

different policy options."

Cluster randomized trial comparing fit tested and non-fit tested N-95 respirators to medical masks for the prevention of respiratory viral infections in health care workers. Not well randomized for age, numbers of adults living in the same home, type of work, procedural risk, vaccination status, handwashing. Rates of infection in medical mask

group were double compared to the N-95 group but the non-fit tested N-95 group had lower infection rates compared to the fit tested N-95 group which may be a function of

a lack of an underpowered study.

MacIntyre 2014 (score=NA) [366]
Category: Mask Efficacy

Comments:

Results:

Comments:

Comparison:

Study Type: Post Hoc analysis of MacIntyre 2011

Sponsored by a strategic research funding from UNSW Medicine, The University of New

Conflict of Interest: South Wales, Australia. One or more authors have received or will receive benefits for

personal or professional use.

Sample size: N = 1922 health care workers from emergency departments and respiratory wards

Age/Sex: No mention of mean age or gender distribution

Group 1: wore medical masks for every shift for 4 weeks (3M Medical mask, catalogue number 1820, St Paul, MN USA) (n=492) vs Group 2: wore N95 fit-tested mask for 4 weeks (3M flat-fold N95 respirator, catalogue number 9132) (n=488) vs Group 3: wore

Comparison: weeks (3M flat-fold N95 respirator, catalogue number 9132) (n=488) vs Group 3: wore N95 non-fit-tested mask for 4 weeks (3M flat-fold N95 respirator, catalogue number

9132) (n=461) vs. Group 4: Control healthcare workers, no masks (n=481)

Follow-up: Follow-up at 4 weeks.

Bacterial colonization percentages among groups: N95 group (combined) = 2.8% (p=0.02); Medical Mask group = 5.3% (p<0.01); Control group = 7.5% (p=0.16). n95

groups showed a protective effect against bacterial colonization (adjusted RR=0.34, 95%

CI [0.21, 0.56])

"N95 respirators were significantly protective against bacterial colonization, cocolonization and viral-bacterial co-infection. We showed that dual respiratory virus or

Conclusion: bacterial-viral co-infections can be reduced by the use of N95 respirators. This study has

occupational health and safety implications for health workers."

N-95 respirators were found to be significantly more effective in the prevention of

bacterial colonization, co-colonization, and viral-bacterial co-infection.

MacIntyre 2017 (score=NA) [365]
Category: Mask Efficacy

Study Type: Pooled analysis of MacIntyre 2011 and 2013

Sponsored by Australian National Health and Medical Research Council of Australia

Conflict of Interest: (#630787). One or more authors have received or will receive benefits for personal or

professional use.

Sample size: N = 3591 health care workers from emergency departments and respiratory wards

Age/Sex: No mention of mean age or sex

Group 1: continuous N95 respirator use for all times on shift for 4 weeks (n=1530) vs Group 2: targeted N95 respirator use, during high-risk procedures for all times on shift 4

weeks (n=516) vs Group 3: medical mask for all times on shift for 4 weeks (n=1064) vs

Group 4: Control group (n=481)

Follow-up: Follow-up at 4 weeks.

The continuous N95 and/or targeted N95 groups consistently showed the best results when compared to the control group for laboratory confirmed bacterial colonization Results:

(Risk Ratio = 0.33, 95% CI 0.21-0.51; p < 0.001) and droplet-transmitted infection (RR =

0.26, 95% CI 0.16-0.42; p < 0.001).

The results suggest that the classification of infections into droplet versus airborne

transmission is an oversimplification. Most guidelines recommend masks for infections

spread by droplets. N95 respirators, as "airborne precautions," provide superior protection for droplet-transmitted infections."

It appears to be a simplification to classify infections into either droplet or aerosol and Comments:

most guidelines recommend masks for the prevention of infections spread via droplets.

Lockdowns and Shutdowns

Restrictions on businesses, schools, and public gatherings have been used in attempts to control the COVID-19 pandemic, including limitations on travel, large gatherings, in-person schools, restaurants, bars, and non-essential businesses. Even under the strictest shelter-inplace jurisdictions in the United States, however, most individuals could continue to visit grocery stores, which may have provided a means for continuing community spread despite masking requirements.

Studies are beginning to be published concerning the efficacy of lockdowns. Most studies have reported reduced COVID-19 transmission after the implementation of a lockdown [382, 383], although it has been reported that lockdowns were not effective in Europe [382]. An ecological study suggested greater spread where restaurant dining was allowed [384]. One analysis of multiple countries found non-significant small reductions in COVID-19 case rates in most countries, which was not felt to be outweighed by the costs [382]. Reports have questioned the cost-benefit efficacy of lockdowns, including in Israel and the United Kingdom [385, 386]. Adverse mental health effects have been reported [387-391]. The subject of lockdowns requires considerably greater research, especially as future surges attributed to variants seem likely; the re-implementation of such lockdown policies may necessitate a stronger evidence base.

Diagnostic Approach

Laboratory Tests

Conclusion:

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 [161, 162]:

- 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 [211]. The 10 variables included in the model are: 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-to-lymphocyte ratio (OR: 1.06), lactate dehydrogenase (OR: 1.002), and direct bilirubin (OR: 1.15). A free online risk calculator is available [392].

Decreases in creatinine kinase (CK) and LDH have been associated with increased COVID-19 viral clearance in a secondary analysis of hospitalized patients treated with varying antiviral and other medications (IFN- α + lopinavir/ritonavir \pm ribavirin) [393].

Diagnostic Testing

Three main types of diagnostic tests are used for COVID-19: (1) polymerase chain reaction (PCR)-based testing, typically using swabs [394]; (2) antigen testing, and (3) antibody testing of blood serum. PCR testing is considered to be diagnostic of the infection because it detects the actual virus or viral particles. Antigen tests have been approved by the U.S. Food and Drug Administration (FDA) and are also considered diagnostic [395]. Antibody testing detects prior infection. All types of testing have had limitations in specificity and sensitivity. A difference in performance over time since symptom onset has been reported [396].

Saliva testing for SARS-CoV-2 detection is also available, which is appealing for ease of collection. Pooled saliva testing has been used in employed populations [397]. One study detected higher SARS-CoV-2 titers in saliva compared to nasopharyngeal swabs, with less longitudinal variability [398]. If validated with larger-scale studies, saliva testing could provide near universal sampling coverage for both symptomatic and asymptomatic patients [399].

Test results, when accurate, may only indicate the presence or absence of infection at the time of the test; thus, the frequency of testing, and which methods to use, are debatable. In university settings, routine surveillance testing of representative subpopulations of students is recommended, with more frequent testing of higher-risk groups such as athletes. More frequent testing with less sensitive (and often cheaper) tests that are capable of detecting infectious virus (rather than any virus) will shortly become available and are recommended [400].

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 [401]. Because they also amplify viral fragments, they can show recent infection among those who are still clearing the viral particles, up to weeks after infection; thus, they may not reflect active viral shedding and/or infectiousness. 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 disease becomes more common, individuals who present with symptoms but test negative are increasingly more likely to represent false-negatives irrespective of testing accuracy. 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 of COVID-19 infection that should be distinguished from non-COVID-19 causes. Because the SARS-CoV-2 virus causes such a wide spectrum of disease, from asymptomatic illness to life-threatening infection, along with the possibility of other co-circulating respiratory viruses at various times (e.g., influenza), the issue of accurate diagnostics for SARS-CoV-2 becomes one of paramount importance for the foreseeable future. The ability to widely perform COVID-19 testing is of particular importance during times of anticipated epidemic waves (e.g., fall/winter 2020–21).

Most of the limited evidence suggests that nasopharyngeal and oropharyngeal samples are comparable for the first week, but then the nasopharyngeal sample becomes more sensitive [402, 403]:

- 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 [404].

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 within several days of the onset of symptoms consistent with a COVID-19 infection. Testing without experienced medical judgment [405] is ill-advised given that the risk of false-negative tests are 20–67% [32]. Thus, there is a strong indication to presumptively treat cases who test negative, which requires experienced medical judgment. Repeat testing may be indicated for those with a negative test but a high index of suspicion.

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).

Antigen Testing

Antigen tests detect viral proteins either on or within the virus. These have been FDA-approved and are considered diagnostic [395]. Antigen testing is growing in popularity as its main strength is rapid test results, which are provided in minutes compared with up to several days for PCR tests.

Antigen testing is recommended for the diagnosis of COVID-19. Testing should be performed either at the time of COVID-19-like symptom onset, or within several days of the onset of symptoms consistent with a COVID-19 infection. Antigen testing has not been validated for asymptomatic persons. However, the sensitivity among symptomatic persons is estimated to be approximately 80%. Thus, testing without experienced medical judgment is ill-advised [405], given the risks of false-negative tests. There is a strong indication to presumptively treat cases who test negative, which requires experienced medical judgment. Repeat testing may be indicated for those with a negative test but a high index of suspicion.

Antigen 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 humoral response to the virus [406-411]. Most antibody tests detect IgG, although some tests 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), although IgM may wane after 2 to 3 weeks, and IgG persists for a far longer period of time [412]. A positive antibody test does not exclude the potential for the patient being infectious with COVID-19. Antibody tests are in early stages of deployment and reported reliability varies widely [408-410]. Because there is no reference standard and widespread testing of large populations have not been reported, the determination of test accuracy, sensitivity, and specificity remain problematic. In addition, the timing of the antibody testing is critical to accurate detection: testing too soon after infection onset, or too late after infection resolution, can further increase risks of negative results.

It has been aspirational that immune status testing (IgG, IgM) would eventually be the most important test for population-based risk assessments, such as herd immunity. This still requires considerable research, including large-scale determinations of sensitivity, specificity, reliability, timing, persistence of the immunoglobulins, and whether the immunoglobulin status identified by testing will be associated with true immunity [413]. Preliminary evidence includes a large population-based Spanish study suggesting a 87.6–91.8% seroprevalence rate among those who had PCR confirmation of infection; yet, individuals meeting a case definition of anosmia or at least 3 relevant symptoms had a seroprevalence rate of only 15.3–19.3% [414]. A large-scale hospital-based study found a sensitivity of 97.6% and 98.8% specificity when performed 14 days

or later after symptoms onset; the immunoglobulins levels were correlated with worse disease, and were detectable in those with negative PCR tests but clinical suspicion of infection [415]. Others have correlated titers with disease severity [409]. An added challenge is that while 1.24% of a community's 5,882 samples showed antibody reactivity to receptor binding domain, 18% of the samples failed to neutralize the SARS-CoV-2 virus [416].

Evidence also suggests immunoglobulins may not be measurable over time [417]. Still, other studies suggest laboratory tests assessing T-cell responses remain robust for some time, even among those with no detectable immunoglobulins and/or those who had mild disease [418, 419]. Hence, a lack of measurable immunoglobulins may not indicate lack of immunity. If these lines of research remain viable, then it is theoretically possible for immunoglobulin testing, perhaps combined with history, to 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). Unfortunately, the currently available antibody tests have yet to be sufficiently validated on a widespread basis, and inaccuracies are increasingly reported [420, 421]. Once these problems are addressed, it is anticipated that antibody testing may become widespread 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. It may be complementary with vaccination, particularly if the virus continues to circulate and cause disease. Workforces with the greatest needs for immune status testing include those with isolated populations, increased 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 experienced medical and/or public health professional(s) who are thoroughly knowledgeable about numerous factors, including the specific test, its reported performance (e.g., sensitivity, specificity), the 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 and at this point, antibody testing should be limited to only mission-critical workers and special populations. As the experience with these tests improves, the populations assessed may markedly expand. As a general statement, a person who has recovered from COVID-19, has a duration of at least 10 days since first symptoms, and has demonstrated antibodies would not be infectious or capable of transmitting infection and scientifically would no longer have to wear a mask or participate in mitigation procedures.

Specific examples where serology might be helpful include the following:

 Patients with symptoms consistent with COVID-19 of more than 1 week in duration, for whom PCR testing has been negative and no alternative diagnosis has been found. For

- these cases, a positive IgG serology would be diagnostic. A negative serology could be repeated at >2 weeks from symptom onset and repeat negative testing would then effectively rule out COVID-19.
- Patients with initial negative PCR and serology at <2 weeks after symptom onset but
 who remain symptomatic beyond 2 weeks without an alternative diagnosis. Repeat
 serology testing documenting seroconversion would be diagnostic, whereas failure to
 seroconvert would help to rule out COVID-19.
- Symptomatic, febrile, PCR-positive patients with an unknown time since infection where presence of antibodies might help in choice of therapeutic modalities (e.g., antivirals and/or convalescent serum before antibodies arise).

Imaging

Although radiographs are usually abnormal for individuals with pulmonary involvement, radiography in general should not be used as a stand-alone screening tool for COVID-19. X-ray abnormalities peak at 10–12 days after onset of symptoms [161, 422]. 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 [422]. Radiographs are recommended as part of the diagnostic evaluation of COVID-19.

Computerized tomography (CT) is commonly performed [423, 424] and shows patchy infiltrates and ground-glass opacities [425-429]. 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 [162]. **CT scans are recommended for the diagnostic evaluation of COVID-19.**

Treatment Recommendations

Overview

Treatment is increasingly guided by RCTs, yet it continues to evolve as data are published. Many additional studies are underway. There are numerous treatment guidelines available; although these guidelines tend to have similar recommendations, there are many differences regarding individual treatments [430-437]. The FDA has provided unprecedented flexibility to accelerate the development of new drugs and testing [438]. No treatment is yet indicated for asymptomatic cases.

The four main classes of interventions with evidence of efficacy for more serious infections are antiviral treatments, cytokine storm-reducing and/or immunomodulating agents, anticoagulants, and ventilatory support (both non-invasive and invasive).

Many medications and agents are being used for treatment, including the following: ACE inhibitors, anticoagulants, bamlanivimab, casirivimab/imdevimab, COVID-19 convalescent plasma, famotidine, monoclonal antibodies, azithromycin, baloxavir, baricitinib, chloroquine,

colchicine, favipiravir, glucocorticosteroids, hydroxychloroquine, immunoglobulin, interferons, ivermectin, lopinavir/ritinovir, nitric oxide, remdesivir, sarilumab, siltuximab, statins, thrombolytics, tocilizumab, zinc [439-442], vitamin C [443], and vitamin D [444-447]. Most of these treatments have no quality evidence of efficacy. There is no clear evidence of lower risk of mortality with statin use [448]. Vitamin D levels have been strongly correlated with COVID-19 disease severity [444, 446, 447]; for example, individuals with low vitamin D levels were reported to have an approximate 8-fold greater risk of a severe outcome and 20-fold greater risk of a critical outcome [444].

Only glucocorticosteroids have thus far been clearly shown in multiple quality trials to reduce mortality [449-451], although data also suggest that low-molecular-weight heparin likely reduces mortality. Remdesivir and low-molecular-weight heparin have proven to be modestly effective at shortening intensive care unit (ICU) stays in a large trial [452].

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 positioning), other respiratory support measures, and prophylaxis for deep vein thrombosis, including low-molecular-weight heparins [453-455]. Evaluations should include exclusion of other causes (e.g., influenza). 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 and foster the development of other infections.

Multiple agents have been studied to attempt to suppress the purported cytokine storm; most of the trials are centered around interleukin-6 (IL-6) [456]. Yet, most quality data on IL-6 receptor antagonists have been negative. There is ongoing controversy regarding a cytokine storm in relation to ARDS caused by COVID-19 [457]. There are many cytokines believed to be involved in the cytokine release syndrome (IL-2, IL-7, G-CSF, IFN- γ , inducible protein 10, MIP 1- β , TNF- α).

Antiviral medications may have minimal to no role in advanced pneumonia or ARDS [458], particularly as viral replication appears to peak at or about the time of symptoms onset. However, antiviral therapies are showing increasing promise to lessen the severity of the disease among outpatients who are treated early in the disease. Two therapies targeting this window have recently been approved by FDA under emergency use authorization: bamlanivimab and casirivimab/imdevimab. Both of these treatments have preliminary data suggesting strong abilities to reduce the risk of hospitalization among those at high risk. Similarly, data on hydroxychloroquine (HCQ) suggest modest efficacy early in the symptomatic phase, but clear evidence of inefficacy for later stage use [459]. There are few studies assessing the efficacy of antiviral medications within the first 1–2 days of symptom onset [460], despite the parallels with influenza medications.

Potential hierarchical approaches for the treatment of COVID-19 are as follows:

Outpatient	Inpatient moderate	Inpatient severe/critical		
Mild: 1. No treatment	 Glucocorticosteroids Low-molecular-weight 	 Glucocorticosteroids Low-molecular-weight 		
unless high risk	heparin/unfractionated	heparin/unfractionated		
for severe	heparin	heparin		
disease	3. Remdesivir	3. Remdesivir		
	4. Oxygen	4. Baricitinib		
Moderate/severe:	supplementation	Convalescent antibodies		
 Bamlanivimab 		Oxygen supplementation		
or casirivimab		7. Prone positioning (due to		
/ imdevimab 2. HCQ for 5 days		shunting) and/or non-invasive ventilation (NIV)		
		8. Mechanical ventilation, prone		
		Extracorporeal membrane oxygenation (ECMO)		

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 that include evidence of an epidemic of depression (50% increased), suicidal ideation, anxiety, post-traumatic stress disorder (PTSD), substance use, divorce (30% increased), and violence [168, 461-468]. An association between adverse mental health and financial concerns has been noted [469].

Hydroxychloroquine has been used for the treatment of COVID-19 [439, 442, 458, 470-511]. There also are many in vitro studies suggesting antiviral activity [512-520].

Hydroxychloroquine for Treatment of COVID-19

Sometimes Recommended.

Hydroxychloroquine (HCQ) is not recommended for the treatment of patients with COVID-19 after the first 3 days of symptoms [492]. HCQ is recommended for use in the first 3 days of symptoms onset.

```
Strength of Evidence – Recommended, Evidence (C)

(First 3 days of symptoms)

Level of Confidence – Low

Strength of Evidence – Moderately Not Recommended, Evidence (B)

(Use beyond first 3 days of symptoms)

Level of Confidence – Moderate
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Indications:

Indicated for early symptom onset, ideally in the first 1–3 days during the COVID-19 phase with viral replication. Not indicated for late symptoms, especially days 5 or later. Generally for moderate to severely affected patients with COVID-19 and would include zinc supplementation. Use in mild cases could be justified, especially for a patient with multiple comorbidities (e.g., pre-diabetes, diabetes, cardiovascular disease, COPD) and thus risk of progression. Meta-analysis evidence of a 24% reduction in composite risk of COVID-

Benefits:

19 infection, hospitalization, and death [459]. Earlier clearance of pneumonia on CT scan [458].

Harms:

Negligible for most patients undergoing short-course use. Gastrointestinal symptoms occur above rates of placebo. Prior concerns about prolonged corrected QT intervals, and thus arrhythmias [490, 500], have been largely resolved among previously healthy patients without risks for arrhythmias who are given HCQ at typical doses. ECG monitoring may be 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. Retinopathy appears highly unlikely with these short courses, as it has been reported at levels of >100-fold greater cumulative doses [521].

Frequency/Dose/Duration:

Multiple regimens have been used. There is both a mechanistic rationale for the concomitant use of zinc to inhibit viral replication and pre-post interventional clinical evidence of efficacy for the adjunctive use of zinc [442]. The following are the most common regimens, the first of which was used in the one quality RCT:

- Hydroxychloroquine 400mg BID x 1 day, then 200mg BID for 4 days [513].
- Hydroxychloroquine 400mg BID x 1 day, then 400mg QD for 4
- Hydroxychloroquine 200mg BID x 5 days [458]
- Hydroxychloroquine 200mg TID x 10 days [477]
- Hydroxychloroquine 200mg TID x 10 days plus azithromycin 500mg x 1 day then 250mg QD x 4 days [477]
- Hydroxychloroquine 600mg BID x 1 day, then 400mg QD for 4

Because the half-life of these medications is long, a loading dose for the first day or two may be preferable.

There are many quality RCTs among hospitalized and/or ICU patients that consistently show late use of HCQ does not improve clinical outcomes, including mortality [492, 493, 522-525]. Because there is consistent moderate-quality evidence that HCQ is ineffective as a solitary intervention in COVID-19 patients treated late after the viral replication phase has largely ceased, the use of HCQ in that timeframe is not recommended.

There are multiple RCTs and studies of early use of HCQ that range from pre-diagnosis to within a few days of symptom onset [459]. These trials are naturally individually underpowered for severe

Rationale:

outcomes such as mortality as they tend to include younger, healthier patients. A meta-analysis of 5 RCTs that analyzed 5,577 patients found that all studies trended towards efficacy and the combined data showed a statistically significant 24% reduction in composite risk of infection, hospitalization, and death [459]. A nationwide cohort study in the Netherlands found evidence of efficacy of hydroxychloroquine for reducing risk of transfer to an ICU by 53% compared with no treatment, but there was no similar effect for chloroquine [526]. A study of 1,274 outpatients in a propensity-matched cohort from New Jersey found a 31.2% reduced risk of hospitalization [527].

One early-use trial found non-significant reductions, with 20% being symptomatic at 14 days and a 60% reduced risk of death [528]. Another trial of HCQ used within 4 days of high-risk exposure found a 17% reduced risk of subsequent infection [487]. Another trial of onceweekly or twice-weekly HCQ as pre-exposure prophylaxis among HCWs found a non-significant 26–28% reduced risk of infection [529]. Because there is quality evidence of efficacy for the early use of HCQ, it is recommended for these select patients.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Hydroxychloroguine; 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; nonrandomized controlled trials as topics. We found and reviewed 528 articles in PubMed, 741 in Scopus, 137 in CINAHL, 425 in Cochrane Library, 9,380 in Google Scholar, and 38 from other sources†. We considered for inclusion 24 from PubMed, 6 from Scopus, 1 from CINAHL, 2 from Cochrane Library, 6 from Google Scholar, and 35 from other sources. Of the 74 articles considered for inclusion, 7 randomized trials, 2 non-randomized trials, 5 case series, 11 retrospective studies, and 5 systematic reviews met the inclusion

[†] 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.

criteria. There were no exclusion criteria.

Chloroquine has been used for the treatment of COVID-19 [526].

Chloroquine for Treatment of COVID-19

Not Recommended.

Chloroquine is not recommended for the treatment of patients with COVID-19 after the first 3 days of symptoms [492]. There is no recommendation for or against the use of chloroquine in the first 3 days of symptoms.

Strength of Evidence - No Recommendation, Insufficient Evidence (I)

(First 3 days of symptoms)

Level of Confidence – **Low**

Strength of Evidence - Not Recommended, Evidence (C)

(Use beyond first 3 days of symptoms)

Level of Confidence - Low

Rationale:

Chloroquine is a closely related compound to hydroxychloroquine. There is no RCT-level evidence that chloroquine has different efficacy. There are sparse trials of chloroquine, especially compared with the evidence base for hydroxychloroquine. One population-based cohort study found evidence of efficacy of hydroxychloroquine but not chloroquine [526]. Thus, by analogy to hydroxychloroquine, chloroquine is not recommended for treatment of hospitalized COVID-19 patients. See the Hydroxychloroquine Rationale for Recommendation for details.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 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 89 articles in PubMed, 3,513 in Scopus, 28 in CINAHL, 0 in Cochrane Library, 11,440 in Google Scholar, and 0 from other sources†. We considered for inclusion 9 from PubMed, 20 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 10 from Google Scholar, and 5 from other sources. Of the 45 articles considered for inclusion, 2 randomized trials, 1 retrospective analysis and 2 systematic reviews 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.

Hydroxychloroguine has been used for prophylaxis for COVID-19, most typically among healthcare workers [508, 530].

Hydroxychloroquine or Chloroquine for Widespread Prophylaxis Against COVID-19 No Recommendation.

There is no recommendation for or against the use of hydroxychloroquine and chloroquine for widespread prophylaxis against COVID-19.

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

Rationale:

multiple RCTs that included early use of HCQ, ranging from prediagnosis to within a few days of symptoms onset [459]. These trials are naturally individually underpowered for severe outcomes such as mortality as they tend to include younger, healthier patients. This meta-analysis of 5 RCTs that analyzed 5,577 patients found that all studies trended towards efficacy and the combined data showed a statistically significant 24% reduction in composite risk of infection, hospitalization, and death [459]. A systematic review found weak and

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 [487]; thus, underpowering is possible. A clusterrandomized trial found a nonsignificant 8.1% reduction in PCRconfirmed COVID [531]. An RCT found lack of efficacy for prophylaxis among healthcare workers [532]. A meta-analysis was performed with

use is weak and conflicting, there is no recommendation. A comprehensive literature search was conducted using PubMed,

Scopus, CINAHL, Cochrane Library, and Google Scholar from January

conflicting evidence [533]. As evidence for widespread prophylactic

2019 to November 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 73 articles in PubMed, 180 in Scopus, 25 in CINAHL, 41 in Cochrane Library, 8,280 in Google Scholar, and 0 from other sources†.

We considered for inclusion 2 from PubMed, 4 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 3 from

Evidence:

other sources. Of the 12 articles considered for inclusion, 3 randomized trials 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 November 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; nonrandomized controlled trials as topics. We found and reviewed 73 articles in PubMed, 18 in Scopus, 4 in CINAHL, 44 in Cochrane Library, 9560 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials, 0 nonrandomized 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 Hydroxychloroguine and Chloroguine

Boulware 2020 (score=9.0) [487]

Category: Hydroxychloroquine Prophylaxis

Study Type: RCT

Sample Size:

Sponsored by several entities, including David Baszucki and Jan Ellison Baszucki, the Alliance of Minnesota Chinese Organizations, the Minnesota

Conflict of Interest: 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.

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%) "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."

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.

Skipper 2020 (score=7.5) [528]

Comments:

Category: Hydroxychloroquine

Study Type: RCT

Conflict of Interest: Sponsored by private donors. COI, one or more of the authors have

received or will receive benefits for personal or professional use.

N = 491 non-hospitalized patients who had 4 or fewer symptomatic days

Sample Size: and either PCR-confirmed COVID-19 or high exposure to a person who was

PCR-confirmed COVID-19.

Age/Sex: Mean age: 40 years; 185 males, 238 females.

Hydroxychloroquine: For the first day, patients received

hydroxychloroquine at 800 mg once, then 600 mg up to 8 hours later. For

Comparison: four more days, patients received 600 mg/day (n=212) vs. Placebo:

Patients were given placebo at an identical dose to the active group

(n=211).

Follow-up: Follow-up after 14 days.

Results indicate that the hydroxychloroquine group had a mean reduction

Results: from 2.60 to 2.33 on the symptom severity score over 14 days (difference

of -0.27 points [95% CI, -0.61 to 0.07] (p=0.117), meaning that

hydroxychloroquine failed to cause a statistically significant difference. "Hydroxychloroquine did not substantially reduce symptom severity in

outpatients with early, mild COVID-19."

Internet bases trial of outpatient adults with probable or early COVID

Comments: disease. (Lack of confirmed COVID infection). Data suggest HCQ did not

substantially decrease hospitalization or morbidity and mortality nor

severity of symptoms in non-hospitalized adults.

Borba 2020 (score=7.5) [474]

Conclusion:

Category: Chloroquine

Study Type: RCT

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

Conflict of Interest: 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

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 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

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%)

"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."

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.

Tang 2020 (score=7.0) [470, 471]

Category: Hydroxychloroquine

Study Type: RCT

Results:

Conclusion:

Comments:

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 the

viral replication stage already completed. Most patients given multiple antiviral 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.

Horby 2020 (score=6.5) [525]

Hydroxychloroquine Category:

RCT Study Type:

Sponsored by Medical Research Council and NIHR. No COI. **Conflict of Interest:**

N = 4,716 hospitalized COVID-19 patients Sample Size:

Mean age: 65.3 years; 2924 males, 1,792 females Age/Sex:

> Usual care (n=3,155) vs. Usual care plus hydroxychloroquine (HCQ): HCQ sulfate (200 mg) with a loading dose of 4 tablets (800 mg) at 0 and 6 hours,

Comparison: followed by 2 tablets (400 mg) starting at 12 hours after the initial dose,

then every 12 hours for 9 days or until discharge (n=1,561)

Follow-up at hospital discharge, at death, or at 28 days Follow-up:

26.8% of HCQ patients died within 28 days while 25.0% of usual care

patients died (rate ratio = 1.09, p=0.18). Those in the HCQ group were less Results:

likely to be discharged from the hospital alive within 28 days (HCQ = 60.3%, Usual care = 62.8%, rate ratio = 0.92, 95% CI [0.85, 0.99]). "In patients hospitalized with COVID-19, hydroxychloroguine was not

associated with reductions in 28-day mortality but was associated with an

increased length of hospital stay and increased risk of progressing to

invasive mechanical ventilation or death."

Open label. Usual care bias. Symptom onset in both groups at 9 days

Comments: before study treatment began. The 28-day mortality was comparable

between both groups.

Rajasingham 2020 (score=6.5) [529]

Hydroxychloroquine Prophylaxis Category:

Study Type:

Conclusion:

Sponsored by Steve Kirsch, David Baszucki and Jan Ellison Baszucki, the

Rainwater Charitable Foundation, the Alliance of Minnesota Chinese **Conflict of Interest:**

Organizations, the Minnesota Chinese Chamber of Commerce, and the

University of Minnesota. No COI.

N = 1,483 healthcare workers with consistent exposure to people with

Sample Size: COVID-19 (including emergency departments, intensive care units, COVID-

19 hospital wars, and first responders)

No mention of mean age, median age: 41 years; 723 males, 760 females Age/Sex:

Hydroxychloroquine (HCQ) once weekly – two 200 mg tablets separated

by 6-8 hours, followed with two 200 mg tablets once weekly (n=494) vs. Comparison: Hydroxychloroquine (HCQ) twice weekly – two 200 mg tablets separated

by 6-8 hours, followed with two 200 mg tablets twice weekly (n=495) vs.

Placebo (n=494). All treatments given for 12 weeks

Follow-up: Follow-up at 12 weeks

Incidence of laboratory-confirmed or symptomatic compatible illness of

COVID-19: HQC once weekly = 0.27 events per person-year, HCQ twice

Results: weekly = 0.28, placebo = 0.38. Hazard ratios of COVID-19 incidence

compared to placebo: HCQ once weekly = 0.72 (p=0.18), HCQ twice weekly

= 0.74 (p=0.22)

"Pre-exposure prophylaxis with hydroxychloroquine once or twice weekly did not significantly reduce laboratory-confirmed Covid-19 or Covid-19-

compatible illness among healthcare workers."

Comments: Dosing is low (only once or twice weekly) likely difficult to show effect.

There is a trend towards HCQ efficacy.

Chen Z 2020 (score=5.5) [534]

Conclusion:

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 SaO₂/SPO₂

ratio > 93% or PaO₂/FIO₂ 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%).

Mitja 2020 (score=5.0) [531]

Category: Hydroxychloroquine
Study Type: RCT (cluster-randomized)

Crowdfunding campaign YoMeCorono (https://www.yomecorono.com/),

Laboratorios Rubió, Laboratorios Gebro Pharma, Zurich Seguros, SYNLAB

Conflict of Interest: Barcelona, and Generalitat de Catalunya. Laboratorios Rubió also

contributed to the study with the required doses of hydroxychloroguine (Dolquine®). No conflicts declared.

Sample Size: N = 2,314 asymptomatic contacts exposed to PCR-COVID-19 cases.

Age/Sex: Mean age: 51.1 years; 60 males, 21 females

Hydroxychloroquine (HCQ) 800mg for 1 day and 400mg QD for 6 days

Comparison: (n=1,116) vs. no specific therapy (n=1,198). Cluster-randomized by

contact.

Follow-up: Follow-up daily for 28 days

Results: Symptomatic disease rate 6.2% vs. 5.7%, (RR=0.89, 95% CI 0.54-1.46).

Higher adverse effects in HCQ group (mostly GI).

"Postexposure therapy with HCQ did not prevent SARS-CoV-2 disease and

Conclusion: infection in healthy individuals exposed to a PCR-positive case. Our

findings do not support HCQ as postexposure prophylaxis for Covid-19." Cluster-randomized by exposure. Underpowered for outcomes as non-

Comments: significant 8.1% reduction in disease risk, but comparison is 6.2% vs. 5.7%.

Unknown if severity reduced.

Cavalcanti 2020 (score=4.0) [493]

Category: Hydroxychloroquine

Study Type: RCT

Conflict of Interest: Sponsored by the Coalition Covid-19 Brazil and EMS Pharma. No mention

of COI.

Sample Size: N = 665 hospitalized patients with suspected or confirmed COVID-19 who

received no supplemental oxygen or a max of 4 liters/minute of

supplemental oxygen

Age/Sex: Mean age: 50.3 years; 388 males, 277 females

Comparison: Standard care alone (n=227) vs. Standard care and hydroxychloroquine

(HCQ) - 400 mg twice daily (n=221) vs. Standard care, hydroxychloroquine (HCQ) - 400 mg twice daily, and azithromycin (AZI) - 500 mg once daily

(n=217). All received treatment for 7 days

Follow-up: Follow-up at 15 days

Results: Compared to standard care alone, the HCQ and HCQ+AZI groups did not

have statistically greater odds of scoring higher on a seven-point ordinal scale for clinical status at 15 days (odds ratio: HCQ = 1.21 [p = 1.00],

HCQ+AZI = 0.99 [p = 1.00])

Conclusion: Among patients hospitalized with mild-to-moderate COVID-19, the use of

hydroxychloroquine, alone or with azithromycin, did not improve clinical

status at 15 days as compared with standard care.

Comments: Open-label trial with stratified randomization. 24.2% of total sample had

either a negative PCR for COVID or testing results were unavailable. Treatment began on average at day 7. In patients with mild to moderate COVID-19, there was no significant difference between the 3 groups as measured by clinical status at day 15 via a seven-level ordinal scale.

Huang 2020 (score=3.5) [535]

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.

Mitja 2020 (score=3.5) [536]

Category: Hydroxychloroquine

Study Type: RCT

Comments: Open-label RCT with non-hospitalized predominantly female participants

with a mean age of 41.6 years. PCR confirmation of COVID cases was less than 5 days after symptom presentation. Median time of symptoms to randomization was 3 days (range 2-4 days). Control group received usual care with no antiviral therapy. Data did not show a significant difference between groups for decreased viral load in the upper respiratory tract nor decreased risk of hospitalization, although study was underpowered to

detect reduction in hospitalization, as stated by author.

Gautret 2020 (score=NA) [477]

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 hydroxychloroguine 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 hydroxychloroguine

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) [478]

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

Participants were non-randomized. Cases were those who accepted

Comparison:

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

Binary regressions used to calculate relative risk for clearance of viremia.

Results: 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

"Results, especially in consideration of the loss to followup of six patients,

Conclusion: 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) [458]

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 hydroxychloroguine made no

difference in the already fast rates of viral clearance.

Million 2020 (score=NA) [479, 480, 537]

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 hydroxychloroguine (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) [538]

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) [490]

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 were associated with higher fatality risks in the medicated groups and preclude

initial assessment of potential suggestion of efficacy.

Molina 2020 (score=NA) [539]

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

Within 5 days, one patient died and two were transferred to the ICU.

Mean trough 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

Conclusion: clinical benefit of the combination of hydroxychloroquine and

azithromycin for the treatment of our hospitalized patients with severe

COVID-19."

Comments: Very small case series

Carlucci 2020 (score=NA) [442]

Results:

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

Hydroxychloroquine (400 mg followed by 200 mg twice daily for 5 days)

and azithromycin (500 mg once daily) alone (n=521) vs.

Comparison: 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

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

Results: 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]).

"This study provides the first in vivo evidence that zinc sulfate in

Conclusion: combination with hydroxychloroquine may play a role in therapeutic

management for COVID-19."

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) [489]

Comments:

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])

"In this observational study involving patients with COVID-19 who have been admitted to the hospital, hydroxychloroquine administration was not

Conclusion: associated with either a greatly lowered or an increased risk of the

composite end point of intubation or death. Randomized, controlled trials

of hydroxychloroguine in patients with COVID-19 are needed."

Consecutive case series. Those treated with HCQ had higher body mass index; had more hypertension; were on steroids, azithromycin, remdesivir,

Comments: or other antibiotics; had lower PaO₂-FlO₂; 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) [540] STUDY RETRACTED

Category: Hydroxychloroquine, Chloroquine

Study Type: Retrospective Analysis

COI, one or more authors have received or will receive benefits for

Conflict of Interest: 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

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

comparison: 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

Mortality of each group compared to control group (9.3%):

Results: 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

"We were unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital

Conclusion: 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."

Large database case series. Multiple variables were worse in the CQ, CQ/macrolide, HCQ, HCQ/macrolide treated groups to the non-

Comments: treated/control groups (control group had the best measures/function of:

CAD, CHF, DM, HTN, current smoking, O₂ saturation and sepsis-related organ failure assessment). Data were unable to address efficacy of

medications. THIS STUDY WAS RETRACTED

Rosenberg 2020 (score=NA) [484]

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

Hydroxychloroquine (HCQ) and azithromycin (AZ) (n=735) vs. HCQ (n=271)

Comparison: vs. AZ (n=211) vs. Neither HCQ nor AZ (n=221)

Follow-up: Followed up to 6 weeks since hospital admission

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%

Results: ([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. "Among patients hospitalized...with COVID-19, treatment with

hydroxychloroquine, azithromycin, or both, compared with neither

Conclusion: treatment, as not significantly associated with differences in in-hospital

mortality. However, the interpretation of these findings may be limited by

the observational design."

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 O₂

saturation, and have abnormal chest imaging. Timing of medications regarding symptom onset was not provided. Data were unable to

cgaranig symptom onset was not provided. Data were a

determine efficacy of medications.

Gendelman 2020 (score=NA) [541]

Comments:

Category: Hydroxychloroquine
Study Type: Retrospective Study

Sponsored by the Canadian Institute of Health Research 2019 Novel Conflict of Interest:

Coronavirus rapid research program. No mention of COI.

N = 14520 subjects screened for COVID-19 Sample Size:

Mean age: 37.3±19.1 years; 6880 males, 7640 females Age/Sex:

Positive Group: subjects that tested positive for SARS-CoV-2 (n=1317) vs. Comparison:

Negative Group: subjects that tested negative for SARS-CoV-2 (n=13203)

No mention of follow-up. Follow-up:

> Only 9.07% of the subjects tested positive for COVID-19. Of the positive group, 0.23% were prescribed hydroxychloroquine compared to 0.25% of

Results: negative group (p=0.877) and 0.53% of positive group was prescribed

colchicine compared to negative group at 0.48% (p=0.817).

"These findings raise doubts regarding the protective role of these Conclusion:

medications in the battle against SARS-CoV-2 infection."

Retrospective screening study of large sample (14,520) young individuals

(mean age 37.5 years) found little difference in rates of SARS-CoV-2 Comments:

between users of continuous HCT or colchicine. Duration and reason for

treatment was unknown.

Arshad 2020 (score=NA) [482]

Conclusion:

Category: Hydroxychloroquine Study Type: **Retrospective Cohort**

No sponsorship. COI: One or more of the authors have received or will **Conflict of Interest:**

receive benefits for personal or professional use. N = 2541 patients with a positive SARS-CoV-2 test

Sample Size: Mean age: 63.7±16.5 years; 1298 males, 1263 females Age/Sex:

Hydroxychloroquine Group: received 400 mg hydroxychloroquine (HCQ) twice daily on day 1, then 200 mg twice daily days 2-5 (n=1202) vs.

Azithromycin Group: received 500 mg azithromycin (AZM) once daily on Comparison: day 1 then 250 mg once daily for next 4 days (n=147) vs. HCQ+AZM Group:

received both dosing of HCQ and AZM (n=783) vs Neither Med: received

no medication (n=409)

Follow-up at 7, 14, 21, and 28 days Follow-up:

Mortality rates were 13.5% in HCQ alone, 20.1% in HCQ+AZM group,

22.4% in AZM alone, and 26.4% in neither med group. In multivariable Cox regression of mortality, the hazard ratio was decreased by 66% in the HCQ

Results: alone group (p<0.001) and by 71% in HCQ+AZM group (p<0.001). Primary

> cause of mortality in 460 patients was 88% respiratory failure, 4% cardiac arrest, 8% other cardiopulmonary arrest and multi-organ failure. "In this multi-hospital assessment, when controlling for COVID-19 risk

> factors, treatment with hydroxychloroquine alone and in combination with

azithromycin was associated with reduction in COVID-19 associated

mortality."

Retrospective observational study from Henry Ford Hospital, robust sample of 2541 patients (consecutive case series). Treatment with hydroxychloroquine or hydroxychloroquine plus azithromycin resulted in

decreased COVID-19 mortality compared to patients receiving only **Comments:**

azithromycin or not receiving hydroxychloroquine, who had the highest mortality hazard ratio. Overall COVID-19 associated mortality was 18.1% and all deaths were reviewed for cause, which found no major cardiac

arrhythmias or torsades de pointes.

Davido 2020 (score=NA) [481]

Comparison:

Conclusion:

Comments:

Category: Hydroxychloroquine/Azithromycin

Study Type: Retrospective Study

Conflict of Interest: No mention of sponsorship. No COI.

Sample Size: N = 132 patients admitted to the ICU for COVID-19 with confirmed SARS-

CoV-2 PCR and/or compatible pulmonary CT-scan

Age/Sex: Mean age: 58.7 years; 86 males, 46 females

Received both Hydroxychloroquine (HCQ) – day 1 at 800 mg/day followed

by 400-600 mg/day for a total of 10 days and Azithromycin (AZI) – 500 mg

on day 1, followed by 240 mg for 4 days, included in study if taking

medication for at least 48 hours (n = 45) vs. Received other regimens or

received HCQ and AZI < 48 hours (n = 87)

Follow-up: Follow-up at hospital discharge

Those who received HCQ and azithromycin showed increased favorable outcomes (not needing ICU treatment and no mortality) (p=0.009), better

Results: oxygen flow (p<0.0001), better lymphocyte count (p=0.002), and better

CRP (p=0.002) compared to those who received other regimens. "In conclusion, our study confirms already known risk factors for

unfavorable outcomes in COVID-19 hospitalized patients. Moreover, the

present work highlights the potential interest of the combination therapy of HCQ/azithromycin (≥48 hours' 274 intake) by limiting the rate of ICU

transfer."

Retrospective study of 132 inpatients with COVID-19 pneumonia. Forty-five who patients received HCQ plus azithromycin for more than 48 hours

had reduced risk of transfer to the ICU or death.

Derwand 2020 (score=NA) [439]

Category: Hydroxychloroquine /Azithromycin

Study Type: Retrospective Case Series

Conflict of Interest: No mention of sponsorship. COI, one or more authors have received or will

receive benefits for personal or professional use.

Sample Size: N = 141 COVID-19 patients with confirmed acute respiratory syndrome

Age/Sex: No mention of mean age, Median age: 58 years; 103 males, 38 females

Received zinc sulfate 220 mg with 50 mg elemental zinc per day,

Comparison: hydroxychloroquine 200 mg twice daily, and azithromycin 500 mg per day

for 5 days (n=141) vs. Received standard care of common upper

respiratory infection (n=377)

Follow-up: Follow-up of at least 28 days

Hospitalization rate was lower in the triple treatment group compared to

the standard care group (2.84% vs. 15.4%, OR = 0.16, p < 0.001). All-cause

death was also lower in the treatment group (0.71%) compared to the

standard care group (3.5%, OR = 0.2, p = 0.16).

"Risk stratification-based treatment of COVID-19 outpatients as early as possible after symptom onset with the used triple therapy, including the

Conclusion: combination of zinc with low dose hydroxychloroquine, was associated

with significantly less hospitalizations and 5 times less all-cause deaths."

Retrospective case serves of 141 outpatients. Early risk stratified

treatment in COVID-19 outpatients after symptom onset using zinc plus

low dose HCQ+AZI resulted in significantly fewer hospitalizations and ${\bf 5}$

times fewer all cause deaths.

Guerin 2020 (score=NA) [483]

Hydroxychloroquine/Azithromycin Category:

Retrospective Study Study Type: Conflict of Interest: No sponsorship or COI.

N = 88 medical doctors or members of their families and caregivers with Sample Size:

COVID-like symptoms (influenza-like illness symptoms)

No mention of mean age, Median age: 52 years; 46 males, 42 females Age/Sex:

No or symptomatic treatment (NST) – commonly paracetamol on demand

(n=34) vs. Azithromycin (AZM) – 500 mg for one day then 250 mg for four Comparison:

additional days (n=34) vs. Hydroxychloroquine (HCQ) plus AZM – 600 mg

for 7 to 10 days (n=20)

No mention of follow-up Follow-up:

The NST group had a significant greater recovery time compared to AZM

group (25.8 days vs. 12.9 days, p < 0.0001) and compared to the HCQ+AZM Results: group (25.8 days vs. 9.2 days, p < 0.0001). The AZM and HCQ+AZM did not

statistically differ (p = 0.26)

"In conclusion, AZM and AZM+HCQ favourably impacted the course of the disease. We need trials, ideally prospective/double blind, to show if a

statistical difference can be evidenced with a broader group, and clarify

the indications of each treatment depending on initial clinical

presentation."

Retrospective study of 3 groups. Study suggests statistically significant improved disease control via reduction in days to recovery for AZM (p<0.001) and AZM+HCQ (p=0.0002). Both treatment groups showed an

approximate median 7.0-day recovery versus non-treatment group of 28

days.

Lagier 2020 (score=NA) [476]

Conclusion:

Comments:

Comparison:

Hydroxychloroguine/Azithromycin Category:

Retrospective Analysis Study Type:

Sponsored by ANR "Investissemests d'avenir", Mediterranee infection,

Conflict of Interest: Région Provence-Alpes-Côte d'Azur and Mediterranean Infection

Foundation. No COI.

Sample Size: N = 3,737 patients with COVID-19 who were undergoing early treatment

Mean age: 45.3 years; 1704 males, 2033 females Age/Sex:

> Hydroxychloroquine (HCQ)-Azithromycin (AZ): 200 mg of HCQ three time daily and 500 mg of AZ for the first day and 250 mg for the next 4 days,

received treatment for at least 3 days (n=3,119) vs. Received other

regimens (n=618)

Follow-up: Follow-up to 45 days

> The HCQ-AZ group was associated with a lower risk of ICU transfer or death (Hazard Ratio [HR] = 0.18, 95% CI [0.11, 0.27], a lower risk for

Results: hospitalization lasting 10 or more days (Odds Ratio [OR] = 0.38, 95% CI

[0.27, 0.54], and shorter duration of viral shedding (HR = 1.29 [1.17, 1.42] "Although this is a retrospective analysis, results suggest that early

diagnosis, early isolation and early treatment of COVID-19 patients, with at **Conclusion:**

least 3 days of HCQ-AZ lead to a significantly better clinical outcome and a

faster viral load reduction than other treatments."

Retrospective analysis of 3737 screened COVID-19 patients. Early Comments:

treatment with HCQ+AZM and hospitalization resulted in faster viral load

reduction and shortened LOS as well as risk of death. Global mortality rate 0.9% and HCQ+AZM mortality rate 0.5% in patients treated for > 3 days.

Lane 2020 (score=NA) [488]

Category: Hydroxychloroquine/Azithromycin

Study Type: Retrospective Cohort

Conflict of Interest: Sponsored by multiple international funders. COI, one or more authors

have received or will receive benefits for personal or professional use.

Sample Size: N = 1,941,802 patients who had rheumatoid arthritis needing COVID-19

management

Age/Sex: No mention of mean age; 346,157 males, 1,595,645 females

Hydroxychloroquine (n=956,374) vs. Sulfasalazine (n=310,350)

Comparison: Hydroxychloroquine plus Azithromycin (n=323,122) vs.

Hydroxychloroquine plus Amoxicillin (n=351,956)

No specific dosages given for any treatment

Follow-up: Follow-up at 30 days post-treatment

Those treated with azithromycin added to hydroxychloroquine had an increased risk of 30-day cardiovascular mortality (Hazard Ratio [HR] = 2.19,

Results: 95% CI [1.22, 3.94]), chest pain or angina (1.15, [1.05, 1.26]) and heart

failure (1.22, [1.02, 1.45]) compared to those who treated with amoxicillin

added to hydroxychloroquine

"Short-term hydroxychloroquine treatment is safe, but addition of azithromycin may induce heart failure and cardiovascular mortality,

potentially due to synergistic effects on QT length. We call for caution if

such combination is to be used in the management of Covid-19."

Retrospective cohort using electronic medical records and claims data of RA patients. Data suggest HCQ appears safe as a single drug, but when

coupled with AZM it may increase the risk of cardiovascular events.

Sbidian 2020 (score=NA) [485]

Conclusion:

Comments:

Comparison:

Category: Hydroxychloroquine/Azithromycin

Study Type: Retrospective Cohort

Conflict of Interest: No mention of sponsorship. COI, one or more authors have received or will

receive benefits for personal or professional use.

Sample Size: N = 4,642 patients who at least one PCR-documented SARS-CoV-2 positive

screening

Age/Sex: Mean age: 66.1 years; 2,738 males, 1,904 females

Hydroxychloroquine (HCQ) – suggested dosage of 600 mg for 1 day and 400 mg for 9 days (n=623) vs. Hydroxychloroquine and Azithromycin

(HCQ+AZI) – suggested HCQ dosage plus suggested dosage AZ of 500 mg

for one day and 250 mg for 4 days (n=227) vs. Control – did not receive

HCQ or AZ but were treated symptomatically (n=3,792)

Follow-up: Follow-up at 28 days

Mortality rates at day 28 was statistically different between groups (HCQ =

17.8%, HCQ+AZI = 23.8%, Control = 21.9%, p < 0.001). After adjusting for

Results: confounding, there was no statistical difference between HCQ and control

groups for 28-day mortality (p = 0.073). There was also no statistical

difference between HCQ+AZI and control (p = 0.057).

"Using a large non-selected population of inpatients hospitalized for

COVID-19 infection in 39 hospitals in France and robust methodological

Conclusion: approaches, we found neither evidence for reduced or excess risk of 28-

> day mortality with the use of HCQ alone. Our findings suggest a possible higher risk of death for patients receiving HCQ combined with AZI." Retrospective cohort from both electronic and claims data. Data suggest lack of efficacy of either HCQ administered alone or in combination with

Comments: AZI for decreasing 28-day mortality. Study reports a possible excess

mortality rush for HCQ-AZI. However, study also suggests HCQ alone group

had higher rates of discharges to home at 28 days.

Ip 2021 (score=NA) [527]

Hydroxychloroquine Category:

Study Type: Retrospective Observational Study

No sponsorship. COI, one or more authors have received or will receive **Conflict of Interest:**

benefits for personal or professional use.

Sample Size: N = 1274 outpatients with a positive SARS-CoV-2 diagnosis

No mention of mean age, median age for HCQ group: 57 years, median Age/Sex:

age for no HCQ group: 56 years; 635 males, 639 females

Prescription for hydroxychloroquine via electronic health records (n=97) Comparison:

vs. No prescription for hydroxychloroquine (n=1177)

Follow-up: Median follow-up of 39 days

> Percentage of participants needing subsequent hospitalization: no HCQ group = 31.4%, HCQ group = 21.6%. Multivariable logistic regression

Results: analysis showed an association between HCQ exposure and reduced rate

of hospitalization (related to COVID-19 illness) (Adjusted OR = 0.53, 95% CI

[0.29, 0.95]).

"In this multicenter retrospective observational cohort study of mildly symptomatic outpatients with polymerase chain reaction documented SARS-CoV-2 infection, we noted an association (OR 0.53; 95% CI, 0.29,

0.95) between outpatient exposure to hydroxychloroguine and a

reduction in subsequent need for hospitalization."

A multi-center retrospective observational study of mildly symptomatic COVID-19 infection in non-hospitalized patients. Data suggest HCQ was associated with a decreased hospitalization rate. QT prolongation events

occurred in 2% of the population with no arrhythmic events reported.

Ladapo 2020 (score=NA) [459]

Conclusion:

Comments:

Comparison:

Category: Hydroxychloroquine

Study Type: Systematic Review and Meta-analysis

No sponsorship. COI, one or more authors have received or will receive **Conflict of Interest:**

benefits for personal or professional use.

N = 5577 patients pooled from five different studies included in the Sample Size:

analysis

Age data provided for individual studies – median/mean age: Boulware 40

Age/Sex: years, Skipper 40 years, Rajasingham 41 years, Mitka A 42 years, Mitka B

49 years; Gender distribution not mentioned

Control subjects who did not receive hydroxychloroquine (n=2596) vs.

Participants who did received hydroxychloroquine (n=2981)

Follow-up: No mention of follow-up Hydroxychloroguine had a 24% reduction association with COVID-19

Results: infection, hospitalization, or death (RR = 0.76, 95% CI [0.59, 0.97), p =

"Hydroxychloroquine use in outpatients reduces the incidence of the

composite outcome of COVID-19 infection, hospitalization, and death. **Conclusion:**

Serious adverse events were not reported and cardiac arrhythmia was

rare."

Systematic review and meta-analysis of RCTs (Boulware 2020, Skipper 2020, Rajasingham 2020, Mitka 2020a, Mitka 2020b). Primary outcomes were hospitalization and death. Data suggest HCQ was associated with a

Comments: statistically significant 24% reduction in COVID-19 infections,

hospitalizations, and deaths (p=.025). Additionally, no serious cardiac-

related adverse effects were reported.

Azithromycin has been suggested to inhibit the growth of both the Zika and Ebola viruses, as well as prevent severe lower respiratory tract infections [542-545]. Azithromycin has been used for treatment of COVID-19, as both stand-alone and combined therapy [546-548].

Azithromycin for Treatment of COVID-19

Not Recommended.

Azithromycin is not recommended for the adjunctive treatment of selected patients with more severe COVID-19. There is no recommendation for or against the use of azithromycin in the first 3 days of symptoms.

Strength of Evidence - No Recommendation, Insufficient Evidence (I)

(First 3 days of symptoms)

Level of Confidence - Low

Strength of Evidence – Not Recommended, Evidence (C)

(Use beyond first 3 days of symptoms)

Level of Confidence - Low

Indications: A moderate-quality RCT found the addition of azithromycin (AZT) to

> standard care that included HCQ produced no apparent benefit among hospitalized patients with severe COVID-19 [549]. A moderate-quality RCT found benefits with shortened hospital stay, improved oxygenation, and reduced respiratory rates associated with the

addition of AZT to a combination of HCQ and lopinavir/ritonavir [510].

There are no quality RCTs regarding early treatment. Adjunctive use with hydroxychloroquine in severely affected patients with COVID-19. For severely affected patients, AZT has been added [477], 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). Low-quality 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 [458].

Benefits: Harms: Theoretical reduced need for a ventilator or ICU stay.

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 [477, 538].

Rationale:

One RCT has suggested no difference between AZT, HCQ, and the combination for treatment of hospitalized patients [493]. Thus, AZQ is not recommended for late treatment of COVID-19.

Most non-randomized but controlled studies have suggested some

evidence of efficacy, particularly for early adjunctive use when combined with HCQ [476, 477, 481-483, 538], although some other studies have suggested a lack of efficacy [484, 485]. Thus, there is no recommendation for use of AZT in the early phase of COVID-19. A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 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 164 articles in PubMed, 1161 in Scopus, 40 in CINAHL, 77 in Cochrane Library, 5170 in Google Scholar, and 16 from other sources*. We considered for inclusion 19 from PubMed, 9 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 16 from other sources. Of the 45 articles considered for inclusion, 2 randomized trials, 2 non-

randomized trials, 4 case series, 9 retrospective studies, and 0

systematic reviews met the inclusion criteria. There were no exclusion

[†] 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:

criteria.

Evidence for the Use of Azithromycin

Cavalcanti 2020 (score=4.0) [493]

Category: Azithromycin

Study Type: RCT

Conflict of Interest: Sponsored by the Coalition Covid-19 Brazil and EMS Pharma. No mention

of COI.

Sample Size: N = 665 hospitalized patients with suspected or confirmed COVID-19 who

received no supplemental oxygen or a max of 4 liters/minute of

supplemental oxygen

Age/Sex: Mean age: 50.3 years; 388 males, 277 females

Comparison: Standard care alone (n=227) vs. Standard care and hydroxychloroquine

(HCQ) - 400 mg twice daily (n=221) vs. Standard care, hydroxychloroquine (HCQ) - 400 mg twice daily, and azithromycin (AZI) - 500 mg once daily

(n=217). All received treatment for 7 days

Follow-up: Follow-up at 15 days

Results: Compared to standard care alone, the HCQ and HCQ+AZI groups did not

have statistically higher odds of scoring higher on a seven-point ordinal scale for clinical status at 15 days (odds ratio: HCQ = 1.21 [p = 1.00],

HCQ+AZI = 0.99 [p = 1.00]

Conclusion: Among patients hospitalized with mild-to-moderate Covid-19, the use of

hydroxychloroquine, alone or with azithromycin, did not improve clinical

status at 15 days as compared with standard care.

Comments: Open-label trial with stratified randomization. 24.2% of total sample had

either a negative PCR for COVID or testing results were unavailable. Treatment began on average at day 7. In patients with mild to moderate COVID-19, there was no significant difference between the 3 groups as measured by clinical status at day 15 via a seven-level ordinal scale.

Gautret 2020 (score=NA) [477]

Category: Azithromycin

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 hydroxychloroguine 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) [478]

Category: Azithromycin

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

Participants were non-randomized. Cases were those who accepted

Comparison: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 hydroxychloroguine treatment (n=16)

Follow-up: Follow-up at 14 days

Binary regressions used to calculate relative risk for clearance of viremia.

Results: 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

"Results, especially in consideration of the loss to followup of six patients,

Conclusion: 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.

Million 2020 (score=NA) [479, 480, 537]

Category: Azithromycin
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) [538]

Category: Azithromycin
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) [490]

Category: Azithromycin
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) [539]

Category: Azithromycin
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

Within 5 days, one patient died and two were transferred to the ICU.

Results: 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

Conclusion: clinical benefit of the combination of hydroxychloroquine and

azithromycin for the treatment of our hospitalized patients with severe

COVID-19."

Comments: Very small case series

Carlucci 2020 (score=NA) [442]

Category: Azithromycin

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

Hydroxychloroquine (400 mg followed by 200 mg twice daily for 5 days)

and azithromycin (500 mg once daily) alone (n=521) vs.

Comparison: 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

Univariate analysis showed additional zinc treatment was not associated with a decrease in hospital stay length, duration of mechanical ventilation,

Results: 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]).

"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."

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.

Rosenberg 2020 (score=NA) [484]

Conclusion:

Comments:

Comparison:

Comments:

Sample Size:

Category: Azithromycin

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
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

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.

Results: ([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. "Among patients hospitalized...with COVID-19, treatment with hydroxychloroquine, azithromycin, or both, compared with neither

Conclusion: treatment, as not significantly associated with differences in in-hospital

mortality. However, the interpretation of these findings may be limited by

the observational design."

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.

Arshad 2020 (score=NA) [482]

Category: Azithromycin

Study Type: Retrospective Cohort

Conflict of Interest: No sponsorship. COI: One or more of the authors have received or will

receive benefits for personal or professional use. N = 2541 patients with a positive SARS-CoV-2 test

Age/Sex: Mean age: 63.7±16.5 years; 1298 males, 1263 females

Hydroxychloroquine Group: received 400 mg hydroxychloroquine (HCQ) twice daily on day 1, then 200 mg twice daily days 2-5 (n=1202) vs.

Comparison: Azithromycin Group: received 500 mg azithromycin (AZM) once daily on

day 1 then 250 mg once daily for next 4 days (n=147) vs. HCQ+AZM Group: received both dosing of HCQ and AZM (n=783) vs Neither Med: received

no medication (n=409)

Follow-up at 7, 14, 21, and 28 days Follow-up:

> Mortality rates were 13.5% in HCQ alone, 20.1% in HCQ+AZM group, 22.4% in AZM alone, and 26.4% in neither med group. In multivariable cox regression of mortality hazard ratio was decreased by 66% in HCQ alone group (p<0.001) and by 71% in HCQ+AZM group (p<0.001). Primary cause

> of mortality in 460 patients was 88% respiratory failure, 4% cardiac arrest,

8% other cardiopulmonary arrest and multi-organ failure.

"In this multi-hospital assessment, when controlling for COVID-19 risk factors, treatment with hydroxychloroquine alone and in combination with

azithromycin was associated with reduction in COVID-19 associated

mortality."

Retrospective observational study from Henry Ford Hospital, robust sample 2541 patients (consecutive case series). Treatment with

hydroxychloroquine or hydroxychloroquine plus azithromycin resulted in

decreased COVID-19 mortality compared to patients receiving only **Comments:**

azithromycin or not receiving hydroxychloroquine who had the highest mortality hazard ratio. Overall COVID-19 associated mortality was 18.1% and all deaths were reviewed for cause which found no major cardiac

arrhythmias or torsades de pointes.

Davido 2020 (score=NA) [481]

Results:

Conclusion:

Results:

Conclusion:

Comments:

Azithromycin Category:

Retrospective Study Study Type:

No mention of sponsorship. No COI. **Conflict of Interest:**

N = 132 patients admitted to the ICU for COVID-19 with confirmed SARS-Sample Size:

CoV-2 PCR and/or compatible pulmonary CT-scan

Mean age: 58.7 years; 86 males, 46 females Age/Sex:

> Received both Hydroxychloroquine (HCQ) – day 1 at 800 mg/day followed by 400-600 mg/day for a total of 10 days and Azithromycin (AZI) - 500 mg

on day 1, followed by 240 mg for 4 days, included in study if taking Comparison:

medication for at least 48 hours (n = 45) vs. Received other regimens or

received HCQ and AZI < 48 hours (n = 87)

Follow-up at hospital discharge Follow-up:

> Those who received HCQ and azithromycin showed increased favorable outcomes (not needed ICU treatment and no mortality) (p=0.009), better

oxygen flow (p<0.0001), better lymphocyte count (p=0.002) and CRP

(p=0.002) compared to those who received other regimens. "In conclusion, our study confirms already known risk factors for

unfavorable outcomes in COVID-19 hospitalized patients. Moreover, the present work highlights the potential interest of the combination therapy

of HCQ/azithromycin (≥48 hours' 274 intake) by limiting the rate of ICU

transfer."

Retrospective study of 132 inpatients with COVID-19 pneumonia. Fortyfive patients received HCQ plus azithromycin for more than 48 hours had

reduced risk of transfer to the ICU or death.

Derwand 2020 (score=NA) [439] Azithromycin Category:

Retrospective Case Series Study Type:

No mention of sponsorship. COI, one or more authors have received or will Conflict of Interest:

receive benefits for personal or professional use.

N = 141 COVID-19 patients with confirmed acute respiratory syndrome Sample Size: No mention of mean age, Median age: 58 years; 103 males, 38 females Age/Sex:

Received zinc sulfate 220 mg with 50 mg elemental zinc per day,

hydroxychloroquine 200 mg twice daily, and azithromycin 500 mg per day

for 5 days (n=141) vs. Received standard care of common upper

respiratory infection (n=377)

Follow-up of at least 28 days Follow-up:

> Hospitalization rate was lower in the triple treatment group compared to the standard care group (2.84% vs. 15.4%, OR = 0.16, p < 0.001). All-cause

death was also lower in the treatment group (0.71%) compared to the

standard care group (3.5%, OR = 0.2, p = 0.16).

"Risk stratification-based treatment of COVID-19 outpatients as early as possible after symptom onset with the used triple therapy, including the combination of zinc with low dose hydroxychloroquine, was associated

with significantly less hospitalizations and 5 times less all-cause deaths." Retrospective case serves of 141 outpatients. Early risk stratified

treatment in COVID-19 outpatients after symptom onset using zinc plus **Comments:** low dose HCQ+AZI resulted in significantly fewer hospitalizations and 5

times fewer all cause deaths.

Guerin 2020 (score=NA) [483]

Comparison:

Results:

Conclusion:

Azithromycin Category:

Retrospective Study Study Type: No sponsorship or COI. **Conflict of Interest:**

N = 88 medical doctors or members of their families and caregivers with Sample Size:

COVID-like symptoms (influenza-like illness symptoms)

No mention of mean age, Median age: 52 years; 46 males, 42 females Age/Sex:

> No or symptomatic treatment (NST) - commonly paracetamol on demand (n=34) vs. Azithromycin (AZM) – 500 mg for one day then 250 mg for four

Comparison: additional days (n=34) vs. Hydroxychloroquine (HCQ) plus AZM – 600 mg

for 7 to 10 days (n=20)

No mention of follow-up Follow-up:

The NST group had a significant greater recovery time compared to AZM

group (25.8 days vs. 12.9 days, p < 0.0001) and compared to the HCQ+AZM **Results:**

group (25.8 days vs. 9.2 days, p < 0.0001). The AZM and HCQ+AZM did not

statistically differ (p = 0.26)

"In conclusion, AZM and AZM+HCQ favourably impacted the course of the disease. We need trials, ideally prospective/double blind, to show if a statistical difference can be evidenced with a broader group, and clarify

the indications of each treatment depending on initial clinical

presentation."

Retrospective study of 3 groups. Study suggests statistically significant improved disease control via reduction in days to recovery for AZM

Comments: (p<0.001) and AZM+HCQ (p=0.0002). Both treatment groups showed an

approximate median 7.0-day recovery versus non-treatment group of 28

days.

Lagier 2020 (score=NA) [476]

Conclusion:

Category: Azithromycin

Study Type: Retrospective Analysis

Sponsored by ANR "Investissemests d'avenir", Mediterranee infection,

Conflict of Interest: Région Provence-Alpes-Côte d'Azur and Mediterranean Infection

Foundation. No COI.

Sample Size: N = 3,737 patients with COVID-19 who were undergoing early treatment

Age/Sex: Mean age: 45.3 years; 1704 males, 2033 females

 $\label{eq:HCQ} \mbox{Hydroxychloroquine (HCQ)-Azithromycin (AZ): 200 mg of HCQ three time}$

Comparison: daily and 500 mg of AZ for the first day and 250 mg for the next 4 days,

received treatment for at least 3 days (n=3,119) vs. Received other

regimens (n=618)

Follow-up: Follow-up to 45 days

The HCQ-AZ group was associated with a lower risk of ICU transfer or

Results: death (Hazard Ratio [HR] = 0.18, 95% CI [0.11, 0.27], a lower risk for

hospitalization lasting 10 or more days (Odds Ratio [OR] = 0.38, 95% CI [0.27, 0.54], and shorter duration of viral shedding (HR = 1.29 [1.17, 1.42] "Although this is a retrospective analysis, results suggest that early

diagnosis, early isolation and early treatment of COVID-19 patients, with at

least 3 days of HCQ-AZ lead to a significantly better clinical outcome and a

faster viral load reduction than other treatments."

Retrospective analysis of 3737 screened COVID-19 patients. Early

Comments: treatment with HCQ+AZM and hospitalization resulted in faster viral load reduction and shortened LOS as well as risk of death. Global mortality rate

0.9% and HCQ+AZM mortality rate 0.5% in patients treated for > 3 days.

Lane 2020 (score=NA) [488]

Conclusion:

Category: Azithromycin

Study Type: Retrospective Cohort

Conflict of Interest: Sponsored by multiple international funders. COI, one or more authors

have received or will receive benefits for personal or professional use.

Sample Size: N = 1,941,802 patients who had rheumatoid arthritis needing COVID-19

management

Age/Sex: No mention of mean age; 346,157 Males, 1,595,645 Females

Hydroxychloroquine (n=956,374) vs. Sulfasalazine (n=310,350)

Comparison: Hydroxychloroquine plus Azithromycin (n=323,122) vs.

Hydroxychloroquine plus Amoxicillin (n=351,956)

No specific dosages given for any treatment

Follow-up: Follow-up at 30 days post-treatment

Those treated with azithromycin added to hydroxychloroquine had an increased risk of 30-day cardiovascular mortality (Hazard Ratio [HR] = 2.19,

Results: 95% CI [1.22, 3.94]), chest pain or angina (1.15, [1.05, 1.26]) and heart

failure (1.22, [1.02, 1.45]) compared to those who treated with amoxicillin

added to hydroxychloroquine

"Short-term hydroxychloroquine treatment is safe, but addition of

Conclusion: azithromycin may induce heart failure and cardiovascular mortality,

potentially due to synergistic effects on QT length. We call for caution if

such combination is to be used in the management of Covid-19."

Retrospective cohort using electronic medical records and claims data of **Comments:**RA patients. Data suggest HCO appears safe as a single drug but when

RA patients. Data suggest HCQ appears safe as a single drug but when coupled with AZM it may increase the risk of cardiovascular events.

Sbidian 2020 (score=NA) [485]

Category: Azithromycin

Study Type: Retrospective Cohort

Conflict of Interest:

No mention of sponsorship. COI, one or more authors have received or will

receive benefits for personal or professional use.

Sample Size: N = 4,642 patients who at least one PCR-documented SARS-CoV-2 positive

screening

Age/Sex: Mean age: 66.1 years; 2,738 males, 1,904 females

Hydroxychloroquine (HCQ) – suggested dosage of 600 mg for 1 day and 400 mg for 9 days (n=623) vs. Hydroxychloroquine and Azithromycin

Comparison: (HCQ+AZI) – suggested HCQ dosage plus suggested dosage AZ of 500 mg

for one day and 250 mg for 4 days (n=227) vs. Control – did not receive

HCQ or AZ but were treated symptomatically (n=3,792)

Follow-up: Follow-up at 28 days

Results:

Conclusion:

Mortality rates at day 28 was statistically different between groups (HCQ = 17.8%, HCQ+AZI = 23.8%, Control = 21.9%, p < 0.001). After adjusting for confounding there was no statistical difference between HCQ and control

groups for 28-day mortality (p = 0.073). There was also no statistical

difference between HCQ+AZI and control (p = 0.057).

"Using a large non-selected population of inpatients hospitalized for COVID-19 infection in 39 hospitals in France and robust methodological approaches, we found neither evidence for reduced or excess risk of 28-day mortality with the use of HCQ alone. Our findings suggest a possible

higher risk of death for patients receiving HCQ combined with AZI."

Retrospective cohort from both electronic and claims data. Data suggest lack of efficacy of either HCQ administered alone or in combination with

Comments: AZI for decreasing 28-day mortality. Study reports a possible excess

mortality rush for HCQ-AZI. However, study also suggests HCQ alone group

had higher rates of discharges to home at 28 days.

Favipiravir, a guanine analogue to inhibit RNA-dependent RNA polymerase, has been used to treat influenza. Favipiravir has also been used to treat severely affected COVID-19 patients [550-557].

Favipiravir for the Treatment of COVID-19

Not Recommended.

Favipiravir is not recommended for the treatment of COVID-19.

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

Rationale:

Evidence:

A moderate-quality RCT found a lack of efficacy for combined favipiravir with interferon beta-1b compared with HCQ for moderate to severe COVID-19 pneumonia patients [558]. A moderate-quality RCT found no evidence of benefit of favipiravir for viral clearance, although there was faster defervescence [559]. 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 [560]. A low-quality RCT of baloxavir, marboxil, and favipiravir found no evidence that favipiravir accelerated viral clearance [561]. There is one non-randomized controlled trial suggesting acceleration of viral clearance compared with lopinavir-ritonavir [562]. Although there is no quality evidence of efficacy, these studies suggest there may be potential efficacy; thus, while needing further quality data, this medication may be helpful in the treatment of patients with COVID-19.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 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 26 articles in PubMed, 2,429 in Scopus, 13 in CINAHL, 52 in Cochrane Library, 6,400 in Google Scholar, and 6 from other sources†. We considered for inclusion 5 from PubMed, 7 from Scopus, 0 from CINAHL, 2 from Cochrane Library, 8 from Google Scholar, and 6 from other sources. Of the 28 articles considered for inclusion, 3 randomized trials, 1 nonrandomized 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) [560]

Category: Favipiravir

Study Type: RCT

Conflict of Sponsored by the National Key Research and Development Program of China. No

Interest: 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.

Khamis 2021 (score=4.0) [558]

Category: Favipiravir, Interferon beta-1b

Study Type: RCT

Conflict of No sponsorship or COI.

Interest:

Sample Size: N = 89 with PCR-confirmed COVID-19 and moderate to severe COVID-

19 pneumonia diagnosed based on WHO case definition

Age/Sex: Mean age: 55 years; 52 males, 37 females

Comparison: Favipiravir, Interferon beta-1b: Received 1600 mg of favipiravir orally twice on day

1 then 600 mg orally twice a day for 10 days and 0.25 mg of interferon beta-1b via nebulizer twice a day for 5 days (n=44) vs Standard: Received 400 mg orally twice

on day 1 then 200 mg twice a day for 7 days (n=45)

Follow-up: No mention of follow-up

Results: No group differences found in the treatment group vs the standard

group. Inflammatory biomarkers: CRP (50 vs. 33mg/dL; p=0.413), ferritin (1107 vs.

993 mg/L; p = 0.968), LDH (452 vs. 366 U/L; p = 0.259), and IL-6 (138 vs. 143 pg/mL; p = 0.410). Clinical outcomes: Length of stay (7 vs. 7 days; p =

0.948), ICU transfers (18.2% vs. 17.8%; p = 0.960), discharges (65.9% vs. 68.9%, p = 0.764), SaO2 (94% vs. 95%; p = 0.324), and mortality (11.4% vs. 13.3%; p = 0.778).

Conclusion: "This randomized open-label controlled study showed no differences in

inflammatory markers or clinical outcomes in COVID-19 patients with moderate to severe pneumonia treated with favipiravir and inhaled interferon beta-1b against

HCQ."

Comments: Open-label trial of pneumonia. Data suggest lack of efficacy compared with

standard therapy.

Lou 2020 (score=3.5) [561]

Category: Favipiravir

Study Type: RCT

Comments: Small samples (total N=30). No statistical analysis performed.

Cai 2020 (score=NA) [562]

Category: Favipiravir

Study Type: Open-label nonrandomized control study

Conflict of Sponsored by National Science and Technology Major Project, Sanming Project of

Interest: 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 has been used for the treatment of COVID-19 [511, 563-571].

Lopinavir-Ritonavir for the Treatment of COVID-19

Sometimes Recommended.

Lopinavir-ritonavir is recommended in combination therapy [572], but is not recommended as a stand-alone treatment for COVID-19.

Strength of Evidence – Recommended, Evidence (C)

(Combination therapy)

Level of Confidence - Low

Strength of Evidence - Moderately Not Recommended, Evidence (B)

(Stand-alone treatment)

Level of Confidence - Low

Indications: Adjunctive use with ribavirin and interferon beta-1b in moderately and

severely affected patients with COVID-19 [572]. 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 [572].

Benefits: Faster symptom resolution, viral clearance, and hospital discharge.

Reduced need for a ventilator or ICU stay.

Harms: Nausea, diarrhea, hepatitis.

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

QT interval.

Frequency/Dose/Duration: 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 [572].

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 [572]. However, another trial found comparable faster clinical improvement (9 vs 11 days), fewer adverse events, and ~67% reduction in mortality (6.1 vs. 18.2%) when comparing treatment with interferon beta-1-b with treatment with the control group (lopinavir-ritonavir/HCQ) or atazanavir/ritonavir/HCQ) [573],

which could suggest that the only medication effective in the triple

therapy is the interferon beta-1b.

Lopinavir-ritonavir as a stand-alone antiviral treatment has been trialed in four RCTs, all of which showed a lack of efficacy compared with standard care [511, 571, 574, 575]. Another double-blind RCT also suggested lack of efficacy, although it may have been underpowered [574]. 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 [562].

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 [572]. However, the combination of only lopinavir-ritonavir is not recommended for the treatment of COVID-19 patients.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Lopinavir-Ritonavir; 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 123 articles in PubMed, 7,275 in Scopus, 68 in CINAHL, 7 in Cochrane Library, 10,610 in Google Scholar, and 11 from other sources†. We

Evidence:

Rationale:

considered for inclusion 11 from PubMed, 1 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 11 from other sources. Of the 30 articles considered for inclusion, 4 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) [571]

Category: Lopinavir-Ritonavir

Study Type: RCT

Conflict of Sponsored by Major Projects of National Science and Technology on New Drug Creation and **Interest:** 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) [574]

Category: Lopinavir/Ritonavir

Study Type: RCT

Conflict ofSupported 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

Lopinavir (200mg) boosted by ritonavir (50mg) LPV/r (oral, q12h, 500 mg each time for 7-

Comparison: 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

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).

"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."

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

Comments: viral clearance. Clinical efficacy unclear, largely due to under-enrollment. No evidence of

efficacy.

Li 2020 (score=6.0) [576]

Results:

Conclusion:

Category: Lopinavir/Ritonavir

Study Type: RCT

Comparison:

Results:

Conflict of Sponsored by project 2018ZX10302103-002, 2017ZX10202102-003-004 and Infectious

Interest: Disease Specialty of Guangzhou High-level Clinical Key Specialty. No COI.

Sample Size: N = 86 patients with mild to moderate COVID-19.

Age/Sex: Mean age: 49.4 years; 40 males, 46 females.

Lopinavir-Ritonavir (LPV/r): Patients were administered 200 mg lopinavir boosted by 50 mg of ritonavir twice daily for 7-14 days (n=34) vs. Arbidol: Patients were administered

100 mg of arbidol 3 times daily for 7-14 days (n=35) vs. Usual Care: Patients did not

receive antiviral treatment but received supportive care and oxygen therapy (n=17).

Follow-up: Follow-up at 3 weeks.

Results indicate that the rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid was similar between all groups (p>0.05). No differences between all groups were found in

the rates of antipyresis, cough alleviation, or improvement of chest computed tomography

at days 7 or 14 (all p>0.05).

Conclusion: "LPV/r or arbidol monotherapy present little benefit for improving the clinical outcome of

patients hospitalized with mild/moderate COVID-19 over supportive care."

Enrolled patients were mild to moderate and not severe COVID patients. Data suggest

Comments: little if any efficacy of either Lopinavir/Ritonavir or arbidol versus usual care in mild to

moderate hospitalized COVID-19 patients.

Hung 2020 (score=6.0) [572]

Category: Lopinavir/Ritonavir

Study Type: Open-label randomized trial

Conflict of Sponsored by the Shaw-Foundation, Richard and Carol Yu, May Tam Mak Mei Yin, and

Interest: 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

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)

"Triple antiviral therapy with interferon beta-1b, lopinavir–ritonavir, and ribavirin were

Conclusion: safe and superior to lopinavir–ritonavir alone in shortening virus shedding, alleviating

symptoms, and facilitating discharge of patients with mild to moderate COVID-19." 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) [577]

Category: Lopinavir/Ritonavir

Study Type: Cohort

Conflict of

Comments:

Comparison:

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

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

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)

"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) [578]

Category: Lopinavir/Ritonavir

Study Type: Cohort

Conflict of Interest:

Results:

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

Lack of LPV/r treatment was an independent risk factor for prolonged SARS-CoV-2 RNA shedding via logistic regression (OR = 2.42, 95% CLI1, 1, 5.351, n = 0.029). Median duration

Results: 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)

"In summary, older age and lack of LPV/r treatment contributed to prolonged SARS-CoV-2

Conclusion: 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) [579]

Category: Lopinavir/Ritonavir

Study Type: Cohort

Conflict ofNo COI. Sponsored by the Zhejiang Natural Science Foundation, Medical Science and Interest:
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

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

Results: 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)

"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 has been used to treat COVID-19 [580-587].

Remdesivir for the Treatment of COVID-19

Recommended.

Conclusion:

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

Strength of Evidence - No Recommendation, Insufficient Evidence (I)

(First 3 days of symptoms)

Level of Confidence - Low

Strength of Evidence – Recommended, Insufficient Evidence (I)

(Beyond 3 days)

Level of Confidence - Low

Indications: Severe COVID-19 patients, with <94% O₂ saturation or need for O₂

supplementation, mechanical ventilation, or extracorporeal membrane oxygenation [588]. Patients included in trials had

creatinine clearance >30 mL/min; ALT and AST <5 times upper limit of

normal.

Benefits: Shortened ICU stay, but minimal to no impact on survival.

Harms: Increased hepatic enzymes, diarrhea, rash, renal impairmen

Increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension. However, the largest RCT did not report significantly

increased adverse events in any category [452].

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

Remdesivir 200 mg IV on day 1, then 100 mg QD for 9 additional days

[452, 589].

Rationale: 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 [590]. A larger, moderate-quality NIH trial showed modest efficacy, including 31% shorter ICU stays and earlier clinical improvements. A RCT comparing remdesivir with standard care found a trend towards better results with a 5-day course of remdesivir [591]. However, one RCT found a lack of efficacy [511]. None of the RCTs was able to show statistically improved survival, although the NIH trial trended toward improved survival [452]. There is one case series suggesting a fairly low death rate (13%) [589] and another nonrandomized study suggesting potential efficacy [592]. A low-quality RCT found no difference between 5 and 10 days of treatment [593]. There is evidence that remdesivir inhibits viral replication in vitro

administered in the viral replication stage.

Remdesivir is invasive (IV), has minimal adverse effects, is high cost, has evidence of modest efficacy (particularly for the treatment of hospitalized patients requiring oxygen), and thus is selectively recommended. There are other treatments with stronger efficacy at reducing mortality (e.g., glucocorticosteroids, low-molecular-weight

studies [516]. It is possible that remdesivir is more effective if

heparin).

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 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 161 articles in PubMed, 3268 in Scopus, 16 in CINAHL, 2804 in Cochrane Library, 10300 in Google Scholar, and 6 from other sources†. We considered for inclusion 11 from PubMed, 6 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 6 from Google Scholar, and 6 from other sources. Of the 30 articles considered for inclusion, 6 randomized trials, 1 case series and 0 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.

Frequency/Dose/Duration:

Fvidence:

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) [590]

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.

Shih 2020 (score=NA) [580]

Category: Remdesivir

Study Type: Post-hoc analysis of Wang 2020

Conflict of Interest:

No mention of sponsorship. COI: Author Shih was a member of the DSMB

of the Remdesivir Chinese trial.

Sample Size: N = 231 hospitalized patients with laboratory-confirmed SARS-CoV-2

infection

Age/Sex: Mean age and sex data not mentioned

Intravenous remdesivir (200 mg on day 1, then 100 mg on days 2-10 in

Comparison: single daily infusions) (n=153) vs. Placebo (same frequency and dosage)

(n=78)

Follow-up: Follow-up through 28 days

On day 14, the response rate for the Remdesivir group was 43% with

Results: baseline disease point 3 (hospitalized, required supplemental oxygen,

moderately severe disease) compared to 33% in placebo group (odd ratio

= 1.53, p = 0.0022). On day 28, the response rate for the Remdesivir group was 85% with baseline disease point 3 compared to 70% in placebo group (OR = 2.38, p = 0.0012). In patients with baseline disease point of 4 (critically severe disease) there were no statistical differences.

"The Chinese trial was not really under-powered as previously perceived or portrayed by many opinions. This result supports the preliminary findings of ACTT that remdesivir is effective for patients who were not critically severe. This result also suggests that remdesivir should be given to hospitalized COVID-19 patients as soon as possible. There is no race

difference in the treatment effect."

Comments: Previously thought original study was underpowered. Data suggest

"remdesivir should be given to hospitalized patients as soon as possible."

Kalil 2020 (score=8.0) [594]

Conclusion:

Category: Remdesivir, Baricitinib

Study type: RCT

Conflict of Interest: Sponsored by the National Institute of Allergy and Infectious Diseases, the

National Institutes of Health, and the National Cancer Institute. No

mention of COI.

Sample size: N = 1033 hospitalized patients with COVID-19.

Age/Sex: Mean age: 55.4 years; 381 males, 652 females.

Comparison: Combination Treatment: Patients received 4 mg/day of baricitinib which

was administered either orally or through a nasogastric tube for 14 days or

until discharge. Patients also received remdesivir administered

intravenously first at 200 mg on day 1 then at 100 mg from day 2-10 or until discharge or death (n=515) vs. Control: Patients received placebo and remdesivir administered intravenously at 200 mg on the first day and at

100 mg from day 2-10 or until discharge or death(n=518).

Follow-up: Follow-up on days 15 and 28.

Results: According to the results, individuals in the combination treatment group

recovered a mean of 1 day faster than those who received remdesivir and placebo (median recovery days: 7 vs. 8; ratio rate for recovery: 1.16; 95% CI: 1.01 to 1.32; p=0.03). Patients in the combination treatment group also had a 30% higher odds of clinical status improvement at day 15 (odds

ratio: 1.3; 95% CI: 1.0 to 1.6).

Conclusion: "Baricitinib plus remdesivir was superior to remdesivir alone in reducing

recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation. The combination was associated with fewer

serious adverse events."

Comments: Placebo-controlled randomized double-blind study of baricitinib plus

remdesivir in hospitalized COVID-19 adults. Primary outcome was time to recovery which was a median of one full day earlier than placebo group (7 days versus 8 days). In patients on high-flow oxygen or receiving non-invasive ventilation, time to recovery for the combo group was 10 days compared to 18 days in the control group. The 28-day mortality was 5.1% in the combination group compared to 7.8% in the control group. The combination group was associated with fewer serious adverse events (16%)

versus 21%). The combination group experienced superior clinical

improvement at day 15.

Beigel 2020 (ACCT-1 Trial) (score=7.5) [452]

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.

Spinner 2020 (score=5.0) [591]
Category: Remdesivir
Study Type: RCT

Age/Sex:

Conflict of Interest: Sponsored by Gilead Sciences. COI, one or more authors have received or

will receive benefits for personal or professional use.

Sample Size: N = 596 hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and moderate COVID-19 pneumonia

No mention of mean age, median age: 57 years; 369 males, 227 females

Remdesivir treatment: administered intravenously, 200 mg on day 1,

Comparison: followed by 100 mg daily. 10-day course of remdesivir (n=197) vs. 5-day

course of remdesivir (n=199) vs. Standard Care (n=200)

Follow-up: Follow-up at days 11, 14, and 28

Those in the 5-day course group had a significantly higher odds of a better clinical status distribution compared to those in the standard care group

Results: (OR=1.65, p=0.02) at day 11. However, the 10-day course group did not

statistically differ from the standard care group (p=0.18). At day 28, both remdesivir groups differed from the standard card group (5-day p=0.08,

10-day p=0.03).

Conclusion: "Among patients with moderate COVID-19, those randomized to a 10-day

course of remdesivir did not have a statistically significant difference in

clinical status compared with standard care at 11 days after initiation of treatment. Patients randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard

care, but the difference was of uncertain clinical importance."

Open-label, confirmed COVID-19 infection with moderate COVID-19 pneumonia. Due to pandemic, effect of remdesivir on viral load not assessed. Average duration of symptoms before remdesivir was

administered was 8-9 days. Data suggest that a 10-day course of remdesivir was not better than standard care at day 11 but 5-day group

trended better than the standard-care group.

Goldman 2020 (score=3.0) [593]

Comments:

Category: Remdesivir
Study Type: Open-label RCT

Comments: Data suggest lack of efficacy of remdesivir in both the 5-day and 10-day

groups in those patients with COVID-19 who did not require mechanical

ventilation.

Grein 2020 (score=NA) [589]

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 period 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% clinical improvement and 13% death rate

among severe COVID-19 patients.

Low-molecular-weight heparin has been used for the treatment of hospitalized, severely affected patients with COVID-19; the degree of coagulopathy has been associated with worsened survival [595-607]. Fondaparinux and unfractionated heparin have also been recommended in the *Chest* guidelines [608]. Thrombectomies and other procedures have been performed in COVID-19 patients with known venous thromboembolism [608, 609].

Low-Molecular-Weight Heparin for the Treatment of COVID-19 Recommended.

Low-molecular-weight heparin is recommended for the treatment of select patients with COVID-19 [598, 601-603, 608, 610-625].

Strength of Evidence – Recommended, Evidence (C) Level of Confidence – Moderate

Indications:	Severely affected C	COVID-19 patients.	especially	those with known

evidence or suspicion of having coagulopathy (e.g., small-vessel thromboses, large-vessel arterial and/or venous thromboses [e.g., infarcts, DVTs, pulmonary emboli], thrombocytopenia, increased D-dimer, increased fibrin degradation products, prolonged coagulation times). May also be indicated for those who are hospitalized and either (i) sedentary, as there is some evidence of post-mortem coagulopathy in those without pre-morbid suspicions of coagulopathy and/or (ii) on a worsening clinical trajectory that suggests trending

towards critical status and/or cytokine storm [626].

Benefits: Possible improved survival, improved oxygenation, reduced time on

ventilator [627], reduced risks of DVT, pulmonary emboli, myocardial

infarction, cerebrovascular thromboembolic disease.

Harms: Usual risks of heparin, particularly bleeding complications.

Indications for Discontinuation: Recovery from COVID-19 and resolution of findings of coagulopathy

with regaining of normal ambulation. Also discontinue for significant adverse effects. May be continued after hospital discharge for a period of time during recovery and while still not as active and ambulatory as

pre-morbid.

Frequency/Dose/Duration: Per manufacturer's recommendations. A stepped approach with more

intensive prophylaxis for more severely affected patients has been reportedly successful [628]. Unfractionated heparin is another

therapeutic option.

Rationale: One RCT reported efficacy of enoxaparin over standard

anticoagulation (unfractionated heparin, generally 5,000U TID) to significantly increase gas exchange and reduce need for ventilatory

support [627]. A trial of sulodexide found reduced need for

hospitalization and oxygen therapy [624]. Reductions in mortality have been reported in non-randomized studies [602, 629-633], including an

estimated 47–50% reduced risk of mortality among those on

therapeutic anticoagulation among 4,389 in a hospital system [626]. Another cohort of patients on mechanical ventilation was found to

have a 54% reduction in mortality [631, 634].

An early escalating thromboprophylactic approach has been suggested as preventive among hospitalized patients with less severe disease [635].

Low-molecular-weight heparins are minimally invasive, have potentially significant adverse effects, are moderately costly, and have evidence suggesting associations with lower mortality rates and fewer complications among severely affected COVID-19 patients; thus, they are selectively recommended.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to December 2020 using the following terms: Low Molecular Weight Heparin; 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; nonrandomized controlled trials as topics. We found and reviewed 60 articles in PubMed, 837 in Scopus, 11 in CINAHL, 22 in Cochrane Library, 4,410 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 16 from PubMed, 21 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 13 from Google Scholar, and 0 from other sources. Of the 51 articles considered for inclusion, 2 randomized trials and 13 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 Low-Molecular-Weight Heparin

Lemos 2020 (score = 6.0) [627]

Category: Low-Molecular-Weight Heparin

Study Type: RCT

Conflict of Interest: No sponsorship. No COI.

Sample Size: N = 20 patients with SARS-CoV-2, acute respiratory distress syndrome,

respiratory failure requiring mechanical ventilation, D-dimer levels above 1000µg/L, prothrombin time/international normalized ratio less than 1.5, activated partial thromboplastin time/ratio less than 1.5, and platelet

count greater than 100,000/mm³.

Age/Sex: Mean age: 57 years; 16 males, 4 females.

Comparison: Group 1: therapeutic enoxaparin received subcutaneous enoxaparin,

maintained over 96 hours, according to age and daily varied according to creatinine clearance (CrCl). Under age 75: CrCl > 50mL/min administered

1mg/Kg BID, CrCl between 30 and 50mL/min administered1mg/Kg OD. Over age 75: CrCl > 50 mL/min administered0.75 mg/Kg BID, CrCl between 30 and 50mL/min administered 1mg/Kg OD, CrCl between 10 and 30 mL/min administered0.75 mg/Kg OD. For both age groups, if patients with CrCl < 10mL/min worsened in condition, they received unfractionated heparin adjusted according to the activated partial thromboplastin time, targeting a ratio between 1.5 and 2.0 (n = 10) vs. Group 2: standard thromboprophylaxis via subcutaneous unfractionated heparin or enoxaparin according to weight (W): W < 120kg: 5000 IU TID unfractionated heparin or 40 mg OD enoxaparin, W > 120kg 7500IU TID unfractionated heparin or 40 mg BID enoxaparin (n = 10)

Follow-up:

Follow-up at 7, 14, 21, and 28 days

Results:

The simplified acute physiology score 3 (SAPS3) and the sequential organ failure assessment score (SOFA) showed no statistical difference between groups. D-dimer levels were roughly equivalent at baseline (3408µg/L [95% CI 1283-5532] vs 4176µg/L [95% CI 1986-6365], p = 0.567). Group 1 had significant increase in PaO2/FiO2 over time (baseline: 163 [95% CI 133-193], 7 days: 209 [95% CI 171-247], 14 days: 261 [95% CI 230-293], p = 0.0004), while Group 2 experienced no significant difference (baseline: 184 [95% CI 146-222], 7 days: 168 [95% CI 142-195], 14 days: 195 [95% CI 128-262], p = 0.487). Group 1 experienced a higher ratio of liberation from mechanical ventilation (hazard ratio: 4.0 [95% CI 1.035-15.053], p = 0.031) after 28 days. Ventilator-free days were higher in Group 1 (15 days [IQR 6-16] vs 0 days [IQR 0-11], p = 0.028). D-dimer levels decreased significantly over time in Group 1 (4176μg/L [95% CI 1986-6365] vs 1469μg/L [95% CI 1034-1904, p = 0.009), while levels significantly increased in Group 2 $(3408\mu g/L [95\% CI 1283-5532] vs 4878\mu g/L [95\% CI 2291-7465], p= 0.004).$ Time difference between measurements between groups was not significant (Group 1: 3.9 ± 1.2 days vs Group 2: 4.3 ± 1.2 days, p = 0.457). No significant difference found in all-cause 28-day mortality rate (Group 1: 1/10 vs Group 2: 3/10, p = 0.264), in in-hospital mortality rate (Group 1: 2/10 vs Group 2: 5/10, p = 0.160), and in ICU-free days (Group 1: 12 days [IQR 2-12] vs Group 2: 0 days [IQR 0-10], p = 0.067). Hemoglobin levels decreased statistically insignificantly for both groups (Group 1: 4g/d: [95% CI 3-6] vs Group 2: 3 g/dL [95% CI 1-4], p = 0.063).

Conclusion:

"This open-label, controlled, randomized clinical trial demonstrated that therapeutic enoxaparin improved gas exchange over time and increased the ratio of successful liberation from mechanical ventilation. After these results, a larger clinical trial is urgently needed to evaluate the anticoagulant therapy in severe COVID-19 patients."

Comments:

HESACOVID Trial. Open label with small sample size (10 per group). One group received prophylactic anticoagulation and the other group received therapeutic anticoagulation. Data suggest therapeutic anticoagulation with enoxaparin increases gas exchange, thus reducing the need for ventilatory support in patients with severe COVID-19.

Gonzales-Ochoa 2020 (score=4.5) [624]

Category: Low-Molecular-Weight Heparin

Study Type: RCT

Conflict of Interest: Sponsored by Alfasigma Mexico. Alejandro Gonzalez-Ochoa received

speaker fees, honoraria, and travel reimbursement from Alfasigma

Mexico.

Sample Size: N = 243 patients age 40 or over with suspected COVID-19 clinical

symptoms and at high risk (greater than 50%) according to estimates given

by the COVID-19 Health Complication Calculator

Age/Sex: No mention of mean age, median age: 52 years; 115 males, 128 females

Comparison: Group 1 received sulodexide at a dose of 500RLU twice daily over a 3-week

period (n = 124) vs. Group 2 received placebo on the same schedule as

Group 1 (n = 119)

Follow-up: Follow-up every 7 days or as deemed necessary for 21 days

Results: Patient risk was similar between groups (Group 1: 67.8% ± 14 vs Group 2:

 $65.8\% \pm 14.1$, p = 0.32). The mean total length of stay (LOD) was

insignificant between groups (Group 1: 6.2 ± 4.1 days vs Group 2: 7.8 ± 4.5 days, p = 0.21). A significant difference in hospitalization was found between groups (relative risk: 0.6 [95% CI 0.37-0.96; p = 0.03) in favor of Group 1. Group 1 required less oxygen support (relative risk: 0.71 [95% CI 0.5-1], p = 0.05) for less days (Group 1: 9 ± 7.2 days vs Group 2: 11 ± 9.6 days, p = 0.02). Patients in Group 1 had lower mortality (Group 1: 2.4% vs Group 2: 5.8%, risk ratio: 0.41 [95% CI 0.10-1.55], p = 0.19). D-dimer levels

were significantly elevated in Group 2 (464.75 \pm 629.81 vs 897.7 \pm 1215.36, p < 0.01). Group 2 patients experienced grater D-dimer levels when compared with Group 1 (risk ratio: 0.46 [95% CI 0.31-0.67], p > 0.01). C-reactive protein levels at week 2 for Group 1 was less than Group 2 (Group 1: 12.55 \pm 10.2 mg/dL vs Group 2: 17.81 \pm 11.56 mg/dL, p < 0.01). Suspended medication was found to be higher for Group 1. (risk ratio: 1/81 [95% CI 0.88-3.74], p = 0.10). Premature interruption of medication due to recovery was higher in Group 1 (risk ratio: 0.56 [95% CI 0.21-1.48], p = 0.24). Novel symptoms reported between groups yielded a (risk ratio: 1.08 [95% CI 0.93-1.25], p = 0.28). Adverse events causing discontinuation of medication between groups yielded a risk ratio of 0.78 (95% CI 0.27-

[95% CI 0.65-0.95], p = 0.01).

Conclusion: "Early intervention in COVID-19 patients with sulodexide reduced hospital

admissions and oxygen support requirements, although with no significant

2.18, p = 0.63). Use of bronchodilator was lower in Group 1 (risk ratio: 0.79

effect on mortality. This has beneficial implications in the patient

wellbeing, making sulodexide a [favorable] medication until an effective

vaccine or an antiviral becomes available."

Comments: Placebo-controlled trial with sulodexide, which is a combination of 80%

low-molecular-weight heparin and 20% dermatan sulphate. Trial was planned to be double-blind, but the lead investigator had to break blinding during the course of the study. Data suggest administration of sulodexide during early stages of COVID-19 reduced both the need for hospitalization

as well as oxygen therapy requirements.

Various interleukin-6 receptor antagonists have been used for the treatment of hospitalized patients with COVID-19 [475, 636-671].

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

Not Recommended.

Interleukin-6 inhibitors (sarilumab, siltuximab, and tocilizumab) are not recommended for the treatment of patients with COVID-19.

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

Rationale:

One moderate-quality trial suggested a reduced need for mechanical ventilation but no improved survival [672], while three other moderate-quality RCTs found a lack of efficacy of tocilizumab [673-675]. One moderate-quality RCT found trends towards reduced mortality by 2 weeks but not 4 weeks associated with tocilizumab [676]. One controlled study suggested increased adjusted survival rates among the group of patients treated with tocilizumab, although there were baseline differences likely favoring survival among the treated [640]. Another controlled but non-randomized study of tocilizumab added to a standard-care regimen of HCQ, lopinavir, plus ritonavir suggested efficacy if administered earlier in the hospital course [475]. One retrospective study found no benefit of tocilizumab [639]. One case series suggested significant survival and oxygenation benefits [636].

As there is now evidence of a lack of efficacy of the IL-6 receptor

Evidence:

antagonists, they are not recommended. There also are currently other treatments with demonstrated efficacy. A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Interleukin-6, tocilizumab, sarilumab, 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, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 436 articles in PubMed, 5,491 in Scopus, 66 in CINAHL, 116 in Cochrane Library, 12,300 in Google Scholar, and 6 from other sources[†]. We considered for inclusion 17 from PubMed, 21 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 8 from Google Scholar, and 6 from other sources. Of the 53 articles considered for inclusion, 5 randomized trials, 1 case series and 5 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 Interleukin-6 (IL-6) Receptor Antagonists

Salama 2020 (score=7.5) [672]

Category: Interleukin-6 Receptor Antagonists

Study Type: RCT

Conflict of Interest: Sponsored by Genentech. No mention of COI.

Sample Size: N = 388 participants with PCR-confirmed COVID-19 and

radiographic imaging confirmed COVID-19 pneumonia

Age/Sex: Age and sex data only available for 377 participants. Mean age: 55.9 years;

223 males, 154 females

Comparison: Tocilizumab: Received standard care and 1 or 2 doses (8 mg per kg,

max 800 mg) intravenously (n=259) vs Placebo: received standard care and 1 or 2 doses intravenously (n=129). Second dose administered only if patients' clinical signs did not improve 8–24 hours after first dose.

Follow-up: Follow-up weekly until day 28 and then again at day 60

Results: Rate of patients who received mechanical ventilation or died by day 28

was 12.0% (95% CI, 8.5%-16.9%) in the tocilizumab group and 19.3% (95% CI, 13.3%-27.4%) in the placebo group. Hazard ratio was 0.56 (95% CI,0.33-

0.97; p= 0.04)

Conclusion: "This trial showed that the likelihood of progression to mechanical

ventilation or death by day 28 was significantly lower among patients who received tocilizumab plus standard care than among those who received

placebo plus standard care."

Comments: Double-blind, placebo-controlled trial. Data suggest probability of

progression to death or mechanical ventilation was significantly lower in

the tocilizumab group vs. placebo/standard care.

Stone 2020 (score=7.5) [673]

Category: Interleukin-6 Receptor Antagonists

Study Type: RCT

Conflict of Interest: Sponsored by Genentech. No mention of COI.

N = 243 patients with confirmed SARS-CoV-2 infection, hyperinflammatory

Sample Size: states, and at least two of these signs: fever, pulmonary infiltrates, need

for supplemental oxygen for oxygen saturation greater than 92%

Age/Sex: No mention of mean age; median age: 59.8 years; 141 males, 102 females

Tocilizumab - standard care plus single dose of tocilizumab (8 mg per

Comparison: kilogram of body weight, administered intravenously, maximum 800 mg)

(n=161) vs. Placebo – standard care plus single dose of placebo (n=82)

Follow-up: Follow-up at 14 and 28 days

The hazard ratio for intubation or death of tocilizumab group versus

Results: placebo group was 0.83 (p=0.64) and the hazard ratio for disease

worsening was 1.11 (p=0.73).

"Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19. Some benefit or harm

cannot be ruled out, however, because the confidence intervals for

efficacy comparisons were wide."

Data suggest lack of efficacy for tocilizumab preventing moderately ill Comments:

COVID-19 patients from either progressing to intubation or dying.

Salvarani 2020 (score=6.0) [674]

Category: Interleukin-6 Receptor Antagonists

Study Type: **RCT**

Conclusion:

Sample Size:

Sponsored by the Italian Ministry of Health. COI, one or more authors have Conflict of Interest:

received or will receive benefits for personal or professional use.

N = 126 patients with confirmed COVID-19 pneumonia, partial pressure of

arterial oxygen – fraction of inspired oxygen ratio between 200 and

300mm Hg (PaO₂/FlO₂), and inflammatory phenotype defined by fever and

elevated C-reactive protein

Age/Sex: No mention of mean age; median age: 60.0 years; 77 males, 49 females

Tocilizumab: given intravenous tocilizumab within 8 hours of

randomization (8 mg/kg with maximum of 800 mg), followed by second Comparison:

dose after 12 hours (n=60) vs. Standard care: supportive care, could

receive tocilizumab as rescue therapy (n=66)

Follow-up: Follow-up at 14 and 30 days

At day 14, 28.3% of tocilizumab group and 27.0% of standard card group Results:

reported clinical worsening (rate ratio = 1.05, 95% CI [0.59, 1.86]).

"In this randomized clinical trial of hospitalized adult patients with COVID-19 pneumonia and PaO₂/FIO₂ ratio between 200 and 300 mm Hg who received tocilizumab, no benefit on disease progression was observed compared with standard care. Further blinded, placebo-controlled

Conclusion:

randomized clinical trials are needed to confirm the results and to evaluate possible applications of tocilizumab in different stages of the

disease."

Data suggest lack of efficacy as tocilizumab was not better than standard

care for slowing disease progression hospitalized COVID-19 patients with

pneumonia.

Hermine 2020 (score=5.5) [676]

Category: Interleukin-6 Receptor Antagonists

Study Type: RCT

Comments:

Sponsored by the Ministry of Health, Programme Hospitalier de Recherche

Clinique, Foundation for Medical Research, AP-HP Foundation and the Reacting Program. COI: Author Tharaux received honorarium fees for

Conflict of Interest:

participation on advisory boards for Retrophin Inc (not related to this

article).

N = 131 patients with confirmed SARS-CoV-2 infection with moderate, Sample Size:

severe, or critical pneumonia

Only 130 participants included in analysis. Mean age not mentioned, Age/Sex:

median age: 64 years; 88 males, 42 females

Tocilizumab intravenously, 8 mg/kg, on days 1 and 3 (n=64) vs. Usual care

alone, which included antibiotic agents, antiviral agents, corticosteroids,

vasopressor support and anticoagulants (n=67)

Follow-up: Follow-up at days 4, 7, 14, and 28

At day 4, a total of 12 tocilizumab patients had a World Health

Organization 10-point Clinical Progression Scale (WHO-CPS) score greater than 5 versus 19 in the usual care group (median posterior absolute risk difference = -0.9%, 90% confidence interval [-21.0, 3.1]). On day 14, in the

tocilizumab group, 12% fewer patients needed noninvasive ventilation, mechanical ventilation, or died compared to the usual care group (24%

versus 36%, hazard ratio = 0.58, 90% CI [0.33, 1.00]).

"In this randomized clinical trial of patients with COVID-19 and pneumonia requiring oxygen support but not admitted to the intensive care unit, TCZ did not reduce WHO-CPS scores lower than 5 at day 4 but might have reduced the risk of NIV MV, or death by day 14. No difference on day 28.

reduced the risk of NIV,MV, or death by day 14. No difference on day 28 mortality was found. Further studies are necessary for confirming these

preliminary results."

Usual care bias. Data suggest lack of efficacy as no difference between

groups at 28 days.

Rosas 2021 (score=4.5) [675]

Comparison:

Results:

Conclusion:

Comments:

Sample Size:

Category: Interleukin-6 Receptor Antagonists

Study Type: RCT

Conflict of Interest: Sponsored by F. Hoffmann –La Roche and by a grant from the Department

of Health and Human Services. COI, Dr. Cooper and Dr. Youngstein were supported by the NIHR and Dr. Malhotra was supported by the NIH.

N = 452 participants with PCR-confirmed COVID-19 and severe COVID-

19 pneumonia confirmed by radiographic imaging

Age and sex data only available for 438 participants. Mean age: 60.8

years; 306 males, 132 females

Comparison: Tocilizumab: Received standard care and 1 or 2 doses (8 mg per kg,

max 800 mg) intravenously (n=301) vs Placebo: Received standard care and 1 or 2 doses intravenously (n=151). Second dose administered only if

patients' clinical signs did not improve 8-24 hours after first dose.

Follow-up: Follow-up at 28 and 60 days

Results: Median score of clinical status (scale ranked 1-7) was 1.0 (95% CI, 1.0-1.0)

in the tocilizumab group and 2.0 (95% CI, 1.0-4.0) in the placebo group. van Elteren test of group difference was -1.0 (95% CI, -2.5-0; p=

0.31)

Conclusion: "In this trial involving hospitalized patients with severe Covid-19

pneumonia, we found no significant difference in clinical status between

the tocilizumab group and the placebo group at day 28."

Comments: Data suggest lack of efficacy at day 28.

Xu 2020 (score=N/A) [636]

Category: Tocilizumab
Study Type: Case Series

No COI. Sponsored by the Department of Science and Technology of Anhui

Conflict of Interest: Province and the Health Commission of Anhui Province and the China

National Center for Biotechnology Development 175.

N = 21 patients diagnosed with several or critical COVID-19 based on

criteria of the Diagnosis and Treatment Protocol for Novel Coronavirus Sample Size:

Pneumonia

Age/Sex: Mean age: 56.8 years; 18 males, 3 females

All patients received lopinavir, methylprednisolone, other symptom

Comparison: 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 **Results:**

tracheal extubating. 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.

"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."

Conclusion:

Case series. Survival of >90% is far above expected rates; provided **Comments:**

evidence is suggestive of efficacy.

Baricitinib is an orally bioavailable reversible inhibitor of Janus kinases 1 and 2 (JAK 1/2) typically used to rheumatoid arthritis. It has anti-inflammatory, immunomodulating, and antineoplastic activities, and has an FDA emergency use authorization (EUA) for use in COVID-19 infection due to its antiviral effects. Baricitinib has been used for the treatment of patients with COVID-19 [677-681].

Baricitinib for the Treatment of COVID-19

Recommended.

Baricitinib is moderately recommended for the treatment of select patients with COVID-19 [594].

Strength of Evidence – Moderately Recommended, Evidence (B) Level of Confidence – Moderate

Indications: Severely affected patients with COVID-19 with cytokine storm

manifestations, including ARDS. Also indicated for those requiring supplemental oxygen and/or mechanical ventilation. Other treatments may be combined (e.g., glucocorticosteroids). The U.S. FDA issued an Emergency Use Authorization for use in combination with remdesivir

[682, 683].

Benefits: Improved recovery time, clinical outcomes, oxygenation, reduced

need for ICU stay. Possible 35% reduced 28-day mortality.

Harms: Fever, chills, tiredness, muscle pain, increased urination, stomach

pain, diarrhea, weight loss, cough, dyspnea.

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

Frequency/Dose/Duration: Doses used have included 4 mg loading then 2 mg/day and 4 mg/day

6781

Rationale: One high-quality trial found that adding baricitinib to remdesivir

compared with remdesivir alone resulted in one less day of ICU stay. The evidence was stronger in the non-mechanical ventilated group with a 44% reduction in recovery time, and there was a trend in a 35% reduction in 28-day mortality [594, 682, 683]. There are multiple non-randomized studies suggesting efficacy at mitigating the cytokine storm. A non-randomized trial found that the addition of baricitinib to glucocorticosteroids was associated with improved clinical outcomes, including an 82% reduced need for supplemental oxygen at discharge [678]. A comparative consecutive case series suggested significant benefits, such as eliminating ICU transfers and 58% vs. 8% discharge at 2 weeks [681]. Baricitinib is invasive, has some adverse effects, is

costly, has some evidence of strong efficacy, and thus is

recommended for select patients.

Evidence: A comprehensive literature search was conducted using PubMed,

Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Baricitinib, Olumiant; 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 15 articles in PubMed, 1,177 in Scopus, 2 in CINAHL, 14 in Cochrane Library, 2,670 in Google Scholar, and 1 from other sources†. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 8 from Google Scholar, and 1 from other sources. Of the 10 articles considered for inclusion, 1 randomized trial 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 Baricitinib

Kalil 2020 (score=8.0) [594]

Category: Baricitinib, Remdesivir

Study type: RCT

Conflict of Interest: Sponsored by the National Institute of Allergy and Infectious Diseases, the National

Institutes of Health, and the National Cancer Institute. No mention of COI.

Sample size: N = 1033 hospitalized patients with COVID-19. Age/Sex: Mean age: 55.4 years; 381 males, 652 females.

Comparison: Combination Treatment: Patients received 4 mg/day of baricitinib which was

administered either orally or through a nasogastric tube for 14 days or until discharge. Patients also received remdesivir administered intravenously first at 200 mg on day 1 then at 100 mg from day 2-10 or until discharge or death (n=515) vs. Control: Patients received placebo and remdesivir administered intravenously at 200 mg on the first day

and at 100 mg from day 2-10 or until discharge or death (n=518).

Follow-up: Follow-up on day 15 and 28.

Results: According to the results, individuals in the combination treatment group recovered a

mean of 1 day faster than those who received remdesivir and placebo (median recovery days: 7 vs. 8; ratio rate for recovery: 1.16; 95% CI: 1.01 to 1.32; p=0.03). Patients in the

combination treatment group also had a 30% higher odds of clinical status

improvement at day 15 (odds ratio: 1.3; 95% CI: 1.0 to 1.6).

Conclusion: "Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time

and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation. The combination

was associated with fewer serious adverse events."

Comments: Placebo-controlled randomized double-blind study of baricitinib plus remdesivir in

hospitalized COVID-19 adults. Primary outcome was time to recovery, which was a median of 1 full day earlier than placebo group (7 days versus 8 days). In patients receiving high-flow oxygen or non-invasive ventilation, time to recovery for the combination group was 10 days compared to 18 days in the control group. The 28-day mortality was 5.1% in the combination group compared to 7.8% in the control group. The combination group was associated with fewer serious adverse events (16% versus 21%). The combination group experienced superior clinical improvement at day 15.

Casirivimab plus imdevimab are recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the SARS-CoV-2 spike protein receptor-binding domain and have been used to treat COVID-19. These have been approved for use by FDA under the emergency use authorization provision [684].

Casirivimab plus Imdevimab for the Treatment of COVID-19 Recommended.

Casirivimab plus imdevimab is recommended for the treatment of patients with mild to moderate COVID-19.

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

Indications: Generally only for outpatient treatment of mild to moderate COVID-19

cases and for those at high risk of disease progression. FDA criteria for adults include BMI 35+, chronic renal disease, diabetes mellitus,

immunocompromising condition, current receipt of

immunosuppressive treatment, age 65+, age 55+ with comorbidity (cardiovascular disease, hypertension, COPD). Oxygen therapy is an

exclusion.

Benefits: Milder case with reduced risk of hospitalization.

Harms: Unclear

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

Frequency/Dose/Duration: N/A

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Rationale:

Evidence:

N/A

Data provided to the FDA suggest a reduction of 67% in the risk of hospitalization (9% vs. 3%) [685]. An NIH panel felt more data are needed prior to a recommendation. Casirivimab plus imdevimab have apparent preliminary evidence suggesting efficacy. Because there are so few medications with proven efficacy for this stage of disease to prevent severe outcomes, these medications are recommended. A comprehensive literature search was conducted using PubMed,

Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to December 2020 using the following terms: Casirivimab, Imdevimab; 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, 0 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 32 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.

criteria.

Zero articles met the inclusion criteria. There were no exclusion

[†] 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.

Bamlanivimab is a neutralizing monoclonal IgG1 antibody that targets the receptor-binding domain of the spike protein of SARS-CoV-2 and has been used to treat COVID-19. It has been approved for use by the FDA under the emergency use authorization provision [686, 687].

Bamlanivimab for the Treatment of COVID-19 Recommended.

Bamlanivimab is recommended for the treatment of patients with mild to moderate COVID-19 [688].

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

Indications: Generally only for outpatient treatment of patients with mild to

moderate COVID-19 cases and those at high risk of disease progression. FDA criteria for adults include BMI 35+, chronic renal disease, diabetes mellitus, immunocompromising condition, current receipt of immunosuppressive treatment, age 65+, age 55+ with comorbidity (cardiovascular disease, hypertension, COPD). Oxygen

therapy is an exclusion.

Benefits: Milder case with reduced risk of hospitalization.

Harms: Unclear. Reported reactions include anaphylaxis and a serious

infusion-related reaction.

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

Frequency/Dose/Duration: N/A

Rationale: One moderate-quality trial found marked reductions in the need for

hospitalization or need for emergency room visits compared with placebo, while also reporting reduced viral loads [689]. Data provided to the FDA suggest a reduction of 68–84% in the risk of combined 28-day hospitalization, emergency department visit, or death [686]. Another study suggested a 72% reduction in the risk of hospitalization among those at high risk [686]. Bamlanivimab has quality evidence of

considerable efficacy and is thus recommended.

Evidence: A comprehensive literature search was conducted using PubMed,

Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to December 2020 using the following terms: Bamlanivimab; 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, 5 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 85 in Google Scholar, and 1 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 1 from other sources. Of the 1 article considered, 1 randomized trial and 0 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 Bamlanivimab

Gottlieb 2021 (score=6.5) [689]

Category: Bamlanivimab

Study Type: RCT

Conflict of Interest: Sponsored by Eli Lilly and Company. COI, one or more authors have received or

will receive benefits for personal or professional use.

Sample Size: N = 613 ambulatory participants who tested positive for SARS-CoV-2, having at

least one mild to moderate symptom

Age/Sex: Age and sex data only available for 577 participants. Mean age: 44.7 years; 262

males, 315 females

Comparison: Group 1: Bamlanivimab 700 mg (n=104) vs. Group 2: Bamlanivimab 2800 mg

(n=109) vs. Group 3: Bamlanivimab 7000 mg (n=104) vs. Group 4:

Bamlanivimab 2800 mg and Etesevimab 2800 mg (n=114) vs. Group 5: Placebo (n=161). All treatments given in a single dose via a 60-minute intravenous

infusion.

Follow-up: Follow-up at days 1, 3, 7, and 11

Results: Log viral load change from baseline to day 11: group 1 = -3.72, group 2 = -4.08,

group 3 = -3.49, group 4 = -4.37, group 5 = -3.80. Differences in the change of log viral load at day 11 compared to placebo: group 1 = 0.09 (p = 0.69), group 2

= -0.27 (p = 0.21), group 3 = 0.31 (p = 0.16), group 4 = -0.57 (p = 0.01).

Conclusion: "Among nonhospitalized patients with mild to moderate COVID-19 illness,

treatment with bamlanivimab and etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11; no significant difference in viral load reduction was observed for

bamlanivimab monotherapy."

Comments: Double-blind placebo-controlled trial with 5 groups. In non-hospitalized

patients with mild-moderate COVID-19, data suggest that treatment combined with etesevimab was associated with significant viral load reduction at day 11 compared with placebo. Differences were shown between each treatment group and placebo group. The percent of patients with hospitalization or ED

visit improved vs. placebo.

Ivermectin has been used for the treatment of COVID-19 [690-697].

Ivermectin for the Treatment of COVID-19

No Recommendation.

There is no recommendation regarding ivermectin for the treatment of patients with mild to moderate COVID-19 [691-708].

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

Rationale:

Evidence:

There is one moderate-quality RCT comparing usual care to usual care plus ivermectin, which found no benefits when started within 7 days of symptom onset [691]. Another found a lack of benefit when started within 7 days of symptom onset [690]. Two small RCTs showed an association of ivermectin with subsequently lower viral loads, but the studies did not have meaningful clinical outcomes [692, 693]. Thus, the available evidence does not well target the high viral replication stage that occurs at symptom onset. Because the quality literature does not clearly show clinical efficacy, there is no recommendation regarding ivermectin.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to December 2020 using the following terms: Ivermectin, Stromectol; 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; nonrandomized controlled trials as topics. We found and reviewed 18 articles in PubMed, 1095 in Scopus, 6 in CINAHL, 35 in Cochrane Library, 2757 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 5 from PubMed, 0 from Scopus, 0 from CINAHL, 2 from Cochrane Library, 11 from Google Scholar, and 0 from other sources. Of the 18 articles considered for inclusion, 8 randomized trials 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 Ivermectin

Chaccour 2020 (score=7.5) [692]

Category: Ivermectin

Study Type: RCT

Sponsored by Idipharma SL, University of Navarra, ISGlobal, Spanish

Conflict of Interest: Ministry of Science and Innovation, and Generalitat de Catalunya. Multiple

authors received salary support from Unitaid through the BOHEMIA grant

to ISGlobal.

Sample Size: N = 24 patients with COVID-19 symptoms, 72 hours of fever or cough, and

a positive SARS-CoV-2 PCR test

Age/Sex: No mention of mean age; median age: 20 years; 12 males, 12 females

Group 1 received a single, 400 mcg/kg, oral dose of Ivermectin (n = 12) vs.

Group 2 received placebo (n = 12)

Follow-up: Follow-up at days 4, 7, 14, 21, and 28

No difference between groups at 7 days post treatment in proportion of PCR-positive results as 12 participants in each group had a positive PCR for

Results: gene N and 11 of the ivermectin group and the entire (12) placebo group

had a positive PCR for gene E (risk ratio = 0.92, p = 1.0).

"The positive signal found in this pilot warrants the conduction of larger trials using ivermectin for the early treatment of COVID-19. Such trials should include patients with risk factors for severe disease as well as patients with pneumonia. The potential for a mechanism of action

different to direct antiviral effect also opens the door for pre-exposure

prophylaxis in high risk groups."

Placebo-controlled pilot study with small sample (n=24). Data suggest in mild COVID-19 patients with no known risk factors for progression to severe disease, on day 4 and day 7 there were lower median viral loads in

the ivermectin group and lower IgG titers at day 21 post treatment. Also, there were fewer patients reporting cough or hyposmia/anosmia in the

ivermectin group.

Krolewiecki 2020 (score=4.0) [693]

Category: Ivermectin

Study Type: RCT

Conclusion:

Comments:

Sample Size:

Sponsored by Agencia Nacional de Promoción, el Desarrollo Tecnológico y

la Innovación, and Laboratorio ELEA/Phoenix, Argentina. Alejandro Krolewiecki received grants from Laboratorio Elea/Phoenix. Marcelo A.

Conflict of Interest: Tinelli, Marcelo D. Golemba, and Eduardo Spitzer are all employed by

Laboratorios Elea/Phoenix. Silvia Gold is on the Board of Directors for

Laboratorio Elea/Phoenix.

N = 45 patients with RT-PCR confirmation, disease stage 3–5, symptom onset at less than or equal to 5 days, no treatment involving anti-virials $\frac{1}{2}$

suspected to be effective against COVID-19, no ICU stay, and no travel

plans

Age/Sex: Mean age: 40.2 years; 25 males, 20 females

Comparison: Ivermectin: oral 0.6 mg/kg/day ivermectin at 24-hour intervals for 5

consecutive days (n=30) vs. Control: received no treatment (n=15)

Follow-up: Follow-up daily for the first 7 days and then at day 21 to 30 relative to

study entry

The ivermectin group had a viral load decay rate of (0.64 d^-1), which was

significantly greater than the control group (0.13 d^-1) (p = 0.041). The ivermectin groups' concentrations did not correlate with respect to body

Results: weight $(r^2 = 0.1)$ or body mass index $(r^2 = 0.07)$. Mean ivermectin

plasma concentrations were correlated positively with the viral decay rate

(r - 0.47, p = 0.02).

"A concentration dependent antiviral activity of oral high dose IVM was identified in this pilot trial at a dosing regimen that was well tolerated.

Large trials with clinical endpoints are necessary to determine the clinical

utility of IVM in COVID-19."

Pilot randomized open-label trial. Claims to be "assessor blinded" but

Comments: could not confirm. Ivermectin appears to show some concentration-

dependent antiviral activity against COVID-19.

Podder 2020 (score=4.5) [691]

Category: Ivermectin

Study Type: RCT

Conclusion:

Results:

Conclusion:

Conflict of Interest: No sponsorship. No COI.

Sample Size: N = 62 patients with consecutive, positive RT-PCR tests with less than 7

days of symptoms

Age/Sex: Mean age: 39.16 years; 44 males, 18 females

Group 1 (G1) (n=32) received usual care, consisting of antipyretic, cough

Comparison: suppressants, doxycycline at 100mg at 12 hr. intervals for 7 days, plus a single dose of ivermectin at 200 mg/kg at randomization vs Group 2 (G2)

(n=30) received usual care only

Follow-up: Follow-up at recovery or resolution of symptoms from onset

No significant differences with regards to recovery time for complete recovery (95% CI: -0.86 to 3.672), fever (95% CI: -1.755 to -6.675), or fatigue (95% CI: -4.164 to 5.306) from illness onset (p > 0.05). No

significant differences with regards to recovery time for complete recovery

(95% CI: -0.776 to 2.808), fever (95% CI: -1.729 to 1.415), shortness of breath (95% CI: -2.187 to 5.187), or fatigue (95% CI: -6.097 to 5.430) from enrollment (p > 0.05). PT-RCR results were insignificant between groups (p = 0.05).

> 0.05).

"In conclusion, adding ivermectin to usual care in the management of mild to moderate COVID-19 patients did not show any benefit. However, since

the sample size was small, future multicentre studies with a larger sample

size could be conducted to confirm the outcome."

Comments: Data suggest lack of efficacy of ivermectin versus standard care for

treating mild to moderate COVID-19 patients.

Ahmed 2020 (score = 3.5) [698]

Category: Ivermectin

Study Type: RCT

Comments: Sparse methods, figures, and tables

Niaee 2020 (score=3.5) [694]
Category: Ivermectin

Category.

Study Type: RCT

Comments: Blinding not well described. Compliance not included. Tables unclear.

Chowdhury 2020 (score = 2.5) [695]
Category: Ivermectin

Study Type: RCT

Comments: No mention of compliance or dropouts

Hashim 2020 (score = 2.5) [696]
Category: Ivermectin
Study Type: RCT

Comments: No mention of compliance, completers, or dropouts

Elgazzar 2020 (score = 2.0) [697]
Category: Ivermectin
Study Type: RCT

Comments: Sparse methods. Groups are not separated in baseline demographic table.

No mention of completers or how compliance was assessed.

Convalescent COVID-19 antibodies have been used to treat COVID-19 [670, 709-724].

Convalescent COVID-19 Antibodies

No Recommendation.

Benefits:

There is no recommendation for or against the use of convalescent antibodies for the treatment of patients with COVID-19.

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

Indications: Generally only for severely affected patients with COVID-19 and after

other exhausting other interventions with stronger evidence of efficacy (especially monoclonal antibodies early in the course of disease). Timing of convalescent antibodies is best in the viral replication stage [725]. There are three pathways for administration: 1) clinical trials, 2) expanded use, and 3) single-patient emergency Investigational New Drug. 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 [726].

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: Multiple moderate-quality trials found lack of efficacy [576, 727-729].

A moderate-quality RCT found significant improvement in dyspnea and fatigue, although no benefits regarding mortality or disease

progression at day 28 [730]. One moderate-quality trial suggested potential reduction in the need for mechanical ventilation [731]. There is one low-quality RCT suggesting a lack of efficacy [724]. There are few other studies of convalescent antibodies [732, 733]. However, they were reportedly successful in one case series [734] and have been successfully used for other diagnoses, including Ebola [735, 736]. Convalescent antibodies are invasive, have adverse effects, and are costly; however, the quality data are conflicting and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: convalescent, 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; nonrandomized controlled trials as topics. We found and reviewed 15 articles in PubMed, 1 in Scopus, 1 in CINAHL, 1 in Cochrane Library, 1 in Google Scholar, and 13 from other sources†. We considered for inclusion 9 from PubMed, 1 from Scopus, 1 from CINAHL, 1 from Cochrane Library, 3 from Google Scholar, and 13 from other sources. Of the 28 articles considered for inclusion, 7 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

Simonovic 2020 (score=7.0) [727]

Category: Convalescent COVID-19 Antibodies

Study Type: RCT

Conflict of Interest: No sponsorship. No mention of COI.

Sample Size: N = 334 hospitalized patients with severe COVID-19 pneumonia

Age/Sex: Age and sex data only available for 333 participants. No mention of mean

age, median age: 62 years; 225 males, 108 females

Comparison: Convalescent Plasma: single dose of infused convalescent plasma with a

median titer of 1:3200 of total SARS-CoV-2 antibodies (n=228) vs. Placebo:

single dose of normal saline solution (n=106)

Follow-up: Follow-up at 30 days

Results: No significant difference between groups at day 30 in clinical outcomes

according to the WHO clinical scale for status (odds ratio = 0.83, p=0.46). Overall mortality for the convalescent group was 10.69% and for the placebo

group was 11.43% (risk difference = -0.46, 95% CI [-7.8, 6.8])

Conclusion: "No significant differences were observed in clinical status or overall

mortality between patients treated with convalescent plasma and those who

received placebo."

Comments: Double-blind, placebo-controlled trial. Data suggest lack of efficacy for

clinical status of mortality.

Li 2020 (score=6.5) [728]

Category: Convalescent COVID-19 Antibodies

Study Type: RCT

Conflict of Interest: Sponsored by the Chinese Academy of Medical Sciences innovation Fund for

Medical Sciences and the Nonprofit Central Research Institute Fund of Chinese Academy of Medical Sciences. COI, Ling Li has a pending COVID-19 testing patent and Wu consults for Verax Medical and Grifols, received royalties from UptoDate and AABB, and received support from Chinese

Institute of Blood Transfusion.

Sample Size: N = 103 patients with severe or life-threatening COVID-19.

Age/Sex: Mean age: 69.5 years; 60 males, 43 females.

Comparison: Convalescent Plasma (CP) Group: Patients received 4-13 mL/kg of their body

weight in Convalescent Plasma at a rate of 10mL for 15 minutes then 100 mL per hour (n=52) vs. Control Group: Patients received standard treatment such as antiviral medication, antibacterial medication, steroids, human

immunoglobulin, or herbal medicine (n=51).

Follow-up: Follow up at 7, 14, and 28 days.

Results: Percent of patients who reached clinical improvement by 28 days in CP vs.

Control Group: 51.9% vs. 43.1% (p=0.26). Percent of patients discharged by 28 days: 51.0% vs. 36.0% (p=0.13). Mortality rate by 28 days for CP vs. Control Group: 15.7% vs. 24.0% (p=0.30). Percent of patients with severe disease to reach clinical improvement by 28 days for CP vs. Control: 91.3% vs 68.2% (p=0.03). Percent of patients with life threatening disease to reach clinical improvement by 28 days for CP vs. Control: 20.7% vs 24.1% (p=0.83).

Conclusion: "Among patients with severe or life-threatening COVID-19, convalescent

plasma therapy added to standard treatment, com- pared with standard

treatment alone, did not significantly improve the time to clinical

improvement within 28 days. Interpretation is limited by early termination of the trial, which may have been underpowered to detect a clinically important

difference."

Comments: Open-label disease severity stratified RCT. Median participant age was 70

years. Many baseline dissimilarities between groups (e.g., sex, CRP, platelet levels). Data suggest no significant difference between groups, but baseline

data suggest bias against convalescent antibody group.

Agarwal 2020 (score=6.0) [730]

Category: Convalescent COVID-19 Antibodies

Study Type: RCT

Conflict of Interest: Sponsored by Indian Council of Medical Research. COI, one or more authors

have received or will receive benefits for personal or professional use.

Sample Size: N = 464 hospitalized patients with confirmed moderate COVID-19

Age/Sex: No mention of mean age; median age for convalescent plasma group: 52

years, median age for standard care group: 52 years; 354 males, 110 females

Convalescent plasma (CP) – two doses of 200 mL convalescent plasma,

Comparison: transfused 24 hours apart, along with best standard of care (n=235) vs. Best

standard of care only (n=299)

Follow-up: Follow-up at 28 days

At 28 days, severe disease progression or all-cause mortality occurred in 44

CP patients (19%) compared to 41 standard care patients (18%). The risk difference was 0.008 (95% confidence interval [-0.063, 0.078]) and the risk

difference was 0.008 (95% confidence interval [-0.062, 0.078]) and the risk

ratio was 1.04 (95% CI [0.71, 1.54])

"Convalescent plasma was not associated with a reduction in progression to severe covid-19 or all cause mortality. This trial has high generalizability and approximates convalescent plasma use in real life settings with limited laboratory capacity. A priori measurement of neutralising antibody titres in

donors and participants might further clarify the role of convalescent plasma

in the management of covid-19."

Open-label Phase II trial (PLACID Trial). Convalescent plasma was associated with improved shortness of breath and fatigue in moderate COVID-19

Comments: patients, but this improvement did not translate to reduced mortality or

disease progression at day 28.

AlQahtani 2020 (score=5.5) [729]

Category: Convalescent COVID-19 Antibodies

Study Type: RCT

Results:

Conclusion:

Conflict of Interest: Sponsored by the Ministry of Health Bahrain and the College of Surgeons in

Ireland-Bahrain. No COI.

Sample Size: N = 40 patients with COVID-19 and evidence of pneumonia who needed

oxygen therapy.

Age/Sex: Mean age: 51.7 years; 32 males, 8 females.

Comparison: Control Group: Patients received routine care for controlling a fever and

antiviral or antibacterial medications (n=20) vs. Plasma Group: Patients received 200ml of convalescent plasma (CP) over 2 hours once per day for 2

days (n=20).

Follow-up: Follow-up at 28 days

Results: Number of patients requiring ventilation in Control vs Plasma Group: 6 vs. 4

(95% CI: 0.22, 2.0), (p=0.72). Mean number of days on ventilation for Control vs Plasma Group: 10.5 vs. 8.2 (p=0.81). There were no significant differences between groups in terms of white blood cell count (p=0.128), lactate

dehydrogenase (p=0.713), C-reactive protein (p=0.043), Troponin (p=0.141), Ferratin (p=0.029), D-Dimer (p=0.115), or procalcitonin (p=0.980) all at

discharge.

Conclusion: "There were no significant differences in the primary or secondary outcome

measures between CP and standard therapy though fewer patients required ventilation and for a shorter period of time. The study showed that CP therapy appears to be safe and it is feasible to perform a definitive phase 3

clinical trial using this study protocol."

Comments: Open-label, pilot study. Data suggest lack of efficacy.

Avendaño-Solà 2020 (score=4.0) [731]

Category: Convalescent COVID-19 Antibodies

Study Type: RCT

Conflict of Interest: Sponsored by the Government of Spain, Ministry of Science and Innovation,

Instituto de Salud Carlos III. No mention of COI.

Sample Size: N = 81 patients hospitalized with COVID-19.

Age/Sex: No mention of mean age; median ages: 59 year; 44 males, 37 females. Comparison: Convalescent Plasma (CP) Group: Patients received standard care and a

single transfusion of 250-300mL of Cp from a donor with IgG anti-SARS-VoV-2

(n=38) vs. Control Group: Patients received standard treatment of care

(n=43)

Follow-up: Follow-up daily until discharge, then at 15 and 29 days.

Results: Patients entering categories 5-7 of the ordinal COVID-19 severity scale

> (category 5 = hospitalized no ventilation, category 6 = hospitalized with ventilation, category 7 = death) by day 15 in CP vs. Control: 0 (0%) vs. 6 (14%), (p=0.57). Patients entering categories 5-7 by day 29 in CP vs. Control: 0 (0%) vs. 7 (16.3%). Mortality rate at day 15 and 29 for CP vs. Control Group:

0% vs. 9.3% (p=0.0555).

Conclusion: "Convalescent plasma could be superior to standard of care in avoiding

> progression to mechanical ventilation or death in hospitalized patients with COVID-19. The strong dependence of results on a limited number of events in the control group prevents drawing firm conclusions about CP efficacy from

this trial."

Comments: Mortality 0% vs. 9%; however, with small study and early termination, the

study data are inconclusive.

Gharbharan 2020 (score=3.5) [724]

Category: Convalescent COVID-19 Antibodies

Study Type: RCT

Comments: Study stopped prematurely. When stopped, there were no differences in

mortality, disease severity, or other measures at day 15.

Duan 2020 (score=NA) [737]

Comparison:

Convalescent COVID-19 Antibodies Category:

Study Type: Case Series

> No mention of COI. Sponsored by the Ministry of Science and Technology China "Preparation of specific plasma and specific globulin from patients with

Conflict of Interest:

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

All patients received a single dose of 200 mL convalescent plasma (CP),

derived from recently recovered donors with neutralizing antibody titers

above 1:640; they also received maximal supportive care and antiviral agents

(n=10)

Follow-up at 3 and 7 days Follow-up:

Level of neutralizing antibodies increased to 1:640 in five cases. Clinical

Results: symptoms improved with increase of oxyhemoglobin saturation within 3

days. Viral load undetectable in seven patients with previous viremia

"This study showed CP therapy was well tolerated and could potentially

Conclusion: 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 recommended for the treatment of COVID-19 [738-741]. 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 [449, 450]).

Strength of Evidence – Moderately Recommended, Evidence (B) Level of Confidence - Moderate

Indications: Hospitalized patients with moderate or severe COVID-19. Especially

effective reportedly for those critically ill on ventilators, requiring

supplemental oxygen and/or cardiovascular support.

Benefits: A meta-analysis estimated a 36% reduction in mortality with

> dexamethasone, 31% reduction with hydrocortisone, and 9% reduction with methylprednisolone [742]. One trial estimated a reduced mortality by 20% if requiring supplemental oxygen and 35% if

ventilated. A reduced number of ventilator days has also been

reported.

Hyperglycemia, risk of secondary infection, higher blood pressure.

Completion of a course, intolerance, adverse effect.

Frequency/Dose/Duration: Different treatments have been used. There are no comparative trials and optimal dosing is somewhat unclear. Medications and doses used

have included:

Dexamethasone 6 mg PO or IV QD x 10 days or until discharge

(or equivalent dose)s.

Hydrocortisone 50mg or 100mg every 6 hours [743].

There are multiple RCTs, with all larger sized studies suggesting efficacy [743-747]. A meta-analysis estimated a 36% reduction in mortality with dexamethasone, 31% reduction with hydrocortisone, and 9% reduction with methylprednisolone [742]. A large RCT found mortality reductions with dexamethasone [449, 450, 745]. An RCT found a 65% increase in ventilator-free days from 4.0 to 6.6 days over a 28-day period, although there was no difference in mortality [744]. Another RCT found superiority of glucocorticosteroid [743]. Two RCTs

of modest size found no significant benefits, but appear underpowered [524, 748]. Another negative study used a low dose of hydrocortisone [748]. As glucocorticosteroids have moderate adverse

effects, low costs, and have significant efficacy in reducing mortality based on meta-analyses, they are moderately recommended for

treatment of COVID-19.

Harms:

Indications for Discontinuation:

Rationale:

Evidence: A comprehensive literature search was conducted using PubMed,

There were no exclusion criteria.

Scopus, CINAHL, Cochrane Library, and Google Scholar from January

2019 to November 2020 using the following terms:

Glucocorticosteroids; 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 137 articles in PubMed, 292 in Scopus, 13 in CINAHL, 6 in Cochrane Library, 4470 in Google Scholar, and 5 from other sources*. We considered for inclusion 22 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 33 from Google Scholar, and 5 from other sources. Of the 63 articles considered for inclusion, 0 randomized trials, 2 cohort studies, and 3 systematic reviews 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.

Evidence for the Use of Glucocorticoid Steroids

Lu 2020 (score=NA) [749]

Category: Glucocorticoid Steroids

Study Type: Cohort

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

Conflict of Interest: 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

Steroid group – given antiviral therapy and adjunct corticosteroid treatment,

Comparison: 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

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

Results: 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]

"Our findings indicated that limited effect of corticosteroid therapy could pose to

Conclusion: overall survival and prudent dose within effective limits may be recommended for

critically ill patients under certain circumstances."

Wang 2020 (score=NA) [750]

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

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)

"Our data indicate that in patients with severe COVID-19 pneumonia, early, low-

Conclusion: 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.

Interferon beta-1b has been used both as sole therapy and combination therapy for the treatment of patients with COVID-19 [556, 751].

Interferon Beta-1b for the Treatment of COVID-19

Recommended.

Results:

Adjunctive use of interferon beta-1b is recommended for the treatment of selected patients with COVID-19.

Strength of Evidence – Moderately Recommended, Evidence (B)

(Stand-alone treatment)

Level of Confidence - Low

Strength of Evidence – Recommended, Evidence (C)

(Combination therapy)

Level of Confidence - Low

Indications: Adjunctive use with lopinavir-ritonavir and ribavirin in moderately and

severely affected patients with COVID-19 [572]. 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 [572].

Benefits: Faster symptom resolution, viral clearance, and hospital discharge.

Reduced need for a ventilator or ICU stay.

Harms:

Nausea, diarrhea, hepatitis.

Indications for Discontinuation:

Completion of a course, intolerance, adverse effect, prolongation of OT interval.

Frequency/Dose/Duration: Two successful trials utilized sole therapy with interferon beta-1b 250ug SQ QOD for 2 weeks [573]. The combination regimen used successfully 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 [572].

Rationale:

Two successful moderate-quality trials utilized sole therapy with interferon beta-1b and one study found accelerated clinical improvement and a non-statistically significant reduction in death by 67% at 1-month [573]. The second trial found comparable results to the other RCT with faster clinical improvement (9 vs 11 days), fewer adverse events, and ~67% reduction in mortality (6.1 vs. 18.2%) when compared with treatment with the control group (lopinavirritonavir/HCQ) or atazanavir/ritonavir/HCQ) [573]. 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 [572]. However, one RCT found a lack of efficacy [511]. Based on the two moderate-quality RCTs showing considerable evidence of efficacy, stand-alone treatment with interferon beta-1b is moderately recommended.

A moderate-quality RCT found a lack of efficacy for combined favipavir with interferon beta-1b compared with HCQ for moderate to severe COVID-19 pneumonia patients [558].

Based on one trial with demonstrated efficacy, the regimen of triple-combination therapy using lopinavir, ritonavir, ribavirin, and interferon beta-1b is recommended [572], although it should be noted that it is possible that the only medication effective in the combination therapy is interferon beta-1b.

Other interferons are being investigated. One successful trial used a different interferon in a Phase 2 trial that was nebulized interferon-1a (SNG001) [752]. A trial with interferon beta-1a when added to (lopinavir-ritonavir/HCQ) or atazanavir/ritonavir/HCQ) found earlier 14-day hospital discharge rates (67% vs. 44%) [753]. A trial on interferon-kappa plus TFF2 and including many potentially active cointerventions found reduced viral RNA [754].

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Interferon Beta-1b; 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 11 articles in PubMed, 814 in Scopus, 7 in CINAHL, 7 in Cochrane Library, 6,630 in

Google Scholar, and 6 from other sources[†]. We considered for inclusion 0 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 6 from other sources. Of the 10 articles considered for inclusion, 7 randomized trials and 0 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 Interferon beta-1b

Monk 2021 (score=7.0) [752]

Category: Interferon beta-1b

Study Type: RCT

Conflict of Sponsored by Synairgen Research. COI, one or more authors have received or will receive

Interest: benefits for personal or professional use.

Sample Size: N = 98 patients admitted to the hospital with coronavirus disease 2019 (COVID-19)

symptoms with either a positive real time polymerase chain reaction (RT-PCR) or point-of-

care test.

Age/Sex: Mean age: 57.2 years; 58 males, 40 females.

Comparison: Recombinant interferon beta-1a (SNG001): Patients received SNG001 delivered through

nebulizer once per day for up to 14 days (n=48) vs. Placebo: Patients received placebo drug which was delivered through nebulizer once per day for up to 14 days (n=50). All patients had Ordinal Scale for Clinical Improvement (OSCI) assessments, blood sampling,

and 12-led electrocardiogram assessments 24 hours after last dose (n=98).

Follow-up: Follow-up at day 28.

Results: Results show that the patients in the SNG001 groups had greater odds of improvement on

the primary outcome, the WHO Ordinal Scale for Clinical Improvement (OSCI), on day 15 or 16 (odds ratio 2.32; 95% CI: 1.07 to 5.04; p=0.033) and were more likely than those receiving placebo to recover to an OSCI score of 1 (hazard ratio: 2.19; 95% CI: 1.03-4.69;

p=0.043).

Conclusion: "In conclusion, SNG001, a treatment already studied and shown to be well tolerated in

patients with asthma and COPD, seems to also be well tolerated in patients admitted to hospital with COVID-19, with a range of clinical outcomes displaying a beneficial pattern of

response to SNG001 therapy."

Comments: Double-blind, placebo-controlled Phase 2 trial. Data suggest patients in inhaled nebulized

Interferon group (SNG001) more likely to improve on days 15 or 16 (p=0.03), and more

likely to recover than placebo group (p=0.43).

Hung 2020 (score=6.0) [572]

Category: Interferon beta-1b

Study Type: Open-label randomized trial

Conflict of Sponsored by the Shaw-Foundation, Richard and Carol Yu, May Tam Mak Mei Yin, and

Interest: 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

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) "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." 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.

Rahmani 2020 (score=4.5) [573]

Category: Interferon Beta-1-B

Study Type: RCT

Conflict of

Comparison:

Conclusion:

Comments:

No sponsorship. No COI.

Sample Size: N = 80 patients with positive SARS-CoV-2 diagnosis and clinical symptoms or signs of

pneumonia

Age/Sex: Only 66 participants included in the analysis. No mention of mean age; median age: 60

years; 39 males, 27 females

Interferon Group: received IFN β -1b, 250 mcg subcutaneously every other day for two weeks, along with national protocol medications (lopinavir/ritonavir (400/100 mg BD) or atazanavir/ritonavir (300/100 mg daily) with hydroxychloroquine (400 mg BD first day,

then 200 mg BD) for 7-10 days) (n=40) vs. Control Group: national protocol medications

without INF

Follow-up: Follow-up at days 7, 14 and 28

In the IFN group, the time to clinical improvement was shorter compared to control group

(9 days versus 11 days, p=0.002, hazard ratio=2.3). Duration of hospitalization and ICU stay did not differ between groups, nor did the all-cause 28-day morality (6.06% versus 18.18%).

did not differ between groups, nor did the all-cause 28-day morality (6.06% versus 18.18%,

p=0.12).

"IFN β-1b was effective in shortening the time to clinical improvement without serious adverse events in patients with severe COVID-19. Furthermore, admission in ICU and need

 $\begin{tabular}{ll} \textbf{Conclusion:} & for invasive mechanical ventilation decreased following administration of IFN β-1b. \end{tabular}$

Although 28-day mortality was lower in the IFN group, further randomized clinical trials with large sample size are needed for exact estimation of survival benefit of IFN β -1b." Time to clinical improvement was significantly shorter in IFN group but hospitalization

Comments: duration nor ICU days were similar between groups 19 (6-10) versus 11 (9-15) days,

respectively (p=0.002).

Fu 2020 (score=4.5) [754]

Category: Interferon beta-1b

Study Type: RCT

Conflict of Sponsored by the National Natural Science Foundation of China, National Major Project for

Interest: Control and Prevention of Infectious Disease in China, Shanghai Science and Technology

Commission, and Shanghai Municipal Health Commission. COI, one or more authors have

received or will receive benefits for personal or professional use.

Sample Size: N = 80 hospitalized patients with confirmed coronavirus disease 2019 (COVID-19).

Age/Sex: Mean age: 35.3 years; 51 males, 29 females.

Comparison: Interferon plus trefoil factor 2 (TFF2): On day 2 of hospital admission, patients received

aerosol inhalation of interferon and TFF2 proteins. This treatment was given to patients through a nasal mask for 20-30 minutes 6 times every 24 hours (n=40) vs. Control: Patients received standard care alone that included hydroxychloroquine, antibiotic agents,

vasopressors, antifever medication, vitamin C, immune enhances, or traditional Chinese

medicine (n=40).

Follow-up: Follow-up 30 days after discharge from hospital.

Results: Results indicate that the time of viral RNA negative conversion in the interferon + TFF2

group was a mean of 3.8- days (95% CI: 2.07-5.53), which was significantly shorter than the control group which had a mean of 7.40 days (95% CI: 4.57 to 10.53) (p=0.031), the

difference between group means was 3.60 days.

Conclusion: "In conclusion, we found that aerosol inhalation of IFN-k plus TFF2 in combination with

standard care is safe and superior to standard care alone in shortening the times for viral RNA conversion of SARSCoV-2 and for CT improvement and facilitating clinical recovery,

thereby resulting in early release from hospitalization."

Comments: Open-label RCT of IFN plus TFF2 vs. standard care (ABX, HCQ, vasopressors, and vC). Data

suggest significant conversion to negative viral RNA and improved imaging studies

(p=0.037 and p-=0.002). Study suggests that the combination treatment is associated with

reduced hospital stay.

Khamis 2021 (score=4.0) [558]

Category: Favipiravir, Interferon beta-1b

Study Type: RCT

Conflict of No sponsorship or COI.

Interest:

Sample Size: N = 89 with PCR confirmed Covid-19 and moderate to severe Covid-

19 pneumonia diagnosed based on WHO case definition

Age/Sex: Mean age: 55 years; 52 males, 37 females

Comparison: Favipiravir, Interferon beta-1b: Received 1600 mg of favipiravir orally twice on day 1 then

600 mg orally twice a day for 10 days and 0.25 mg of interferon beta-1b via nebulizer twice a day for 5 days (n=44) vs Standard: Received HCQ 400 mg orally twice on day 1 then 200

mg twice a day for 7 days (n=45)

Follow-up: No mention of follow-up

Results: No group differences found in the treatment group vs the standard

group. Inflammatory biomarkers: CRP (50 vs. 33mg/dL; p=0.413), ferritin (1107 vs. 993

mg/L; p = 0.968), LDH (452 vs. 366 U/L; p = 0.259), and IL-6 (138 vs. 143 pg/mL; p

= 0.410). Clinical outcomes: Length of stay (7 vs. 7 days; p = 0.948), ICU transfers (18.2% vs. 17.8%; p = 0.960), discharges (65.9% vs. 68.9%, p = 0.764), SaO2 (94% vs. 95%; p = 0.324),

and mortality (11.4% vs. 13.3%; p = 0.778).

Conclusion: "This randomized open-label controlled study showed no differences in inflammatory

markers or clinical outcomes in COVID-19 patients with moderate to severe pneumonia

treated with favipiravir and inhaled interferon beta-1b against HCQ."

Comments: Open-label trial for pneumonia. Data suggest lack of efficacy compared with standard

therapy.

Davoudi-Monfared 2020 (score=4.0) [753]

Category: Interferon beta-1b

Study Type: RCT

Conflict of No sponsorship or COI.

Interest:

Sample Size: N = 92 patients with severe coronavirus disease 2019 (COVID-19)

Age/Sex: Age and sex data only available for 81 participants. Mean age: 57 years; 44 males, 37

females.

Comparison: Interferon group: Patients received 44 micrograms/milliliter of interferon injected

subcutaneously 3 times a week for 2 weeks along with 250 milligrams of national protocol medication, which included: hydroxychloroquine, lopinavir-ritonavir, or atazanavir-ritonavir (n=46) vs. Control group: Patients received only 250 milligrams of the national

protocol medication for 10 days (n=46).

Follow-up: Follow-up on days 7, 14, and 28.

Results: Time to clinical response did not show statistically significant differences between the

interferon and control groups (9.7 \pm 5.8 vs. 8.3 \pm 4.9 days, p=0.95). On day 7, results showed no statistically significant results regarding discharge: 19% of patients receiving interferon were discharged with no deaths compared to 28% of discharged patients in the control group, in which 25% died (odds ratio: 0.60; 95% confidence interval (CI): 0.21 to 1.69). On day 14, statistically significant results were found regarding discharge: 66.7% in the interferon group and 43.6% in the control group (odds ratio: 2.5; 95% CI: 1.42 to

11.55).

Conclusion: "Although IFN did not change the time to reach the clinical response, adding it to the

national protocol significantly increased discharge rate on day 14 and decreased 28-day

mortality."

Comments: Sparse methods. Data suggest time to clinical response comparable, but at day 14, 66.7%

of IFN were discharged vs. 43.6% of controls. Also, IFN was associated with reduced 28-day

mortality.

Ribavirin has been used to treat patients with COVID-19 [755-758].

Ribavirin for the Treatment of COVID-19

Recommended.

Adjunctive use of ribavirin is recommended for the treatment of selected patients with COVID-19.

Strength of Evidence – Recommended, Evidence (C)

(Combination therapy)

Level of Confidence - Low

Strength of Evidence – No Recommendation, Insufficient Evidence (I)

(Stand-alone treatment)

Level of Confidence - Low

Indications: Adjunctive use with lopinavir-ritonavir and interferon beta-1b in

> moderately and severely affected patients with COVID-19 [572]. 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 [572].

Benefits: Faster symptom resolution, viral clearance, and hospital discharge.

Reduced need for a ventilator or ICU stay.

Harms: Nausea, diarrhea, hepatitis.

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

QT interval.

Frequency/Dose/Duration: 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 [572].

Rationale: 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 [572]. Two other RCTs were underpowered for

meaningful clinical differences [759, 760].

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 [572]. However, there is no quality evidence demonstrating efficacy and thus no recommendation for stand-alone treatment with ribavirin.

A comprehensive literature search was conducted using PubMed,

Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: ribavirin; 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 47 articles in PubMed, 1,529 in Scopus, 11 in CINAHL, 9 in Cochrane Library, 6,580 in Google Scholar, and 1 from other sources†. We considered for inclusion 3 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 1 from other sources. Of the 8 articles considered for inclusion, 1 randomized trial and 1

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

systematic review met the inclusion criteria. There were no exclusion

Evidence:

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 Ribavirin

Hung 2020 (score=6.0) [572]

Category: Ribavirin

Study Type: Open-label randomized trial

Conflict of Sponsored by the Shaw-Foundation, Richard and Carol Yu, May Tam Mak Mei Yin, and

Interest: 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

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

Comparison: mg, every 12 nours, 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) "Triple antiviral therapy with interferon beta-1b, lopinavir–ritonavir, and ribavirin were

Conclusion: safe and superior to lopinavir–ritonavir alone in shortening virus shedding, alleviating

symptoms, and facilitating discharge of patients with mild to moderate COVID-19." Data suggest early administration of combination therapy (lopinavir-ritonavir, ribavirin, and β -interferon was significantly superior to control group (lopinavir-ritonavir) in shortening modian time to possitive passophary goal swah (7 days versus 12 days

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.

Zinc serum levels have been found to be low in those with more severe COVID-19 disease [761-763]. Zinc supplementation has been used typically as adjunctive treatment to reduce severity of COVID-19 [442, 764].

Zinc for the Treatment of COVID-19

Recommended.

Comments:

Zinc is recommended for potential prevention of more severe disease as well as for the treatment of patients with COVID-19.

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

Indications: Ongoing use during the epidemic, as well as for mild, moderate, and

severe COVID-19 disease. Also especially recommended for those with

zinc deficiency.

Benefits: Potential to reduce disease severity

Harms:

Negligible

Indications for Discontinuation: Frequency/Dose/Duration:

After cessation of the epidemic

Rationale:

10-15 mg/day (>100% Recommended Daily Allowance)

There are no quality RCTs testing the value of zinc alone [439-442]. There is one low-quality study suggesting lack of efficacy of zinc added to HCQ [765] and another low-quality trial found lack of efficacy of high-dose zinc and ascorbic acid added to usual care [443]. However, one study of HCQ, AZT, and zinc suggested earlier treatment resulted in 84% lower risk of hospitalization and lower risk of death among patients treated by ~day 4 [439]. 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 [442]. This is supported by evidence that hydroxy/chloroquine are zinc ionophores, which increase intracellular zinc and reduce or prevent viral replication in laboratory studies [472, 473].

Zinc supplementation has negligible adverse effects and has been associated with improved outcomes in non-randomized studies; thus, it is recommended with insufficient evidence.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Zinc; 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 4 articles in PubMed, 562 in Scopus, 8 in CINAHL, 5 in Cochrane Library, 40,610 in Google Scholar, and 4 from other sources†. We considered for inclusion 0 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 7 from Google Scholar, and 4 from other sources. Of the 13 articles considered for inclusion, 2 randomized trials, 1 case study, 1 retrospective analysis and 0 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:

Evidence for the Use of Zinc

Abd-Elsalam 2020 (score=3.5) [765]

Category: Zinc Study Type: RCT

Comments: Data suggest lack of efficacy for addition of Zn to HCQ for enhanced

recovery at 28 days.

Thomas 2020 (score=3.5) [443]

Category: Zinc Study Type: RCT

Comments: Open-label, 4-arm study. Data suggest lack of efficacy of combination

therapy, although study was terminated early due to low power and no

significant difference in shortening symptom duration.

Derwand 2020 (score=NA) [439]

Category: Zinc

Study Type: Retrospective Case Series

Conflict of Interest:

No mention of sponsorship. COI, one or more authors have received or will

receive benefits for personal or professional use.

Sample Size: N = 141 COVID-19 patients with confirmed acute respiratory syndrome

Age/Sex: No mention of mean age; Median age: 58 years; 103 males, 38 females

Received zinc sulfate 220 mg with 50 mg elemental zinc per day,

Comparison: hydroxychloroquine 200 mg twice daily, and azithromycin 500 mg per day

for 5 days (n=141) vs. Received standard care of common upper

respiratory infection (n=377)

Follow-up: Follow-up of at least 28 days

Hospitalization rate was lower in the triple treatment group compared to

Results: the standard care group (2.84% vs. 15.4%, OR = 0.16, p < 0.001). All-cause

death was also lower in the treatment group (0.71%) compared to the

standard care group (3.5%, OR = 0.2, p = 0.16).

"Risk stratification-based treatment of COVID-19 outpatients as early as

Conclusion: possible after symptom onset with the used triple therapy, including the

combination of zinc with low dose hydroxychloroquine, was associated with significantly less hospitalizations and 5 times less all-cause deaths."

Retrospective case serves of 141 outpatients. Early risk stratified

Comments: treatment in COVID-19 outpatients after symptom onset using zinc plus

low-dose HCQ+AZI resulted in significantly fewer hospitalizations and 5

times fewer all-cause deaths.

Carlucci 2020 (score=NA) [442]

Category: Zinc

Study Type: Retrospective Analysis

Comments: Data suggest addition of zinc increased frequency of home discharge and

mortality after adjusting for timing of zinc administration.

Vitamin D levels have been low in those with more severe COVID-19 disease and supplementation has been used for the treatment of patients with COVID-19 [766-783]. It has also been used in patients with COVID-19 to maintain bone health.

Vitamin D for the Treatment of COVID-19

Recommended.

Rationale:

Vitamin D is recommended for potential prevention of more severe disease as well as for the treatment of patients with COVID-19.

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

Indications: Ongoing use during the epidemic, as well as for mild, moderate, and

severe COVID-19 disease. High-dose use may be considered for those with onset of COVID-19 disease. Also recommended for those with

vitamin D deficiency and/or risks for deficiency.

Benefits: Potential to reduce disease severity

Harms: Negligible

Indications for Discontinuation: After cessation of the epidemic

Frequency/Dose/Duration: A moderate-quality trial utilized calcifediol 0.532mg on day 1, 0.266mg

days 3 and 7 and weekly in addition to HCQ+AZT until hospital

discharge [784]. Other daily dosing used among healthy individuals at risk include 600 IU/day for up to 70 years of age and 800 IU/day for those over 70 years of age (>100% Recommended Daily Allowance). A moderate-quality RCT used calcifediol compared with no calcifediol

in addition to HCQ+AZT until hospital discharge and found a 96% reduction in risk of needing an ICU stay [784]. Another RCT for treatment of asymptomatic of mildly symptomatic but vitamin D deficient individuals treated with vitamin D supplementation cleared virus sooner and with reduced fibrinogen levels [785]. One RCT found lack of efficacy using only one administration of 200,000 IU, although the risk of mechanical ventilation trended towards reduction by 51% (p=0.09) [786]. Vitamin D levels have been strongly correlated with COVID-19 disease severity [444, 446, 447], with a reported ~8-fold risk

those with low vitamin D levels [444].

Vitamin D supplementation has negligible adverse effects, especially over shorter periods of time, and low vitamin D levels have been strongly associated with worse outcomes in non-randomized studies. Vitamin D levels also fall with illness status affecting bone health.

of a severe outcome and ~20-fold risk of a critical outcome among

Thus, vitamin D supplementation is recommended.

Evidence: A comprehensive literature search was conducted using PubMed,

Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: Vitamin D; 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 29 articles in PubMed, 2706 in Scopus, 11 in CINAHL, 27 in Cochrane Library, 11,210 in Google Scholar, and 3 from other sources†. We considered for inclusion 5 from PubMed, 11 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 7 from Google Scholar, and 3 from other sources. Of the 26 articles considered for inclusion, 3 randomized trials, 3 retrospective studies, and 0 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 Vitamin D

Murai 2020 (score=8.0) [786]

Comparison:

Category: Vitamin D
Study Type: RCT

Conflict of Interest: Sponsored by Sao Paulo Research Foundation and Conselho Nacional de

Desenvolvimento Científico e Tecnológico. No COI.

Sample Size: N = 240 hospitalized patients with severe COVID-19

Age/Sex: Mean age: 56.3 years; 135 males, 105 females

Vitamin D₃ Group: received vitamin D3 supplementation single dose of

200,000 IU dissolved in 10 mL of peanut oil solution on day of

randomization (n=120) vs. Placebo Group: received single dose 10 mL of

peanut oil solution on day of randomization

Follow-up: Follow-up at hospital discharge or death

Of the 240 participants, 232 were included in the analysis. Mean hospital length of stay was 7 days for vitamin D group and 7 days of placebo group (hazard ratio = 1.12, 0.379). No significant associations were found when

Results: (nazard ratio = 1.12, 0.379). No significant associations were round when using a Cox regression model on this outcome and potential confounders.

No significant differences in mortality, admission to ICU, and mechanical

ventilation requirement between groups (all p>0.05).

"Among hospitalized patients with severe COVID-19, vitamin D_3

supplementation was safe and increased 25-hydroxyvitamin D levels, but did not reduce hospital length of stay or any other relevant outcomes vs

Conclusion: did not reduce hospital length of stay or any other relevant outcomes vs placebo. This trial does not support the use of vitamin D₃ supplementation

as an adjuvant treatment of patients with COVID-19."

Single-dose vitamin D only showed "apparent lack of efficacy." Although

Comments: vitamin D levels increased in the interventional group, neither mortality

nor length of stay decreased.

Rastogi 2020 (score=4.5) [785]

Comparison:

Results:

Conclusion:

Comparison:

Conclusion:

Category: Vitamin D **Study Type: RCT**

Conflict of Interest: No sponsorship or COI.

N = 40 patients with SARS-CoV-2, who were asymptomatic or mildly Sample Size:

symptomatic and were vitamin D deficient (25(OH) D<20 ng/mL)

Age/Sex: Mean age: 48.5 years; 20 males, 20 females

> Vitamin D: received daily 60,000 IU of cholecalciferol, for 7 days. 25(OH)D levels assessed at day 7 and weekly supplementation of 60,000 IC given to

those with 25(OH)D > 50 ng/mL or continued on vitamin D 60,000 IU supplementation for another 7 days (n=16) vs. Placebo: received no

cholecalciferol supplementation (n=24)

Follow-up: Follow-up at days 5, 7, 10, 14, 18, and 21

> In the vitamin D group, 10 of 16 patients could achieve 25(OH)D > 50 mg/mL by day 7 and 12 could achieve it by day 14 (day 14 25(OH)D levels:

vitamin D = 51.7, placebo = 15.2 (p<0.001)). By week 3, 10 vitamin D participants and 5 placebo participants became SARS-CoV-2 RNA negative

(p<0.018).

"Greater proportion of vitamin D-deficient individuals with SARS-CoV-2 infection turned SARS-CoV-2 RNA negative with a significant decrease in

fibrinogen on high-dose cholecalciferol supplementation."

Asymptomatic or mild COVID patients. Short-term intervention only (7 days). Baseline calcium levels different (9.4 mg/d versus 8.8 mg/d).

Comments: Statistically significant decrease in fibrinogen in experimental group and

decreased numbers of CoV-2 RNA negative results.

Castillo 2020 (score=4.5) [784]

Category: Vitamin D **Study Type: RCT**

Conflict of Interest: No mention of sponsorship or COI.

Sample Size: N = 76 hospitalized patients with COVID-19 infection

Age/Sex: Mean age: 53 years; 45 males, 31 females

> All participants given the same standard care: hydroxychloroquine (400 mg every 12 hours on day one, then 200 mg every 12 hours for 5 days) and azithromycin (200 mg every 12 hours for 5 days). Vitamin D Group: Took

> oral calcifediol (0.266 mg) on days 3 and 7, and then weekly until discharge or ICU admission (n=50) vs. Standard Care: received no calcifediol (n=26)

Follow-up: Follow-up at admission to ICU, hospital discharge or death

1 patient in the vitamin D group required ICU admission (2%) compared to

13 patients (50%) in the control group (p<0.001). The univariate risk Results:

estimate odds ratio for ICU between groups was 0.02 (95% CI [0.002, 0.17]) while the multivariate OR was 0.03 (95% CI [0.003, 0.25]). "Our pilot study demonstrated that administration of a high dose of Calcifediol or 25-hydroxyvitamin D, a main metabolite of vitamin D endocrine system, significantly reduced the need for ICU treatment of

patients requiring hospitalization due to proven COVID-19. Calcifediol seems to be able to reduce severity of the disease, but larger trials with Pilot RCT with unclear methods ("open label" vs. "double masked"). Data

Comments: suggest high dose of calcifediol or 25-hydroxyvitamin D decreased ICU

admissions in hospitalized COVID-19 patients.

Alipio 2020 (score=NA) [444]

Category: Vitamin D

Study Type: Retrospective Review **Conflict of Interest:** No sponsorship or COI.

Sample Size: N = 212 cases with laboratory-confirmed infection of SARS-CoV-2.

Age/Sex: No mention of age or sex.

Serum 25(OH)D levels were extracted from the onset of symptoms.

Comparison: Patients' serum 25(OH)D levels were tested 3-7 times a day depending on

severity (n=212).

Follow-up: No mention of follow-up.

Results indicate that the mean serum 25(OH)D level was 23.8 ng/ml. Serum 25(OH)D were significantly associated with clinical outcomes

Results: (p<0.001). Results also show that vitamin D levels were significantly

associated with clinical outcomes (p<0.001), with an increase in serum

25(OH)D resulting in a mild case and decrease in a critical case.

"Vitamin D supplementation could possibly improve clinical outcomes of

Conclusion: patients infected with Covid-2019 based on increasing odds ratio of having

a mild outcome when serum 25(OH)D level increases."

Retrospective review of 212 cases suggests a correlation between vitamin

Comments: D serum 25(OH)D levels and COVID-19 outcomes as milder cases of COVID-

19 were associated with higher levels of vitamin D.

D'Avolio 2020 (score=NA) [447]

Category: Vitamin D

Study Type: Retrospective Review **Conflict of Interest:** No sponsorship OR COI.

Sample Size: N = 107 patients with SARS-CoV-2.

Age/Sex: Mean age: 70.8 years; 58 males, 49 females

Repository data of patient's plasma was evaluated for those who

Comparison: underwent a nasopharyngeal swab PCR analysis for SARS-CoV-2 and a

25(OH)D measurement within 7 weeks of PCR analysis (n=107)

Follow-up: No mention of follow-up.

Results indicate significantly lower serum 25(OH)D levels (p=0.004) in PCR-

Results: positive for SARS-CoV-2 patients (median value: 11.1 ng/mL) compared to

negative patients (24.6 ng/mL).

"In conclusion, this study represents a preliminary observation justified by

Conclusion: several described mechanisms through which 25(OH)D can reduce the risk

of infections."

Data suggest PCR-positive SARS-CoV-2 patients had significantly lower

Comments: 25(OH)D levels as compared to PCR-negative patients. When stratified by

age, the differences are more pronounced in PCR-negative patients, suggesting vitamin D could potentially decrease COVID-19 activity.

Lau 2020 (score=NA) [446]

Category: Vitamin D

Study Type:Retrospective Observational ReviewConflict of Interest:No mention of sponsorship or COI.Sample Size:N = 20 patients with severe COVID-19.Age/Sex:Mean age: 65.2 years; 9 males, 11 females.

Comparison: Medical reports of COVID-19 patients were reviewed for cases where

25(OH)D levels were determined (n=20).

Follow-up: No mention of follow-up.

Results indicate that 11 patients in the intensive care unit had vitamin D insufficiency (VDI) compared to 4 floor patients. Among these patients,

65% had critically low 25(OH)D (<20 ng/mL) and 3 had <10 ng/mL.

Conclusion: "Anecdotal and observational data indicate that VDI may play a significant

role in the progression of the COVID-19 disease state."

Retrospective observational review of small sample (n=20) of COVID-19

Comments: patients suggests an association between presence of vitamin D

insufficiency and COVID-19.

Rehabilitation

Overview

Although most patients with COVID-19 completely recover, some cases may experience a multitude of disorders [787]. It is beyond the scope of this guideline to address every possible presentation, combination, and permutation. Indeed, it is arguably impossible to do so. Instead, this guideline addresses what currently appear to be the most common conditions needing rehabilitative services after COVID-19. This also may suggest a framework for approaching treatment of less common presentations.

For simplicity, clarity, and consistency with other diagnoses and the general medical literature, this review defines symptoms lasting less than 1 month as *acute*, from 1–3 months as *subacute*, and more than 3 months as *chronic*. Some of the alternate terms for these conditions include "ongoing symptomatic," "post-COVID syndrome" [292], "post-acute sequalae of COVID," and "long COVID."

The severity of the COVID-19 infection has been associated with the risk of long-term symptoms and impairments [788]. For example, approximately two-thirds of outpatients diagnosed with COVID-19 return to normal health by the fourth week [789]. In contrast, of those who were evaluated in an emergency department (66% hospitalized), 50.9% developed chronic COVID-19 symptoms [790]. Yet, a mild case does not preclude development of chronic COVID-19 symptoms. The comparatively large numbers of mildly affected patients likely mean that most patients with chronic symptoms will be found in this group, despite the higher risk among those who are more severely affected.

Evidence also suggests that symptoms improve over time. Overall, 5–51% of patients have symptoms persisting up to 12 weeks [293, 791-793], whereas 2–15% have symptoms beyond 12 weeks after onset [790, 791, 793-795]. Long-term symptoms have wide-ranging estimates of prevalence and include fatigue (17–98%) [293, 790-793, 796-798], dyspnea (17–93%) [293, 790-793, 796-798], cough (29–43%), chest pain (44–88%) [293, 790-792, 796, 797], back pain, muscle pain, and headache (38–91%) [790]. Cognitive changes, such as impaired memory, concentration, and multitasking ability, are also reportedly common. Risk factors for chronic COVID-19 beyond severity of the initial disease appear to include increased age, having more comorbidities, and psychological disorders [793, 799].

Acute mental health disorders are common and reportedly affect 55% of those having visited an emergency department (75% were hospitalized) in the first month [800]. New-onset psychiatric illness was reported in 5.8% [801]. Of these, 4.7% were anxiety disorders and 2% were depression [801]. One report noted persistence of post-traumatic stress among survivors [802]. Another reported PTSD symptoms related to illness at 4–8 weeks after discharge among 46.9% of ICU survivors and 23.5% of ward survivors [788].

Some rehabilitation protocols are heavily multidisciplinary, reportedly including pulmonologists, physiatrists, neurologists, cardiologists, physical therapists, occupational therapists, psychologists, neuropsychologists, psychiatrists, speech therapists, and nutritionists [803, 804]. Telemedicine has been used for rehabilitation of COVID-19 patients [804, 805]. There are no quality trials to assess the various disciplines on rehabilitation teams, comparative trials of different treatment regimens, and/or efficacy of telemedicine approaches.

Pulmonary Rehabilitation

Dyspnea is typically the presenting complaint for emergency and hospitalized treatment. However, dyspnea has been shown to persist into many chronic COVID-19 case histories [788]. The most common spirometric abnormalities after initial recovery are reduced diffusion capacity and restrictive ventilatory defects [806, 807]. Risk and severity of spirometric abnormalities are correlated with COVID-19 severity [807].

Pulmonary rehabilitation is used for COVID-19 [808] and has been shown to be successful for functional improvements in individuals with non-COVID-related pulmonary deficits [809, 810], including those from pneumonia [811], interstitial lung disease [812], and SARS [813]. It commonly includes behavioral components [814].

Pulmonary Rehabilitation for Treatment of Pulmonary Problems Related to COVID-19 Recommended.

Pulmonary rehabilitation is recommended for the treatment of pulmonary problems related to COVID-19.

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

Indications:

Indicated for COVID-19 affected patients with pulmonary dysfunction and/or dyspnea, especially when combined with activity reductions or exercise intolerances attributed to the infection's pulmonary complications. Earlier institution of exercises, as tolerated, is advised to counter the debility associated with the disease [814]. Careful cardiac evaluation (e.g., 24-hr ECG, echocardiogram, exercise testing,

MRI [815]) is also indicated due to the probability of cardiac

abnormalities.

Benefits: Improved pulmonary function, maximum ventilation, health-related

quality of life, emotional involvement in everyday life, activity levels, 6-minute walk distance, peak workload, exercise and/or activity

endurance.

Harms: As fatalities in the recovery period have been thought to be due to

arrhythmias, a careful assessment of cardiac involvement is advised to help guide the onset and progression of exercises. Those with evidence of thrombotic tendencies and/or multi-system involvement may have greater risk of harm from aggressive exercise regimens.

Indications for Discontinuation: Completion of a treatment course, noncompliance, reaching a plateau

in recovery.

Frequency/Dose/Duration: An individualized but interdisciplinary treatment regimen is usually

formulated based on a comprehensive baseline assessment [812, 816]. Careful cardiac evaluation (e.g., 24-hr ECG, echocardiogram, exercise testing, MRI [815]) is also indicated due to the probability of cardiac abnormalities, which may result in a recommendation to delay onset of exercises and/or slow the rate of progression. While program components include education, exercise training, and behavior change to "promote the long-term adherence to health-enhancing behaviours [816]," exercise training is the central component, and is usually either walking or cycling. One consensus statement recommended beginning at not more than 3 METS, especially when supplemental oxygen is needed [815]. Another review suggested an exercise regimen of 18-60 min at 55–80% of VO₂Max or 60–80% of heart rate maximum, 1–3 times per week [817]. Program duration is typically at least 4 weeks.

Rationale: There is one low-quality pilot study suggesting efficacy for treatment

of COVID-19 patients [818], but no quality trials. There are many trials documenting efficacy for other pulmonary conditions [809-813]. Pulmonary rehabilitation has negligible adverse effects, is moderate to high cost depending on number of treatments and durations required,

and is recommended for patients meeting indications.

Evidence: A comprehensive literature search was conducted using PubMed,

Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to February 2021 using the following terms: rehabilitation;

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 112 articles in PubMed, 4,699 in Scopus, 3 in CINAHL, 13 in Cochrane Library, 34,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 8 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 13 articles considered for inclusion, 1 randomized trial and 8 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.

Cardiac Rehabilitation

Cardiomyopathy, cardiac muscle damage, and arrhythmias have been reported to affect 30–78% of patients [304], and cardiac problems contribute to COVID-19 fatalities [304-307]. Vascular inflammation, hypotension, and direct muscle damage are all potential mechanisms [819, 820]. The probability of cardiac problems is correlated with the severity of the COVID-19 infection, including cardiac biomarkers (e.g., troponin) and numbers of comorbidities [819, 820], although ongoing, subclinical cardiac problems have been detected among recovered patients [307, 821].

Cardiac rehabilitation is used for COVID-19 [822] and has been shown to be successful for functional improvements in individuals with non-COVID-related cardiac deficits [823-827], including those from myocardial infarction [819], as well as quality-of-life measures.

Cardiac Rehabilitation for Treatment of Cardiac Problems Related to COVID-19 Recommended.

Cardiac rehabilitation is recommended for the treatment of cardiac problems related to COVID-19.

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

Indications:

Indicated for COVID-19 affected patients with cardiac dysfunction and/or dyspnea, especially when combined with activity reductions or

exercise intolerances attributed to the infection's cardiac complications. A consensus statement advises waiting 2–3 weeks after cessation of COVID-related symptoms to start exercise [815], although there is no quality evidence to support the expert consensus. Improved cardiac function, health-related quality of life, 6-minute walk test, time to perform 10 sit-to-stands, emotional involvement in everyday life, activity levels, exercise and/or activity endurance [828]. As fatalities in the recovery period have been thought to be due to arrhythmias, a careful assessment of cardiac involvement is advised to help guide the onset and progression of exercises. Those with evidence of thrombotic tendencies, and/or multi-system involvement may have greater risk of harm from aggressive exercise regimens. Completion of a treatment course, noncompliance, reaching a plateau

in recovery.

An individualized but multidisciplinary treatment regimen is usually formulated based on a comprehensive baseline assessment [829, 830]. Careful cardiac evaluation (e.g., 24-hr ECG, echocardiogram, exercise testing, MRI [815]) is indicated due to the probability of cardiac abnormalities, which may result in a recommendation to delay onset of exercises and/or slow the rate of progression. Program components typically include education, aerobic exercise training, strength/resistance training, and psychological factors [831]. Exercise training is the central component. Aerobic exercise is usually either walking or cycling. Strength training is another component thought to be important in cardiac rehabilitation [830]. A slowed and cautious progression may be indicated in COVID patients due to the underlying cardiac disease, and tailoring regarding arrythmias and monitoring for exercise-induced arrythmias has been recommended [830]. Program duration is typically at least 4 weeks.

High-demand occupations may be analogized to sports, where a consensus recommendation is for resumption of sports if: (1) left ventricular systolic function is normal, (2) serum biomarkers of cardiac injury are normal, (3) absence of relevant cardiac arrythmias on 24-hr monitoring, and (4) absence of relevant cardiac arrythmias on 24-hr monitoring on exercise testing [815].

There is one low-quality pilot study suggesting efficacy for treatment of COVID-19 patients [832], but no quality trials. There are many trials documenting efficacy for other pulmonary conditions. Cardiac rehabilitation has negligible adverse effects, is moderate to high cost depending on numbers of treatments and durations required, and is recommended for patients meeting indications.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to February 2021 using the following terms: rehabilitation; 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 112 articles in PubMed, 4,699 in Scopus, 3 in CINAHL, 13 in Cochrane Library, 34,300

Benefits:

Harms:

Indications for Discontinuation:

Frequency/Dose/Duration:

Rationale:

Evidence:

in Google Scholar, and 0 from other sources†. We considered for inclusion 8 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 13 articles considered for inclusion, 1 randomized trial and 8 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.

Exercise Therapy

Research has supported rehabilitation for hospital-associated deconditioning prior to the COVID pandemic [833-835]. Early mobilization of COVID-19 patients has been encouraged [836], yet others suggest delaying until after the acute COVID-related symptoms have been resolved for 2-3 weeks [815]. Early therapy has also been used in the ICU and pre-discharge for COVID patients [837-839]. A review of physical therapy suggests that there will eventually be efficacy, but currently the available literature is sparse and mostly low quality [840].

For those with fibromyalgia, please refer to the <u>ACOEM Chronic Pain Guideline</u>. Also consider chronic fatigue syndrome and myalgic encephalomyelitis [841].

Exercise Therapy for Physical Debility and/or Chronic Fatigue Associated with COVID-19 Recommended.

Exercise therapy is recommended for the treatment of physical debility and/or chronic fatigue associated with COVID-19.

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

Indications: Indicated for COVID-19 affected patients with debility and/or chronic

fatigue attributed to the COVID-19. Baseline testing should indicate the area(s) of deficits (e.g., 6-min walk test; sit to stand; leg strength; grip strength). Rehabilitation should target, measure, and track

progress for those specific areas.

Benefits: Improved distance walked, strength, functional gains, ability to

perform ADLs independently, return to work.

Harms: As fatalities in the recovery period have been thought to be due to

arrhythmias, a careful assessment of cardiac involvement is advised to help guide the onset and progression of exercises. Those with evidence of thrombotic tendencies and/or multi-system involvement may have greater risk of harm from aggressive exercise regimens.

Indications for Discontinuation:

Completion of course of treatment, noncompliance, reaching a

plateau in recovery.

Frequency/Dose/Duration:

A multidisciplinary approach may be beneficial (e.g., physical therapy, occupational therapy, medical, psychology). Generally, sets of appointments are ordered (e.g., 6-8). Two to three appointments per week plus a home exercise program are normally prescribed. Those with marked deficits may benefit from more intensive regimens (e.g., 5 times/week). Aerobic and strengthening exercises are normally prescribed. Some exercises are ideally repeated exertions that directly target specific deficits (e.g., sit to stand or walking endurance). Objective improvement should be tracked. When there is a lack of further improvement, the course of treatment should be discontinued.

Web-based programs are also possible.

Rationale:

There are no quality trials of exercise therapy for the treatment of physical debility and/or chronic fatigue attributed to COVID. Exercise therapy has negligible adverse effects, is moderate to high cost depending on numbers of treatments required and is recommended

for patients meeting indications.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to February 2021 using the following terms: rehabilitation; 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 112 articles in PubMed, 4,699 in Scopus, 3 in CINAHL, 13 in Cochrane Library, 34,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 8 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 13 articles considered for inclusion, 0 randomized trials and 8 systematic reviews met the inclusion criteria. There were no exclusion criteria.

Memory and Cognition

Memory issues are also potentially problematic for some workers. One report noted new or worsened short-term memory problems at 4–8 weeks after discharge among 18.8% of ICU patients and 17.6% of ward patients [788], yet that same study found strong relationships for some other data such as COVID severity for breathlessness and any PTSD symptoms related to illness. It is recommended that these problems be evaluated and treated. Cognitive

[†] 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.

rehabilitation has been successfully used for various infectious disease complications, especially for HIV [842] and severe malaria [843].

Cognitive Rehabilitation for Treatment of Cognitive Problems Related to COVID-19 Recommended.

Cognitive rehabilitation is recommended for the treatment of cognitive problems related to COVID-19.

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

Indications: Indicated for COVID-19 affected patients with evidence of ongoing

cognitive dysfunction attributed to the infection without trending towards rapid resolution. Screening for cognitive function should be performed. Testing should indicate the area(s) of deficits and the rehabilitation should target, measure, and track progress for those

specific areas.

Benefits: Improved memory and executive functions.

Harms: Negligible

Indications for Discontinuation: Completion of course of treatment, noncompliance, reaching a

plateau in recovery.

Frequency/Dose/Duration: Generally, sets of appointments are ordered (e.g., 6-8), most

commonly with psychology, neuropsychology and potentially speech pathology. Depending on the severity, more intensive regimens may be indicated, e.g., in acute inpatient stroke patients, daily regimens of 30min/day for 4 weeks have been used, but likely would only be indicated for the most severely affected COVID patients. Objective improvement should be tracked. When there is a lack of further improvement, the course of treatment should be discontinued and/or

re-evaluated and changed to a more effective approach (e.g., addressing a different aspect of cognitive function). Web-based programs and virtual reality [844-846] are also possible. There is some evidence in stroke patients that combining cognitive rehabilitation

with aerobic exercise results in superior outcomes [847].

Rationale: There are no quality trials of cognitive rehabilitation for the treatment

of memory and executive problems attributed to COVID. Cognitive rehabilitation has negligible adverse effects, is moderate to high cost depending on numbers of treatments required and is recommended

for patients meeting indications.

Evidence: A comprehensive literature search was conducted using PubMed,

Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to February 2021 using the following terms: rehabilitation; 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 112 articles in

PubMed, 4,699 in Scopus, 3 in CINAHL, 13 in Cochrane Library, 34,300 in Google Scholar, and 0 from other sources[†]. We considered for inclusion 8 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 13 articles considered for inclusion, 2 randomized trials and 8 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.

Joint Pain

Joint pain is common in subacute and chronic COVID [289, 831, 848], with 27.3% reporting joint pain at 2 months after COVID onset [289]. Detailed guidance is available by body part in other <u>ACOEM guidelines</u> (see, e.g., Ankle and Foot Disorders, Elbow Disorders, Chronic Pain, Hand/Wrist/Forearm Disorders, Hip and Groin Disorders, Knee Disorders, Low Back Disorders, Neck Disorders, Shoulder Disorders).

Mental Health Disorders

Treatments for mental health disorders that result from COVID-19 have not undergone rigorous trials for efficacy. Only low-quality trials have thus far been reported. One combined anxiety, depression, and stress, reporting that cognitive behavioral therapy (CBT) was effective [849]. Another trial found progressive muscle relaxation helpful for anxiety and sleep quality [818]. Another trial found an internet-based intervention on depression and anxiety to be effective [850].

In the absence of quality evidence specific to COVID-19, analogy to existing quality evidence and evidence-based guidance is recommended for screening, diagnosis, and treatments. These are addressed in detail in guidelines on Anxiety Disorders, Depressive Disorders, and Posttraumatic Stress Disorder.

Utilizing evidence for generalized anxiety disorder, anxiety related to COVID-19 is recommended to be best initially treated with education (I), CBT (B,C), aerobic exercise (C), and strengthening exercise (I). Due to strong addictive potential, benzodiazepines are not recommended for routine use (C). Other potential early treatments include insight-oriented therapies (I), distractive methods (C), exposure therapy/prolonged exposure therapy (I), virtual reality exposure therapy (I) and mindfulness therapy (I). Other medications with evidence of efficacy include buspirone (C), quetiapine (B), beta-blockers (B), pregabalin (B), and hydroxyzine (C). Details are in the Anxiety Disorders Guideline.

Utilizing evidence for major depressive disorder, depression related to COVID is best treated initially by reducing or eliminating sedating medication (I), education (I), antidepressant medication (SSRI, SNRI, TCA, MAOI) (B), cognitive behavioral therapy (B), aerobic exercise (C), and strengthening exercise (I). Benzodiazepine medication is not recommended. Other recommended medications include antipsychotics, olanzapine/fluoxetine, agomelatine, eszopiclone, nefazodone, zolpidem for sleep disorders (C). Weight loss may be selectively indicated in patients with obesity (B). Transcranial magnetic stimulation (C), repetitive transcranial magnetic stimulation (C), low-field magnetic stimulation (B), and light therapy (C) are also potential treatments. Severe cases may be treated with electroconvulsive therapy (B). See Depressive Disorders Guideline.

Utilizing evidence for posttraumatic stress disorder, PTSD related to COVID is best treated initially with aerobic exercise (B), strengthening exercise (B), cognitive behavioral therapy (B), exposure therapy (B), prolonged exposure therapy (B), virtual reality (B), imagery rehearsal training (B), and narrative exposure therapy (C). Medications with evidence of efficacy include sertraline (B), paroxetine (B), fluoxetine (I), escitalopram (I), citalopram (C), venlafaxine (B), mirtazpine (B), phenelzine (C), nefazodone (C), quetiapine (I), olanzapine (C), and prazosin (I). Other treatments potentially indicated include guided imagery (I), deep breathing exercises (I), meditation (I), and mindfulness (I). See the Postraumatic Stress Disorder Guideline.

Evidence for the Use of Rehabilitation

<u>Li 2020</u> (score-4.0) [849]

Comparison:

Category: Rehabilitation

Study Type: RCT

Conflict of Interest: Sponsored by Department of scientific center of Bengbu Medical College. No

COI.

N = 93 patients who tested positive for COVID-19 by the real-time florescent

Sample Size: reverse transcription polymerase chain reaction (RT-PCR) test and had mild

symptoms

Age/Sex: Mean age: 47.7 years; 33 males, 60 females.

Intervention Group: Patients received cognitive behavior treatment once per day for 30 minutes, which included cognitive intervention, relaxation and problem-solving training, and social support to try to remove false

misconceptions about the disease and educate them on real-time knowledge (n=47) vs. Control Group: Patients received standard care

including antiviral treatment, treatment of fever and symptoms, and nursing care (n=46). Both groups received care for the duration of their hospital stay,

which was an average of 14.4 days (n=93).

Follow-up: Follow-up at discharge (about 14.4 days)

Percent of patients with normal depression levels post-intervention for Intervention vs Control Group: 78.7% vs 73.9%, (p=0.59). Percent of patients with normal anxiety levels post-intervention for Intervention vs Control

Results:

Group: 46.8% vs 28.3%, (p=0.06). Percent of patients with normal stress levels post-intervention for Intervention vs Control Group: 61.7% vs 71.7%

(p=0.30)

Conclusion: "The patients with COVID-19 experienced high levels of anxiety, depression

and stress. Our study result highlights the effectiveness of CBT in improving

the psychological health among patients with COVID-19, also suggests that CBT should be focused on patients with chronic disease and those who have longer hospital stays. These results have important implications in clinical practice in improving psychological health in the context of COVID-19

pandemic."

Pilot study with unknown/short intervention time and lack of long-term follow-up. Data suggest a non-significant trend in improved depression,

Tollow-up. Data suggest a non-significant trend in improved depression

anxiety, and stress in the CBT group.

Liu 2020 (score=3.5) [832]

Comments:

Category: Rehabilitation

Study Type: Quasi-experimental observational

Comments: Quasi-experimental observational study. Data suggest a 6-week respiratory

rehabilitation program may improve respiratory function.

Liu 2020 (score=3.5) [818]

Category: Rehabilitation

Study Type: RCT

Randomized pre-test post-test. Small sample with short intervention time (5

Comments: days) and without long-term follow-up. Improved sleep and anxiety

observed in interventional group.

Wei 2020 (score=3.5) [850]

Category: Rehabilitation

Study Type: RCT

Comments: Small sample with short intervention time (2 weeks), making efficacy

difficult to assess.

Appendix A. Additional Considerations for School Re-opening

Efforts at reintegration in the school environment present multiple challenges. Different stakeholders will have responsibilities that must be communicated to be effective. Below are the identified groups and potential guides. Many US districts have reopened. The guidance below is particularly designed for districts that have not yet reopened and/or for those continuing to experience community-based COVID-19 spread. Physical distancing and other measures may not be needed in districts without ongoing community spread.

Administration

- Oversee all communications to stakeholders
- Hold explanatory sessions for all groups beginning at least 1 month before the resumption of school year
- Provide written documentation to all groups identifying each one's responsibilities and expectations, such as the following:
 - Wash hands after blowing nose, coughing, sneezing, eating food, using a restroom, or working in close proximity to a colleague/student.
 - Use masks where there is community prevalence ≥5%.
 - Provide security staff with gloves and perform visual inspections of any packages, but avoid touching those packages.
 - Limit the doors for ingress and egress. Only security staff, administration, and teachers should open or close doors. Students avoid opening or closing doors.
 - If possible, have doors left open.
- Place disposable alcohol wipes throughout the facility with open garbage cans nearby, particularly near student lockers.
- Provide disposable gloves and alcohol wipes in each classroom.
- Function as an employer by following the ACOEM guidelines on return to work.
- Oversee cleaning and disinfection of the school:
 - Cleaning and disinfection should ideally be done at night after all parties have left the facility. This also allows any virus located on a fomite to degrade during that waiting period.
 - Staff should have their symptoms assessed and take their temperature every evening. If they have an elevated temperature and/or feel ill, they may not report to school.
 - Cleaning staff should use disposable gloves and gowns. After removal, they should wash hands in soap and water.
 - Cleaning staff should follow physical distancing guidelines.
 - Most dirty surfaces should be cleaned with standard cleaning products before disinfectant is used.
 - Electronic surfaces and peripheral pieces should be cleaned per manufacturer's recommendations for disinfection. These recommendations may include, e.g.,

- cleaning with 70% alcohol with EPA-approved disinfectants for COVID-19** then applied. Caution is warranted as a 70% alcohol solution is flammable.
- Trash should be removed nightly.
- Regularly monitor state and local health authority guidelines.
- Establish a stakeholder committee to monitor school issues and progress.
- Establish regular staff and student avenues to report distress from the new school experience.
- Assemblies should be avoided.
- If there is widespread transmission, consider avoiding most sport teams with some exceptions (e.g., tennis, golf, baseball, and certain track events).
- Physical education can proceed, especially outdoors, with distancing standards.
- Stagger school start times and end times to minimize crowds.
- Stagger mealtimes and break times.
- Consider bringing in portable classrooms to allow for decreased class size.
- If there is a proven or suspected case of COVID-19, the following steps are recommended:
 - All students and faculty who were in contact with the student should be informed. They do not have to get tested but should isolate for 14 days.
 - All rooms and areas used by the student should be wiped down with disposable alcohol wipes.

Security Personnel

- Continue to practice physical distancing when possible.
- Monitor symptoms with an electronic questionnaire and take temperature every morning. If they have an elevated temperature and/or feel ill, they should not report to work.
- If outdoors, a face covering is recommended.
- If indoors, a face covering is required, although it does not have to be N95. N95 respirator use is a consideration for those at highest risk (e.g., oldest age groups and those with multiple comorbidities).
- Gloves should be worn.
- Request a visual inspection of any items, rather than physical, hands-on inspection.
- Doors should ideally be opened and closed by security or staff members only. Limit the doors that are used for regular ingress and egress.
- Consider using a volunteer at each entrance to provide a pumped dose of hand sanitizer for each person entering the building.
- Have a volunteer temperature-screen all entering students and staff.

^{**} https://www.epa.gov/pesticide-registration/list-n-disinfectants-use-against-sars-cov-2

Teachers and the Classroom

- Continue to practice physical distancing when possible (see current CDC guidance at https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/operationstrategy.html).
- Monitor symptoms with an electronic questionnaire and take their temperature every morning. If they have an elevated temperature and/or feel ill, they should not report to work.
- Wipe down each desk with alcohol disposable wipes between classes.
- Wear simple face coverings of loose cloth. Masks are not needed unless the teacher is in an increased risk group or community prevalence is rising above 5%.
- Teachers with multiple risk factors who are not vaccinated (e.g., comorbidities and increased age) should wear an N95 respirator if available in the classroom and must maintain strict physical distancing. If the teacher is unable to maintain strict physical distancing, then the teacher should wear an N95 respirator at all times, unless vaccinated.
- Classroom desks should ideally be set up for physical distancing (see current CDC guidance at https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/operation-strategy.html).
- Teach the science and math of COVD-19 as a practical benefit and to inform students so they can have a reasoned understanding of the pandemic.
- In space that does not allow ideal physical distancing (see current CDC guidance at https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/operation-strategy.html), considerations can include the following:
 - Half the class should participate in the class online. Online students may be at home for that day with all classes or in another room of the school.
 - Divide the lesson plan so that each group of students receives instruction but at different times of the day.
 - Increase the total amount of instruction days for the year to compensate for missed days or class size.
 - Increase the amount of distance learning material (online courses) that is covered in a topic to supplement reduced class time.
 - Install clear plastic shields on the desks and/or as room dividers. A physical barrier has a greater chance of success as an engineering solution that would minimize disruption of regularly scheduled activities.

Parents

- Continue to practice physical distancing when possible.
- Monitor symptoms with an electronic questionnaire and take their temperature every morning. If they have an elevated temperature and/or feel ill, they should not drive a carpool or enter the school.

- Discourage gatherings of large groups of children, especially if the group includes regular friends seen commonly.
- Continue an open dialogue with children about current science and best practices.
- Direct questions to their family doctor.

Students

- Continue to practice physical distancing when possible.
- Monitor symptoms with an electronic questionnaire and take their temperature every morning. If they have an elevated temperature and/or feel ill, they should not report to school.
- Assist the teachers and staff in wiping down each desk with disposable alcohol wipes between classes.
- Do not share food, drinks, or snacks with classmates.
- Wear simple face cloths. Masks are not needed unless community prevalence is ≥5%.
- Avoid large group gatherings, especially if other children are unknown.
- Do not provide transportation for classmates to and from school unless families involved are in agreement.
- Outdoor exercise is strongly encouraged.
- Meet with faculty or staff if they are experiencing difficulties in adjusting to the current social requirements.
- Special circumstances include the following:
 - Special needs children may find resources strained and their ability to comply highly limited. Unless a dedicated caregiver can be provided, they may be safer to remain in distance learning for the current time, although the balance between successful learning and safety must be addressed.
 - Nursery/preschool and kindergarten-age children cannot be expected to have reasonable boundary control. The recommendation for this group would be that each school have staggered drop-off and pick-up times. All children should stay in the same group (cohorting) and not switch rooms or be in the play areas outside with other children from another cohort. All toys, games, books, and outdoor play equipment will need to be wiped with alcohol at the end of the day. Outdoor games, if to be used by a different class, would need to be wiped down after each class. During times of close contact (children sitting on a lap, reading time), the teacher should use an appropriate mask. Depending on the children being taught, glove use and/or disposable gown use may be needed.
 - o Elementary school should ideally use staggered drop-off and pick-up times.

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