AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

COVID-19

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1. SUMMARY OF UPDATES

Note: This guideline and its recommendations were last reviewed and updated on **March 6, 2023.** (prior versions: April 8, 2020; April 24, 2020; May 8, 2020; June 12, 2020; June 17, 2020; August 19, 2020; December 14, 2020; March 29, 2021; and April 29, 2022).

The total depth and breadth of quality literature is growing. Caution is warranted for the potential for changes in efficacy that may be present for current virus variants compared with the variant(s) studied in the existing publications. Some of the studies may continue to be particularly fluid due to the continuing pace of change in knowledge. Research data, especially those associated with treatments, continue to be published prior to peer review. Some newer treatments do not yet have published peer review papers; thus, reliance for those is necessarily on press releases, FDA documents, and other non-peer-reviewed sources. Under normal circumstances, such data would not be considered for an evidence-based guideline. Much has now been clarified, with many earlier treatment paths eliminated. 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 of papers.

With the tenth version of this guideline, the document and updated guidance are transitioning to management of an endemic virus from an epidemic/pandemic, as the omicron variant was highly adept at worldwide dissemination in a matter of a few weeks.

The **March 6, 2023** update includes the following major changes:

- Transitioning of the guidance from managing an epidemic/pandemic to managing SARS-CoV-2 as an endemic virus
- Recommendations to promptly perform after-action reviews at the federal, state, and local levels. These reviews should define (in)effective responses to the pandemic and help to prepare for the next viral surge and/or epidemic/pandemic.
- Recommendation to develop multi-arm randomized trials of therapeutics for the early (24- to 48-hour) timeframe with existing evidence of potential efficacy to be implemented at the beginnings of the next variant surge
- Increased emphasis on management of the virus as being primarily spread by aerosols
- De-emphasis on contact spread and recommendations against regular cleaning of surfaces purely for the purpose of control of the pandemic
- Recommendations against lockdowns
- Recommendations for selective use of N95/KN95 respirators for significantly immunosuppressed population
- Recommendation to discontinue masking in the general population
- Guidance for schools to remain open and without masking
- Recognition of the durability of natural immunity, while supporting vaccination
- New recommendations in support of Paxlovid and pegylated interferon lambda
- Recommendations against most monoclonal antibodies which targeted pre-omicron strains
- Emphasis on prevention and early outpatient treatment, with reliance on NIH Guideline for hospitalized patients due to the ongoing development of variants that are and have been developing

2. STRENGTH OF EVIDENCE RATINGS

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

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

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

Please see our full methodology for more information.

[1]For therapy and prevention, randomized controlled trials (RCTs) with narrow confidence intervals and minimal heterogeneity. For diagnosis and screening, cross-sectional studies using independent gold standards. For prognosis, etiology or harms, prospective cohort studies with minimal heterogeneity.

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

[3] Van Tulder et al., 2003

3. INTRODUCTION

Novel coronavirus 2019 (COVID-19) is an acute respiratory infection caused by the coronavirus SARS-CoV-2. The disease it causes has been named “coronavirus disease 2019” (abbreviated “COVID-19”) (180).

The pandemic began in Wuhan, China in November 2019, then expanded markedly throughout the Wuhan region. The importance of the source is critical to prevent and/or for early identification of the next pandemic. Based on prior research and experience with coronavirus infections, the origin of this pandemic was initially suggested as having an animal host reservoir such as pangolins with origination from horseshoe bats in caves in Yunnan province, in southwestern China, which are located approximately 800 miles from Wuhan. However, an intermediate animal species (e.g., pangolins) has not been found (181) (182). The genetic sequencing of the virus uniquely includes furin cleavage sites typical of bioengineered viruses, and the Wuhan laboratory was conducting research with coronaviruses.

There is indirect and strongly disputed evidence suggesting that the epidemic may have begun in Wuhan earlier than November, including increased hospital traffic, web searches for potential COVID-related symptoms beginning in August 2019, and other information that suggested a potential virus laboratory shutdown in October 2019 (183) (184) (185) (186) (187). Yet, the source of the virus remains highly disputed (188) (189), with conflicting evidence surrounding gain-of-function experiments and viral alterations (190), and early publications denouncing the laboratory leak theory (189) were subsequently retracted (191). On balance, the most likely source was the Wuhan laboratory and, ideally, processes can be learned or studied to help prevent future outbreaks. Regardless of the source, the Chinese New Year and lack of early travel cessation to/from Wuhan likely accelerated the spread of the virus through global travel hastening the development of a pandemic. COVID-19’s SARS-CoV-2 virus is now found on all seven continents and is ubiquitous.

Quarantines were implemented early in the pandemic. However, they were likely ineffective at slowing or preventing the pandemic (192) for several reasons, including delays in implementing local, regional and global quarantining; late enactment of travel bans; early lack of rapid and accurate viral testing; early emphasis on contact instead of respiratory precautions; subsequent emphasis on droplet spread with neglect of the potential for aerosol spread; ongoing delays in the institution of, and lack of attention to, aerosol precautions; large numbers of undiagnosed, mild, or asymptomatic patients spreading the virus (193,194); and inadequate detection of the spread of cases in regions prior to the recognition of hospitalized cases with COVID-19 within that area (195). An added fact later identified that precludes eliminating the virus from the global human population is the susceptibility of animals, (e.g., felines, deer) although the importance of this potential factor regarding subsequent spread back to humans is still poorly documented. Evidence of infections in many species of animals, presumably documenting the potential for developing 'animal reservoirs' (196,197,198,199,200), also precludes eliminating the virus from the global human population, without consideration of the other required criteria for viral eradication (e.g., no asymptomatic cases; no cases among the vaccinated; ability to geographically restrict the virus; an effective method to interrupt disease transmission).

Public health management of this pandemic has varied markedly across countries, states, and jurisdictions. Because there was no quality evidence to support any of these measures early in the pandemic, expert opinion was naturally relied upon for enactment of these measures. The initial guidance focused on handwashing and restricting travel to and from China (January-February 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). Eight US states never instituted lockdown orders. Many US states began to reopen most, if not all businesses, starting in May-June 2020. Subsequently, restrictions waxed and waned largely in response to rising and falling COVID-19 incidence rates. However, jurisdictions varied widely regarding what local health authorities deemed to be concerning rates.

Furthermore, larger or more dense jurisdictions often lacked the ability to discriminate within their geographic areas, leading to health orders that might not have been warranted in rural areas or smaller population centers. Over time and with subsequent waves of variants spreading globally rapidly, the numbers and degree of restrictions implemented has gradually been reduced regardless of magnitudes of disease transmission and burden. Typically, a combination of approaches was initially 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 (57).

The pandemic subsided markedly in the summer of 2020 in northern latitudes. However, as fall/winter 2020–21 began, the pandemic surged in northern, cold climates possibly facilitated by conditions of lower temperatures, lower humidity, less intense ultraviolet (UV) irradiation, and higher indoor population densities combining contribute to record levels of cases in nearly all jurisdictions (201) (202) (203). In addition, the more recent variants have been associated with less lethality. Additionally, controversy regarding the efficacy and sustainability of various public health measures, especially the (re)closure of businesses and schools, intensified as the case rates plummeted in 2021, economic and social costs accrued and utility of the public health measures were increasingly questioned by research. Quality data are weak; yet, some countries (e.g., Japan, South Korea) instituted less stringent measures with seemingly somewhat comparable or better results (204) (205) (206) (207,208,209) (210) (211) (212) (213) (214). Most but not all publications and a metanalysis found lack of efficacy of lockdowns (5), while economic impacts of lockdowns were severe (215,216,217,218) and effects on children's educations were stark (see below).

However, beginning in approximately October 2020, the delta variant (B.1.617.2) began to circulate in India (219). This variant was estimated to be approximately twice as contagious as the alpha variant (46), which was approximately twice as contagious as the original virus. The delta variant was found in the United States in spring 2021 and subsequently spread globally. While the original delta variant arose in a largely unvaccinated population, delta infections also occurred among those fully vaccinated in the United States and elsewhere. The relatively low levels of viral spread in spring 2021 were replaced by surges by mid-summer that peaked in the United States in late August to early September.

Still, while there have been fatalities among those vaccinated, particularly among the immunocompromised (220) (221), most of the delta variant fatalities were among the non-vaccinated, as the vaccines still proved to be highly effective in preventing hospitalizations (221) (222) (223)(224,225,226) (227)(228). There were few moves to reinstate restrictions in the United States during that period; however, Australia and some other countries re-instituted severe restrictions with no quality evidence of commensurate benefits. Subsequently, there were another two variants of concern that were identified: lambda (which was identified in Peru in December 2020) and mu (which was identified in Columbia in January 2021) (219). However, those variants were eventually displaced by omicron.

In mid-November 2021, the omicron variant (B.1.1.529) was described in Botswana and South Africa (229). Retrospectively, omicron was identified in a November 11, 2021 sample from recently-arrived international diplomats November 11, 2021 in Botswana (230). Eventually, there were earlier cases described in the Netherlands. Other samples in multiple countries (e.g., England, South Africa, Nigeria, USA) date the detection of omicron to November 1, 2021, thus assuring it had arisen weeks to months earlier although it had apparently gone undetected. The origin of this markedly different variant with large numbers of mutations (approximately 4 times the spike protein mutations compared with the original strain; 3 times compared with the delta variant) is unclear, whether arising from a long-term host, going undetected over a series of mutations, arising from an animal reservoir, or originating from another source (231)(232). Omicron has been estimated to be more than twice as contagious as delta. It rapidly spread around the world, including to the United States by early December, being isolated from a person without a travel history on December 2, 2021. Omicron was so efficient at spreading that the peak case rate in South Africa occurred on approximately December 15, 2021. By December

25, 2021, omicron displaced delta as the predominant variant in the United States in less than one month, by December 25, 2021 (233). The speed of spread has also effectively precluded proactive updating of vaccinations using existing techniques. The peak U.S. omicron-related COVID-19 case rate occurred on approximately January 14, 2022.

In late 2022, additional subvariant mutations of omicron (e.g., BQ.1, BQ.1.1, BF.7) were reported to be gradually displacing earlier omicron variants (especially BA.2, BA.4, BA.4.6, BA.5.) as the predominant strains. By late summer 2022, the US FDA approved bivalent COVID-19 boosters developed by Pfizer-BioNTech and Moderna to cover omicron as well as the original SARS-CoV-2 strain (234). In late 2022 to early 2023, another omicron variant was displacing the others in the US and elsewhere (XBB.1.5) and again showing evidence of an even more efficient rate of spread.

Worldwide, the virus continues to provide numerous challenges, especially in regards to the increasingly rapid rates of successive variant transmission. Challenges include surges, hotspot outbreaks, attempts at surge prevention, and mitigation; COVID-19 diagnostic testing accuracy and limitations; unique treatment challenges and sparse to varying evidence of efficacy; development of resistance to many targeted therapies; global public resistance to restrictions; and increasing business/economic/educational concerns surrounding any restrictions. Evidence of vaccine efficacy is strong (see below). Evidence of efficacy of public health measures other than vaccines is limited and suggests low, if any efficacy at this point in the endemic evolution (late 2022-2023). The economic damages have included loss of employment, income, and housing; closure of in-person school instruction; as well as worsening supply chain disruptions involving quite diverse sectors and products (235) (236) (237) (238).

Successes in reducing impacts of the first phases of the COVID-19 pandemic are primarily credited to rapid vaccination uptake, residual immunity due to prior infections, and initially falling infection rates. However, the concept of "termination" of the COVID-19 pandemic has necessarily been either eliminated or redefined, as it is now clear that eradication is impossible with current science. Omicron's substantially lower severity, including an ~91% lower risk of mortality (239), is also facilitating the transition from pandemic to endemic management. Attention is now turning to issues such as cases among those fully vaccinated, the frequency of booster immunizations, efficacy of boosters that currently are addressing prior variants, speed of new booster development to address new emerging variants, speed of deployment of new boosters, the duration of vaccine-related immunity, the relative importance of vaccine-related compared with natural immunity, therapeutics, prevention and mitigation of severe disease and death among the immunocompromised, and detection and addressing of endless, subsequent viral variants.

3.1. VIRUS CHARACTERISTICS

Contagiousness

COVID-19's SARS-CoV-vacc2 virus appears to be more contagious than the prior coronaviruses, and each successive widespread variant has been ever more successful at spreading (692). The omicron variant has been estimated to be 2 to 3.3 times as infective as delta and 10 times more infective than the original virus (693) (694), while the latest omicron sub-variants are still more transmissible. These markedly increased rates of transmission are explaining how a new variant could be identified in South Africa/Botswana, rapidly spread globally, and displace USA's predominant strain all in only 6 weeks (233).

Initially, the virus was thought to be primarily spread largely through direct contact, resulting in a primary inter/national focus on handwashing (695) (696) (697) . Yet, contact spread could not explain the rates of spread. Then, the theory changed to droplets as the primary spread. These beliefs starkly changed and the science has now coalesced around this guideline's prior position early in 2020 that the virus is primarily spread by microdroplets/aerosols (defined as <0.5 µm) followed by respiratory

droplets (defined as >100 µm in size) (698,699,700,701,702,328,703,704,705,706,707) (708) (709,710,711,712,713,714,715,716,717,718,719,720).

Aerosols can potentially remain suspended in the air for hours (707,721) and well beyond the 6-feet (or 1-meter, per the World Health Organization) physical distancing guideline, with one estimate for need of up to 10-meter distances (719) (722) (12,723,724). One experimental study estimated aerosolized virions retained infectivity and virion integrity for up to 16 hours (725), thus likely explaining the widespread and reproduced patterns of viral epidemic spread despite institution of physical measures. Still, to what extent an infectious dose can be generated, what is an infective dose, and what is present at varying distances has yet to be clearly demonstrated (726,727,728,729,730,731,712). There is some evidence of a dose-response relationship between dose and clinical severity (261). Regardless, the recognition of aerosol spread has significant impacts on the utility of various public health measures and the selection of potential preventive interventions.

The contagiousness and virulence of the SARS-CoV-2 virus delta variant appears to be about 6-fold greater than that of influenza. Estimates of the contagiousness or transmission rate without interventions (e.g., physical distancing) of the original virus ranged from 2.0 to 3.9—that is, 2 to 3.9 new cases arise from each known case (i.e., R_0,) (732), which is far higher than typical influenza transmission rate of ~1.3 (733). The Ro for delta has been estimated at 5 and the Rho for omicron is estimated at over 7, although the ability to accurately determine Ro in a population that has individuals who had the infection is challenging it not impossible . Also, the reproduction number varies markedly and as the epidemic curve surges or tails off, the reproduction number rises or falls respectively. 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 (734). Superspreading has continued to be a purported major mechanism of spread with successive variants (735) (736) (707) (249) and some evidence suggests omicron as having a greater superspreading potential than earlier variants (737).

Spread by those asymptomatic was always an important mechanism to propagate this pandemic, but may now be a major problem. The asymptomatic infection rate of omicron in South African healthcare workers was initially reported at 16%, which is approximately 6-fold higher than that reported with the beta or delta variants (738) (739,740) (741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,315,760). Subseq uent reports found approximately 10-fold higher rates of asymptomatic omicron carriage compared with earlier variants (761). Other estimates have ranged as high as 70-90% of cases worldwide being asymptomatic (762) (763). A metanalysis of 7,640 omicron cases calculated an overall asymptomatic infection rate of 32.4% of cases (299). This striking asymptomatic carriage rate is theorized to strongly contribute to the rapid dissemination of omicron.

Although not thought to be an important mechanism of spread, the virus's survivability on surfaces varies depending on the material; it has been estimated with experimental methods to survive up to 9 days (764), although those experimental methods are limited by not including environmental settling rates, inactivation by UV light, or diffusion., and use of doses unlikely to be found under normal non-experimental conditions. 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 (719). 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 (764). 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) (765). Survival of the virus in aerosols is thought to be as long as 16 hours (725). 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 (201) (766,767,768,202), and prior data on the SARS coronavirus are corroborative (769). 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 (770). The ecological data indicate that there were slower rates of infection with higher temperatures in Delhi, India, and Pakistan (201) (202), although there was no correlation with humidity (201). 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 (202). Other data suggest lower infections with higher humidity (203) (771). This suggests variable disease transmission risks based on seasonality and in indoor compared with outdoor environments, although the extraordinarily high rates of disease transmission have, and will foster year-round spread.

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 original SARS-CoV-2 virus was initially estimated to be approximately 5–6 days (193,772,773), while the estimate for delta was 4 days, and the estimates for omicron are only ~3 days (774). Previously, 97.5% of cases occurred by 11.5 days after exposure and infrequent cases of up to 14 days (255,250,775). There are some recent reports suggesting infectivity is still possible at 10 days (776) (777). Viral shedding may antedate symptoms by 1–2 days, peak viral load occurs 1-3 days before symptoms, (778) and viral titers are highest in the earliest phases of infection; however, a study has suggested the peak shedding for omicron infections may be 3-6 days after the onset of symptoms (779), although this study measured peak RNA material, which would reflect total accumulated viral material but would not be expected to correlate directly with maximum viral replication or infectivity (779).

The duration of infectious viral shedding remains 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) (780,781). Yet, it is less clear at what point these particles become non-infectious, and there are far fewer studies of viral shedding that relied on viral culture techniques. Culturing is critical to know if viral particles may be active in transmission. Even those few studies with viral culture results may not yield enough virus particles that are sufficient to provide an infectious dose (781).

A pooled study prior to omicron 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 (782,783). Omicron studies suggest somewhat comparable results (784). 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 (785,786,787). 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 (785). No study detected live virus beyond the ninth day (782). These findings contrast with those of MERS and SARS, which peaked after symptom onset and lasted for shorter durations. it is also apparent that a positive PCR test is not a binary (yes or no) answer; the threshold cycle count should be reported, as counts above 28-30 are more likely to be false positive or have residual particles more likely to be incapable of transmitting infection

There have been many reports of re-infections (788,789,790,791,792,793), which accelerated markedly with omicron. The risk of re-infection with omicron has been estimated at 5.4 times that of delta (794). Previously, a prior infection was estimated to have provided 85% protection against

reinfection, but this estimate has now fallen to 19% (794). Yet, the cases are on average milder. A case-control study found a pre-omicron infection at least 90 days before re-infection was 35.% effective at preventing symptomatic omicron infection while a prior omicron infection provided 76.2% efficacy at preventing infection against the BA4 or BA.5 omicron variants (795).

Due to the extent of re-infections and especially the problems with omicron, the concept of herd immunity is undergoing reevaluation. It is unclear if it will be resurrected for COVID-19.

3.2. CLINICAL PRESENTATION

The clinical presentation of COVID-19 has substantially evolved over the course of the pandemic, with both a shift towards milder presentations and some differences in the prevalence rates of specific symptoms. There continue to be 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 (240):

- asymptomatic
- pre-symptomatic
- mild, subclinical infection (e.g., mild rhinorrhea, pharyngitis)
- upper respiratory tract infection (URI), which also may include gastrointestinal symptoms
- lower respiratory tract infection, including pneumonia
- acute respiratory distress syndrome (ARDS)

Treatments differ for each presentation (see Treatment Recommendations for more details).(241,242,243,244,245,246)(247)

Symptoms and Signs

The symptoms of COVID-19 vary but are generally typical of respiratory infections, such as fever and cough. The symptoms with the omicron variant are primarily rhinorrhea, headache, fatigue, sneezing, and sore throat (248); these symptoms differ compared with prior variants. COVID-19 symptoms may include the following, listed here for all variants including omicron (249) (250) (251,252,253,254):

- fever, low or high grade (80–88%; omicron: 54%)
- dry cough (63–69%; omicron: 83%) (255,256)
- loss of appetite (39–84%; omicron: 33%) (257)
- fatigue (38–46%; omicron: 74%)
- 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%; omicron: 58%)
- sore throat (12–14%; omicron: 72%)
- headache (11–15%; omicron: 68%)
- chills (6–11%)
- nausea or vomiting (5–10%)
- diarrhea (4–29%) [124]
- nasal congestion (4–5%)
- abdominal pain (4%; omicron: 6%)
- conjunctivitis (pink eye; 1%) (258)
- blepharitis
- hemoptysis (1%)
- rhinorrhea (runny nose; omicron: 78%)
- sneezing (omicron: 43%)
- oral ulcerations and xerostomia
- anosmia and dysgeusia (loss of smell and taste; 85% moderate/severe or anosmic; omicron: 12-23%) (259)

Severity of disease may be related to the inoculation dose (260,261). In earlier stages of the pandemic with less transmissible variants than omicron, the wearing of masks was theorized to potentially increase the proportion of asymptomatic cases by lowering the inoculation dose (260,262). This may be less likely with aerosolized transmission.

All widespread variants identified appear capable of causing severe disease and death, however, the virulence has decreased over time (263). Hospitalization data suggest the risk of death among those hospitalized in the omicron-predominant timeframe was 4.9% compared with 15.1% during delta-predominant spread (264). Deaths in the omicron period have been largely in the elderly (81.9% at least 65yo) among those with at least three underlying conditions (73.4%).

Cardiovascular symptoms and signs were sometimes noted on initial presentation with prior variants (241,242,243,244,245,246). Immunothrombotic dysregulation associated with COVID-19 pneumonia has been described (265). Coagulopathy associated with antiphospholipid antibodies and multiple infarcts have been reported (266,267). Seizures have been reported as a presenting disorder (268). Young and old patients have presented with large-vessel strokes as an initial manifestation of COVID-19 infection (268,269). Pulmonary arterial thromboses have been reported (270). Among ICU patients, 31–59% of patients incurred venous or arterial thromboembolic event(s) (271,272), compared with 10–25% of patients hospitalized for other reasons (272,273). Heparin-induced thrombocytopenia (HIT) is a severe adverse reaction to heparin caused by heparin-dependent, platelet-activating anti-platelet factor 4 (PF4)/heparin antibodies frequently found in acute severe COVID-19 infections and is associated with thrombotic events (274). Anti-phospholipid antibodies associated with thrombosis have also been identified in severe COVID-19 pneumonias (274). Recovering competitive athletes also have been found to have cardiac abnormalities on magnetic resonance imaging (MRI) (247).

Dermatological abnormalities such as urticaria, vasculitides, and pityriasis rosea have been described (275,276,277,278). The most common dermatological presentations have been polymorphic and erythematous, chilblain-like, and urticarial lesions (279). Various neurological and psychiatric presentations including stroke-like symptoms, altered mental status, dementia-like syndromes, and new or recurrent affective disorders have been reported (280,281,282,283,284,285,286,287)(288)(289)(290). 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 (291). 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 (292), along with the isolation of viral RNA from urine (293). Most (71%) of those who die from COVID-19 have findings consistent with disseminated intravascular coagulation (294).

Because the symptoms for most patients are typical of nonspecific respiratory tract infections, they can be difficult to distinguish from other diseases (58,59). 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 (295). 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 (296).

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 (297,295,298). The CDC estimates that 40–45% of transmission occurs prior to symptom onset and that the infectiousness is comparable between asymptomatic and symptomatic individuals (297,193). A meta-analysis

comparably suggested 32.4% of omicron infections are due to asymptomatic spread (299). Children tend to be asymptomatic or have milder symptoms, which suggests a mechanism that may accelerate disease transmission throughout the population (295), although this is not proven and is somewhat controversial. Viral load estimates conflict among children compared with adults (300,301,302,303). 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 (304,305). Regardless, one-third of hospitalized children require ICU stays (306). 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 (307).

Mortality

The mortality rate for COVID-19 has changed markedly over the course of the pandemic, being much lower through successive waves of variants and with widespread immunization (308) (47). The mortality risk for omicron was ~15% of the risk of delta (309). CDC reported that in-hospital mortality reduced from 15.1% in the delta period to 4.9% in the late omicron period , with residual mortality largely limited to the elderly with multiple medical conditions. In South Africa, there was a 90.7% reduction in the death rate with omicron compared with delta. Findings in South Africa also include a 76% reduction in oxygen therapy requirements and a 62.5% reduction in hospital stay (days) (309). The risk of mortality continued to be much higher among the unvaccinated in the omicron era (310). Data are somewhat unclear regarding the degree to which the reduction in mortality is primarily attributable to reduced variant lethality or vaccination (311,312,313).

The mortality of COVID-19 was initially estimated to be approximately 10-fold higher than that of typical seasonal influenza (314). Subsequently, severity estimates were reported as low enough to be comparable with prior influenza epidemics (315,316,317,318), with and a systematic review found the median infection fatality rate of 0.0003% at 0-19 years, 0.003% at 20-29 years, 0.011% at 30-39 years, 0.035% at 40-49 years, 0.129% at 50-59 years, and 0.501% at 60-69 years. (319,320). The CDC also estimated the overall *symptomatic* case fatality ratio is 0.004, or 1 in 250 (193). Mortality can be predicted based on risk factors and clinical findings on presentation (321). A seroprevalence study of 35,309 Danish blood donors estimated the case fatality rate at 6.2/100,000, which may be a better approximate risk in a healthy working age population rather than that of the entire population (322).

Mortality risks with all variants have increased sharply with age, including with omicron, with which an overwhelming majority of fatalities are among the elderly (264). Prior to omicron, the symptomatic case fatality ratio was 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 (193). The mortality rate for males is 57–64% higher than that for females, although that risk was reduced to 51% of fatalities in the more recent omicron era (264). Nursing home residence is a particularly potent fatality risk (323,324,325,326,327). 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 (328,329,330,331,332,333,334)(335). During the late omicron era, 0.9% of in-hospital fatalities have had no underlying medical conditions while that rate was 1.8% in the early omicron era and 2.9% in the delta era. Auto-antibodies to type I Interferon-alpha were found to be more prevalent in patients older than 65 years old, and were associated with an increased risk of severe disease and death from COVID-19 pneumonia (336). The O and Rh- blood group types appear to have slightly lower risk of infection and severe disease(337). 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 (338). Past outbreaks of other types 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. Early in the pandemic from March-June 2020, the case fatality rate was estimated at approximately 5-6% (314).Thus, in using an actual rate from a systematic review and meta-analysis of 0.095% (320), a 5.5% estimated risk was more than 58-fold higher. These errors in estimated risk had grave implications for public policy, as the implementation of lockdowns and other severe measures were largely driven by the early estimates of fatality risk; it is suggested they be memorialized and used for future pandemic planning, where early estimates are typically overestimated due to spectrum biases.

3.3. BUSINESS CONSIDERATIONS

The actions an employer may take to mitigate the risk of COVID-19 infection are changing as the virus transitions to being endemic and highly contagious with omicron. The actions primarily center on the current omicron variants, having aerosol transmission and rapid spread combined with lowered morbidity/mortality. Industry sectors with higher risks of workplace COVID-19 outbreaks have reportedly included manufacturing, agriculture, forestry, fisheries, transportation, and warehousing (2), although with the transition to endemic status, all workforces have risks that are likely comparable. Regardless and importantly, there now exists a patchwork of different health department regulations in different jurisdictions during this transition from a pandemic to endemic state; naturally, it is important to adhere to those laws and regulations. Managing a company operating in multiple jurisdictions may accordingly become more complex.

One major difference between epidemic and endemic management is that modified **ring isolation** around those at high risk may be helpful in protecting those more vulnerable, particularly during or just before forecasted variant surges. This includes:

- greater caution around those at high risk (e.g., cancer, undergoing chemotherapy, other immunosuppressed state);
- institute N95/KN95 for those at high risk, if able to tolerate;
- institute N95/KN95 for those in close contact with those at high risk; and
- reduce and avoid contacts among those at high risk (e.g., avoid grocery stores, other large and densely populated retailers, restaurants, other locations with large numbers of people).

Because some individuals at high risk will not desire some, or any, of these measures (e.g., nearing end of life and/or risk/benefit tolerances/rewards), institution of these measures should only be done after a well-informed discussion and N95 fitting and assessment of tolerance.

There are multiple domains for an employer's actions. Please see the following sections on:

- Employee issues (e.g., education and medical surveillance)
- Travel issues
- Physical distancing methods
- Personal protective equipment (e.g., respirators, masks, gloves, face shields)
- Ventilation issues
- Disinfection practices and contact spread measures
- Policies and procedures
- 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- and workplace-specific risks (3). This is probably important given that the current vaccination rates vary more than 100-fold across the globe (4), and it can be anticipated that differences in northern/southern hemisphere and other environmental issues (i.e., heat, humidity, UV, use of air conditioning) may persist.

Should a variant arise with significantly greater morbidity than the omicron (sub)variants, then consideration of re-institution of select, limited public health measures may be indicated, which should likely focus on the elderly or those with multiple medical risk factors as opposed to blanket recommendations for an entire geographic area. Most public health measures are proving of little if any use for omicron and appear to have provided little help with the prior variants (5).

3.3.1. EMPLOYEE ISSUES

COVID-19 VACCINATION

Employers are recommended to strongly encourage vaccination of their entire workforce at the earliest date, including internationally (see also Vaccination recommendations). The CDC has produced many publications to support these efforts (339,340). 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), incentives, and hosting on-site vaccination clinics.

The omicron surge(s) have occurred with most of the population protected by vaccines which were proven to be partially effective. To attempt to mitigate subsequent surges and especially to continue the protection demonstrated by the prior vaccines against severe disease, updated vaccines have been released in September 2022 to include targeting of both the original variant and omicron. Evidence of subsequent efficacy for this logical approach during coming surges is planned, however while expected, there is as yet no quality clinical evidence of efficacy of this approach (341). There is evidence of prior efficacy of vaccination as preventing mortality including from omicron (310). As the updated vaccinations released is after the omicron surge and related variants BA.4 and BA.5 have been exhausted, adverse effects on a population basis may be greater due to widespread natural immunity, especially if given too quickly after a given individual sustained a case when the antibody levels are highest. While not a requirement, CDC is now advising consideration of waiting 3 months after an infection before boosting (342) Given the mild clinical omicron variant presentations in most of the vaccinated population and unknown long-term effects of repeated boosters, further benefits and requirements for the young, healthy population are especially needed, as well as benefits on an overall population basis.

COVID-19 surveillance

Employers do not typically perform surveillance for influenza or other communicable diseases. As the US transitions to an endemic state with the now highly communicable SARS-CoV-2 virus variants, it may also transition away from employer-based surveillance for COVID-19. The following section retains prior recommendations for this period of transition and in the event that there is another variant with substantially higher morbidity than omicron or delta.

Prior to omicron, employers were recommended to have implemented a surveillance system that included 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 Temperature measurement screenings were previously used but were problematic because they miss subclinical and presymptomatic cases, while 69% of seriously ill individuals are afebrile (343). Subsequent evidence suggests temperature screening is ineffective and detected only one case for every 40 cases missed (344) (193). In the event of a serious surge, 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 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% (250); thus, cases with high indices of clinical suspicion should typically be treated as presumptive cases (250). Home testing kits have not been found to be highly reliable for omicron; testing frequency, in order to make a difference for preventing spread, appears to require a minimum of thrice-weekly testing of the entire target population. 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

Prior to omicron, sick employees were removed from work even if mildly ill. With the omicron surge, it has become necessary for some mildly affected workers to remain at work with adequate respiratory protection to attempt to prevent transmission to coworkers for a given industry to continue to function (e.g., health care, air travel) (345) (346). Accordingly, the CDC modified the return-to-work provisions to 5 days (347) with a high-quality mask (ACOEM recommends ideally an N95 respirator) through day 10 or at least two negative antigen tests to remove the mask/respirator sooner (348). This phenomenon is typical of an endemic disease where infected and asymptomatic or minimally ill workers are not removed (345) (346). As this is recommended to be a transition point to an endemic state, the remainder of this section addresses when medical removal may be used by employers wishing to remove such employees. Such policies may still be more supportable with the advent of a variant with higher morbidity/mortality than omicron or delta. Local public health requirements may also require select actions.

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 (349). If there is believed to be significant SARS-CoV-2 virus transmission in the area, then individuals with mild, undiagnosed symptoms of an upper respiratory tract infection (e.g., cough, fever, fatigue) are advised to stay home to be sure they do not progress to a clear, and potentially severe, COVID-19 infection (295), 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 public health department, which has the expertise and personnel to investigate outbreaks and perform contact tracings (provided they are not overwhelmed by the current pandemic). 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.

Readers are advised to refer to current CDC guidance, as this changes frequently (350) (347). 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 (351,352). 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 5 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; however, as noted above, PCR tests can mislead as viral particles may be detected but they may not be infectious. 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.

Employees in contact with an infected coworker

This section assumes a transition back to an epidemic/pandemic state with a much more severe variant than the milder delta or omicron variants.

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 (353). Otherwise, employees in contact with an infected coworker should continue to undergo medical screening (354,355). 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) (356). 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 higher-risk 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 self-quarantine and work from home for at least 5 days. Initially, the reduction to 5 days was primarily driven by the very high rate of disease transmission, relatively low risk after 5 days, and high and incapacitating numbers of individuals projected to be out of work; 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 (357,358). The CDC has changed their quarantine recommendations for exposed but asymptomatic workers to wearing a mask and testing if possible on day 5.

In certain worker 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 (359). This option is becoming less controversial, although it is not without risks because pre-symptomatic spread is believed to be a primary source of epidemic spread. This option should be 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 (343,360):

- age 65 years and older
- chronic lung disease, including moderate to severe asthma
- serious heart condition (e.g., history of heart attack or heart failure)
- immunocompromised (e.g., having had bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS; using corticosteroids or other immune-modulating medications; undergoing cancer treatment)
- smoking, current or former
- obesity, especially severe (329)
- 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 number and severity of the conditions increase. The presence of multiple conditions increases the risk of severe disease and mortality (60,264).

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.
- reduce public-facing work.
- provide the affected worker with a fitted N95 or KN95 respirator to protect from exposure.
- consider placing high-risk individuals closer to ventilation that provides fresh air.

Some educational videos have been developed to illustrate the spread of aerosols, as they are now thought to be the primary mechanism of disease spread (video 1, video 2, video 3). It is advised that high-risk individuals develop a plan with their healthcare provider for rapid testing and treatment if symptoms develop, as timely and effective treatment affects prognosis,

3.3.2. TRAVEL ISSUES

Travel bans, restrictions, and broad testing are no longer recommended. They may be central tools for early control and management of an epidemic. However, these tools are not useful to manage an endemic disease. They are also especially not useful for a variant, such as omicron that moves rapidly and without quick detection to a peak surge in 1-2 months in essentially all countries. Such restrictions may again be attempted should a future variant surge have markedly higher mortality rates above that associated with the delta or omicron variants.

Currently, there continue to be some potentials for added risks, especially for some employees on business trips. However, among those vaccinated, these risks are likely reasonable and tolerable for most businesses. Travel risks include those associated with travel to and from a site, as well as business conducted at those sites (6). Risks differ 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, especially those not known to have natural or vaccine-related immunity, travel valuations should include costs associated with any potential illness, distance medical care, potential for medical evacuation, and any post-trip isolation period. Caution is advised for non-essential travel by non-vaccinated and non-immune employees to locales with outbreaks or significant community spread in progress (6), which includes the entirety of the United States and most of the world during most of 2022 (see map to help with other risk considerations (7).

International trips may be affected among countries limiting travel to and from countries with outbreaks, despite the increasingly dubious value of these restrictions as demonstrated by the universal and rapid spread of omicron. Air travel may be considerably safer than some other forms of travel (8), although the primary risks of air travel are more likely to be exposure risks at the destination, which may be challenging or impossible to control.

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

For vaccinated employees returning to work after travel, limitations or quarantines are not advised. For non-vaccinated and non-naturally immune employees returning from personal or work-related travel to areas with community-based COVID-19 spread, the safest course of action is to self-isolate while working from home for 5 days.

3.3.3. PHYSICAL DISTANCING METHODS

In the transition to an endemic disease spread by aerosols, physical distancing is increasingly of limited if any use, particularly for what has become an easily-transmitted, aerosol-spread disease. The primary exceptions may involve the unproven potential of ring isolation to protect those who have major immunosuppressive conditions (e.g., leukemia, chemotherapy treatment). Otherwise, physical distancing methods are no longer recommended. CDC has also removed referencing to a 6-foot physical distance, although still recommending distancing; it has also reduced emphasis on other methods such as erecting barriers (9).

Institution of effective physical distancing controls for immunosuppressed people is challenging. With the recognition that the disease is mostly aerosol spread and apparently outdoor spread (e.g., widespread infection among wild deer populations), physical distancing may need to be at least 30 feet, while also avoiding being downstream or crossing "vapor trails" from other people for an as-yet unclear length of time which may well be at least 30 minutes to a 3-4 hour period, and using an N95/KN95 respirator for theoretical added protection. These criteria preclude grocery shopping, walking in malls, going to church, walking on a sidewalk in a large city, and most other common experiences of life. Thus, the practicality of physical distancing for an aerosol-spread virus, even for immunocompromised individuals, is increasingly dubious. It may be better to expect those at high risk to decide whether to protect themselves as opposed to the majority of the population who do not need to mask or physically distance.

Physical distancing was believed to be one of the more effective control measures, particularly when the disease was believed to be due to droplets and contact-spread, because the distance spread is limited, it does not rely on training and compliance, and in the initial stages was thought to involve a 6-foot distance (10). The following are some physical distancing options to consider if a considerably more lethal variant arises:

- work from home when feasible.
- consider rotating workers between home and work settings to reduce workplace population densities while facilitating functions that are best performed at work.

The following are examples of commonly instituted physical distancing methods that were previously recommended, are likely to be either minimally or wholly unsuccessful with aerosol-spread viruses, and are thus no longer recommended (11,12):

- **NOT RECOMMENDED**: 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).
- **NOT RECOMMENDED**: 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.
- **NOT RECOMMENDED**: where there are two options for walking through a workplace, set up one-way walkways.
- **NOT RECOMMENDED**: reorganize shifts to spatially and temporally spread workers.
- **NOT RECOMMENDED**: route shifts of workers to enter through one entrance and exit through a different one.

- **NOT RECOMMENDED**: 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).
- **NOT RECOMMENDED**: 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).
- **NOT RECOMMENDED**: 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.

3.3.4. PERSONAL PROTECTIVE EQUIPMENT

PPE recommendations have changed with the endemic nature of the virus, recognition that the virus is largely aerosol-spread, vaccination of the population, and the communications challenges caused by masking. PPE is no longer recommended for immunocompetent individuals in the general population. As the virus is aerosol spread, and in the potential future event of a variant with much higher morbidity, N95 respirators and other devices (e.g., PAPR) would be a priori recommended. N95/KN95 respirators are selectively recommended for those with immunocompromised states as reasonable, though unproven options, although there is not consistent quality evidence of efficacy for either masking or N95 respirators.

PPE measures (respirators, masks, gloves, and eye protection/face shields (13,14,15,16,17,18) were recommended, but they are lower on the list of controls. The speed with which the omicron variant spread and failure to slow or blunt the epidemic curves, irrespective of a state's or country's masking mandates and business openness status highlights the apparent ineffectiveness of masks and other methods at this stage of the pandemic with this degree of aerosol-spread contagion.

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. However, a future surge of a variant with high morbidity could easily again exhaust supplies of N95 respirators. In such a case, extended use and re-use of respirators will be essential. Stockpiling of N95 respirators is a part of normal emergency preparation and thus recommended for routine emergency planning, along with other supplies. Such stockpiles should currently be (re)supplied.

3.3.5. VENTILATION ISSUES

Ventilation issues (general and local fresh air supply) have been markedly underutilized as potential COVID controls (19,20,21,22,23). Ventilation may still be of some assistance with management of aerosols, although it may be less effective than for management of a droplet-spread virus. This issue also has potentially major implications for future control of other epidemics, such as influenza or resurgences of COVID-19. Consultation with an HVAC expert may be helpful. Area ventilation may 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 (24,25).
- air disinfection, such as ultraviolet germicidal irradiation, can be placed within the central HVAC system (22,25). 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, generally 8-10L/s.

3.3.6. DISINFECTION PRACTICES AND CONTACT SPREAD MEASURES

Ventilation and other control measures addressing aerosols and microdroplets are far more important than disinfection of surfaces for COVID-19 (26). Disinfection of surfaces appears to have a quite limited, theoretical role in reducing spread. Disinfection of surfaces has not been shown to be effective, distracts and diverts attention from more effective control measures, incurs considerable time and expense, and is no longer recommended for purposes of control of the COVID-19 pandemic.

3.3.7. POLICIES AND PROCEDURES

At this point in the COVID-19 endemic, it is anticipated that subsequent variant surges may be relatively mild in infection severity, although they may be quite widespread. Regardless of whether the next variant is mild or severe, now is the time for comprehensive after-action reviews (aka, critical incident stress debriefings). The purpose of such reviews is to define successes and failures, and plan how to better respond in the future. To be successful, these reviews require a focus on what was done, what happened according to plans, what went astray, why things happened, what would have been better response(s) and action(s), avoid finding fault, identify the approaches that did or did not meet expectations, and require broad participation from all key stakeholders. These reviews should include public health officials from federal, state, and regional/local levels, healthcare organizations, as well as representatives from large and small employers, with the goal to define effective responses to the pandemic and prepare for the next viral surge or epidemic/pandemic. These reviews should also be based at large employers and moderate-sized employers may also wish to devote the resources to accomplish a more limited, internal review.

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).
- assess the ventilation system, filtration, air exchanges and potential to use ultraviolet to reduce risk of transmission
- 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.
- teach workers about the principles of microdroplet/aerosol spread viruses.
- implement N95/KN95 respirators for select workers, especially those immunosuppressed in contact with others. Use and stockpile powered air-purifying respirators (PAPR), N95/KN95, and other respirators for select workers.
- teach workers to use tissues to catch a cough or sneeze, then throw that tissue away and wash their hands.

- in the event of a surge with a high morbidity variant, avoid scheduled aggregate meetings. If so, encourage use of teleconferences and/or other virtual meeting formats.
- in the event of a surge with a high morbidity variant, 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 (27,28,29,30).
- in the event of a surge with a high morbidity variant, and 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).
- in the event of a surge with a high morbidity variant, consider having employees who develop symptoms stay away from the workplace until clinically evaluated and/or until the symptoms are resolved and any isolation period has expired.
- in the event of a surge with a high morbidity variant, consider having employees who could be in the incubation stage work from home for at least 10-days after the possible exposure.
- in certain workforce shortage situations, medical centers and critical service workers may be allowed to work while asymptomatic with self-surveillance for symptoms and consistent N95 respirator-wearing instead of being quarantined for 5-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).
- assess testing accuracy as, e.g., antibody testing is now widely available, but the sensitivity and specificity vary greatly between kits (see Diagnostic Testing). With further validation, antibody testing may likely become useful in assessing possible susceptibility to infection versus protective response to prior infection. In the future, COVID-19 serology may be able to 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.

3.3.8. INDUSTRY-SPECIFIC RECOMMENDATIONS

Industry-specific guidelines are no longer advised at this point in the pandemic. Instead, attention to ventilation and other generic industry practices above are recommended.

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 (361,362,363). 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 (364,365). Initial reports that children do not become infected were erroneous (366); 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 poor, with the largest widespread reductions in standardized testing on record (367). 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 (368,369,370,371,372). 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 (370). 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 (373). Schools also play important roles in students' social development and mental health (374,375,376).

Restarting of schools was controversial, seemingly more so in the US than elsewhere, and widely divergent strategies were deployed. Nearly all reports 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 opening without physical distancing, masking, alternate school schedules, or other mitigations (377). The main contrary example is Israel, where school-based transmission to teachers was briefly noted (378,379).

The worldwide omicron surge produced nearly identical epidemic curves, regardless of whether the country or state had in-person mask-less teaching on one extreme to distance-based education on the other extreme of a spectrum. Accordingly, a rationale for masking students and/or not having in-person classes is not apparent.

For those teachers and other staff who have severe immunosuppressed states, there may be modest protection with fitted N95 respirators and use of online teaching methods.

There may be a consideration for institution of distance-based teaching methods with a future surge involving a markedly more virulent variant; however, this would not be a priori recommended due to adverse effects, including marked reductions in learning associated with lockdowns (380). If subsequent variants become more transmissible, It is also highly improbable that masks will be effective in schools regardless of any potential increases in morbidity. Thus, due to an absence of evidence of efficacy and evidence of stark harms, including marked reductions in learning associated with lockdowns (380), physical methods such as moving classes to online learning, masking and physical classroom distancing are not recommended for schools.

3.4. DISABILITY AND RETURN-TO-WORK CONSIDERATIONS

Disability from COVID-19 is being refined with studies over time. Extrapolation using recovery from other conditions, such as pneumonia and ARDS, continues to set some expectations and provide estimates. The principles of return-to-work have also been explored in many sources (381).

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 (169,382). In a cohort consisting primarily of patients treated for COVID in an outpatient setting, 39% reported symptoms at 7-9 months, with fatigue (21%), loss of taste or smell (17%), dyspnea (12%) and headache (10%) being the most common (383). However, persistent symptoms are reported in individuals with mild cases, and long-term symptoms have been reported (384,385,386,387,388). There also are many cases that require home healthcare after discharge (389).

Permanent disability is determined by the existence of some combination of fixed deficits when a healing plateau has been reached (see the ACOEM Disability Prevention Guideline). 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 (390,391). Another factor that may be uniquely affecting disability during this pandemic is a lack of capacity, especially for mental health treatment.

Permanent disability is only appropriate for those with fixed, non-improving chronic impairments (see Rehabilitation). 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” (392). The term “post-acute sequelae of COVID" and "post-acute sequelae of SARS-CoV-2 (PASC)” has also been used by the National Institutes of Health.

Factors contributing to disability beyond fixed but remediable deficits may include a lack of full implementation and utilization of evidence-based treatments, and lack of effort and compliance. The shortage of skilled mental health providers and other specialists may also contribute to prolonged disability. Prolonged symptoms has also been correlated with persistence of viral antigen in the gut (393). Neural dysregulation has been reported in those with post-COVID fatigue (394).

Other factors may potentially involve psychological, advocagenic (i.e., a response to legal counsel or legal system, induced or magnified by the counsel or system itself; usually used for unfavorable responses) and other influences. While vaccination likely reduces the risk of chronic symptoms, it does not eliminate that risk (395).

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 sparse data on returning to work, short-term disability, or long-term disability. A large sample reported 15.1% of patients still had symptom(s) at 12 months (396). 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 (397). 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. Chronic pulmonary manifestations have been reported, including a case series of ICU patients having 3-month prevalence of symptoms and signs of 46.7% dyspnea, 34.4% cough, 82% with reduced diffusion capacity, 49.1% with reticular lung CT patterns and 21.1% with fibrotic patterns on CT (398). Prior experience with similarly manifesting diseases, 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 (399,400). 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 (401). Lung diffusion abnormalities can take up to 5 years to resolve in ARDS cases (401,402). 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 (400,401,402,403,404,405,406).

Generalized skeletal muscle deconditioning is expected in patients who are intubated for any extended duration; these patients require graded return to activity and/or exercise programs and possibly rehabilitation, which often results in residual incapacity (400,403,407,408). Cardiac problems are common with COVID-19, with cardiomyopathy, arrhythmia, and direct cardiac muscle injury affecting approximately 30%, 20%, and 10% of patients, respectively (409); they are contributing causes to fatality (409,410,411). COVID-19 survivors who did not have cardiopulmonary disease reportedly also have risk of persistent exercise intolerance (412).

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 (413). 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 (400,401,402,403,404,414). There is also the potential for a minority of patients to be permanently totally impaired (404).

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

- 6-minute walk test and/or sit to stand testing
- 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 (415). 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 (416) and 6th Edition (417).

4. VACCINES

4.1. OVERVIEW

Vaccine development progressed at record speed on more than 270 COVID-19 vaccine candidates during Operation Warp Speed (349,418,419,420). These efforts used at least four types of vaccine classes or approaches against this infection (virus, viral vector, nucleic acid, and protein-based) (419). Although vaccine development was estimated to require 12–18+ months if successful, it was achieved in approximately 9–10 months (421). Four vaccines are currently approved for use in the United States. Several more of these COVID-19 vaccines are in advanced stages of development and have potential for approval (see Table 1). Efficacy data have been published. Safety data suggest the vaccines are largely safe. Reported rates of initial vaccine efficacy range from 62% to 95% (422) (423)(424) (425). After initiating vaccination programs, COVID-19 infections declined markedly (426). However, vaccine efficacy fell with subsequent waves of new variants (427). The risk of mortality continued to be much higher among the unvaccinated in the omicron era (310). Accordingly, booster shots which have increasingly been suggested to have retained partial efficacy against the delta and omicron variants have been emphasized (427,428,429). As some of the initial purposes of the vaccines have not been met (e.g., eliminating infection risk, terminating the pandemic, herd immunity), it is important to communicate regarding the current purposes of vaccination (e.g., reducing infection and severity risks including hospitalization and death).

The CDC has also provided guidance regarding what is recommended for those who have been vaccinated (430). Healthcare professionals (HCPs) are encouraged to take steps to help ensure that patients are immunized against COVID-19. If HCPs are unable to administer vaccines, it is

recommended to refer patients to a vaccination provider. For additional guidance, please refer to the Centers for Disease Control and Prevention's Standards for Adult Immunization Practice resource.

The vaccines have very good to excellent rates of efficacy both in randomized trials and in reports from large population-based studies and surveillance systems, which underscores evidentiary support for broad-scale vaccination programs. The following questions require answering going forward, although they should not delay the continued implementation and completion of the vaccination programs:

- duration of vaccine-induced immunity and whether there are differences between the types of immunizations
- whether duration of immunity differs in different subgroups, suggesting the need for (earlier) re-vaccination
- whether immunity is shorter-lived in vaccinated patients or in naturally infected patients
- whether annual immunizations are needed
- 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
- risk/benefit ratios in children, whether all children should be immunized, or whether natural infection is preferable whereby immunity is more durable (431).

Table 1. 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	Incidence of COVID-19 cases at days 43 to 759 Participants AEs and MAAEs leading to withdrawal up to day 759	Fatigue, 9.7%; myalgia, 8.9%; arthralgia, 5.2%; headache, 4.5%; injection site pain, 2.7%;	Vaccine efficacy against COVID-19 was 94.1%; vaccine efficacy against severe COVID-19 was 100% (90 vs. 5

Vaccine / Manufacturer	Type (Platform)	Participant Characteristics	IM Doses	Special Handling	Primary Outcomes	Adverse Events	Efficacy / Interim Analysis
					Participants with solicited local and systemic ARs up to day 8 and 36 and unsolicited AEs up to day 57	erythema at injection site, 2.0%; headache, 2.0%; fever, <2.0%	COVID cases; 11 vs. 0 severe COVID cases occurred)
Novavax	Recombinant glycoprotein nanoparticle (NVX-CoV2373)	30,000 participants aged ≥18 years	2 doses; days 1 and 29	None; safe to store at normal refrigeration temperatures	Incidence of COVID-19 cases at days 29 to 750	Reports include injection site pain, rash, headaches, muscle pain, fever, nausea, and vomiting.	Currently unknown
Pfizer (BioNTech / Fosun Pharma	3 LNP-mRNA (mRNA BNT 162)	43,998 participants aged ≥12 years	2 doses, days 1 and 22	Yes; requires storage at –20°C	Incidence of COVID-19 cases at days 29 to 730 (per 1000 person-years of follow-up) Incidence of AEs and SAEs after doses and up to day 202	Influenza-like symptoms, injection site pain, rash, fever, headaches, muscle soreness, and nausea. Grade 3 adverse effects >2% were fatigue (3.8%) and headache (2.0%).	95% meeting all primary efficacy endpoints (162 vs. 8 COVID cases; 9 vs. 1 severe COVID cases occurred)

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 (432). Data supplemented from (397).

Healthcare professionals are encouraged to take steps to help ensure that their adult patients are fully immunized against COVID-19. For additional guidance, please refer to the Centers for Disease Control and Prevention's Standards for Adult Immunization Practice resource."

4.2. ADVERSE EFFECTS

The vaccines have been associated with a relatively 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* (31), 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 systematic review and metanalysis of 22 studies of patients who had had an immediate allergic reaction after their first vaccination, included 1,366 individuals with 6 (0.16%) having had severe immediate allergic reactions after the second dose, and 232 (13.65%) had mild symptoms (32).

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 (33). 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 (34). 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.

The risk of myocarditis among young males after vaccination is estimated from population-based data at 5.3-fold overall, with highest risk of 13.6-fold among 16-19 year old males (35). Conversely, myocarditis in young males following an acute COVID-19 infection occurred at a rate of as high as 450 per million infected in young males. Young males infected with COVID-19 were up to 6 times more likely to develop myocarditis compared to those who have received the vaccine (36). Due to reported risks of thrombosis and thrombocytopenia, the Janssen vaccine is recommended only for limited use (37).

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 (38), 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.

A case series has reported ongoing symptoms among those having received one dose of vaccine and who had been previously hospitalized with COVID (35).

4.3. VARIANT CONCERNS

The spike protein of the SARS CoV-2 virus is the focus of currently available vaccines. A parade of successive variants have developed and most that become common, have more genetic variation and consequential transmissibility. The omicron has had, by far the most mutations in the spike protein to date.

The spike protein is the primary viral protein responsible for entry into host cells by attaching to the ACE2 cellular receptor present on multiple human tissue cells, 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 significant 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 (39,40).

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 (alpha, UK), B1.351 (beta, South Africa), and P.1 (Brazil). The B.1.1.7, or beta 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 (41). 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 less 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 alpha variant had been detected in 12 U.S. states. This became the dominant strain in the United States in 2021 (42).

The beta B.1.351 variant 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.

The vaccines proved effective against the alpha and beta variants. However, one report suggested a poor ability of the ChAdOx1 nCoV-19 vaccine to prevent mild to moderate COVID illness caused by the B.1.351 strain (43).

The P-1 gamma variant of SARS-CoV-2 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 (44).

The most important variants to subsequently arise are the Delta (B.1.617.2) and Omicron (B.1.1.529)(45). Delta became the predominant variant by summer 2021 (46). The Omicron variant, however broke new ground. It both had far more mutations, while far more transmissible, and from detection to becoming the predominant strain only took approximately 6 weeks (47); several subsequent omicron mutations have now arisen.

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 (48). 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 and will continue as the transition to an endemic disease proceeds. As host susceptibility to infection changes, the virus, under these selection pressures, will change accordingly. More variants will emerge, and in general, it is in the virus' best interest to become more transmissible and less lethal, producing an expectation of generally diminished severity with successive waves. 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 (49). While the vaccines are being altered going forward to address novel variants that have already emerged, as well as those yet to emerge, the speed with which the omicron variant arose raises practical questions about the ability to develop a timely targeted vaccine. Nevertheless, the original vaccine given as a booster shot has shown an ability to reduce severe disease including hospitalizations (50).

Breakthrough infections among healthcare workers have been associated with young age, Hispanic/Latino workers, those having clinical roles, and those having had a vaccination series with Pfizer-BioNTech (51).

Research into addressing vaccine hesitancy is sparse (52,53,54). Neutralizing antibody levels were modestly higher for those with a history of natural infection compared with those with only vaccinations (55).

4.4. VACCINE RECOMMENDATIONS

VACCINES FOR THE PREVENTION OF COVID-19

Recommended

A primary vaccination series 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., elderly, obesity, diabetes mellitus, COPD, cardiovascular disease, renal disease, immunosuppressed states).

Common RCT exclusion criteria include immunodeficiency, immunosuppression, use of glucocorticoids 20+ mg/day in the past 6 months, and prior vaccine allergic reactions. Studies suggest there are no increased adverse risks among pregnant women.

How, and whether to integrate prior COVID-19 infection into the decision to vaccinate and timing of vaccination is somewhat controversial, although growing evidence supports durability of the antibody responses from natural immunity (Schmidt et al., 2022). A systematic review and metanalysis of 65 studies found 78% effectiveness against hospitalization and death for pre-omicron and omicron variants, while also showing durable protection at 40 weeks pre-omicron, but protection against symptomatic re-infection was lower for omicron (Stein, 2023). Evidence also suggests boosters do not substantially increase antibody levels if given less than 3 months after an infection (Herring et al., 2022). CDC guidance now recommends consideration of a delay in vaccination if there has been an infection in the prior 3 months (Prevention, 2023) (Magnus et al., 2021, Shimabukuro et al., 2021, Zauche et al., 2021). Regardless, those with immunosuppressed states would be potentially high-impact populations and are recommended to receive early vaccination.

There is evidence from large population-based studies that booster immunizations raise antibody levels and markedly lower risk of mortality or hospitalization (Choi et al., 2021, Intapiboon et al., 2021, Li et al., 2021, Munro et al., 2021)(Thompson et al., 2022)(Schmidt et al., 2022, Accorsi et al., 2022, Arbel et al., 2021, Dhingra et al., 2022, Mattiuzzi et al., 2022).

CDC recommends a single booster immunization at 5+ months for the Pfizer-BioNTech and Moderna vaccines and at least 2 months for the Janssen/Johnson & Johnson vaccine (CDC, 2022)(Mbaeyi et al., 2021). For those who received the Janssen/J&J vaccine as their primary series, the CDC recommends a bivalent booster with the Pfizer or Moderna vaccine.

Benefits

Reduced risk of COVID-19 infection, as well as serious COVID-19 disease. Two 2-shot series of mRNA vaccines (Pfizer and Moderna) have ~95% efficacy, whereas the single shot (Janssen/Johnson & Johnson) has ~67% efficacy (FDA, 2021). Booster immunizations have reportedly resulted in ~90% reductions in risk of hospitalization and death.

Harms

Serious adverse effects shown in a 1.7M population-based study of the Pfizer vaccine were a 3.2-fold risk of cardiomyopathy, 2.4-fold risk of adenopathy and 1.4-fold risks of both herpes zoster and appendicitis (Barda et al., 2021). There are no similar high-quality data yet published for the other vaccines.

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%). The population-based risk estimate for cardiomyopathy has been estimated at 5.3-fold overall, with highest risk of 13.6-fold among those 16-19 years old males.

Anaphylactoid reactions are quite rare (4.5 per million doses administered (Gee et al., 2021); 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% (Soiza et al., 2021).

There is an increased risk of shoulder conditions, particularly among women and elderly recipients (Zheng et al., 2022), which may be related to accidental subacromial injection especially among those with lower deltoid muscle mass.

Frequency/Dose/Duration

The CDC recommends a single booster immunization at 5+ months for the Pfizer-BioNTech and Moderna vaccines and at least 2 months for the Janssen/Johnson & Johnson vaccine (CDC, 2022)(Mbaeyi et al., 2021).

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.

Rationale

Multiple RCTs (Bonelli et al., 2021)(Polack, 2020, Heath et al., 2021, Mulligan et al., 2020)(Madhi et al., 2021, Goepfert et al., 2021, Keech et al., 2020, Ella et al., 2021, Chappell et al., 2021, Baden et al., 2021, Logunov et al., 2020, Bonelli et al., 2021)(Borobia et al., 2021, Liu et al., 2021, Folegatti et al., 2020, Li et al., 2021, Pan et al., 2021, Al Kaabi et al., 2021, Pu et al., 2021, Ramasamy et al., 2020, Richmond et al., 2021, Sadoff et al., 2021, Stephenson et al., 2021, Zhu et al., 2020, Zhang et al., 2021, Zhang et al., 2021, Wu et al., 2021, Xia et al., 2021, Shu et al., 2021, Tanriover et al., 2021, Walsh et al., 2020, Xia et al., 2020, Shinde et al., 2021, Chu et al., 2021, Che et al., 2020, Yang et al., 2021) and large population-based studies (Thompson et al., 2021, Thompson et al., 2021) have all documented efficacy of the initial vaccinations of ~85-95%. Subsequent large population-based studies show that booster immunizations raise antibody levels and lower risk of mortality or hospitalization (Arbel et al., 2021)(Mattiuzzi et al., 2022)(Accorsi et al., 2022)(Schmidt et al., 2022)(Dhingra et al., 2022)(Thompson et al., 2022). Evidence also suggests comparable efficacy of prior infection of approximately 90% reductions in hospitalization and death (Abu-Raddad et al., 2021). Current CDC guidance is to not incorporate prior infections in decisions to (re)vaccinate (CDC, 2021), although there are no long-term studies to address that question.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 using the following terms: COVID-19 Vaccines, Vaccination, Pfizer, Moderna, Johnson & Johnson, vaccines; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 2,058 articles in PubMed, 95,514 in Scopus, 366 in CINAHL, 124 in Cochrane Library, 36,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 18 from PubMed, 0 from Scopus, 12 from CINAHL, 7 from Cochrane Library, 7 from Google Scholar, and 0 from other sources. Of the 44 articles considered for inclusion, 34 randomized trials and 6 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.

5. MASKS AND RESPIRATORS

Mask use was initiated part-way through the COVID-19 pandemic to attempt to control SARS-CoV-2 exposures thought to be largely by droplets (56). Masks are easier to use than respirators, and do not require special fitting. Respirators have much higher performance standards, are more challenging to use correctly, have higher cardiorespiratory physiological demands, and require fit testing to assure protection meets standards. Masks of widely varying quality, including those which are non-commercial and of single-ply material, have been commonly used by the public in attempts to control SARS-CoV-2 exposure. Respirators have been selectively used to attempt to control COVID-19 viral exposures among higher-risk workers or individuals. Still higher levels of respiratory protection have been used in healthcare settings (e.g., PAPR). Masking mandates have been used for control of COVID-19 both in the workplace and in some jurisdictions (e.g., statewide) (57).

MASKING FOR THE PREVENTION OF COVID-19 TRANSMISSION

Not Recommended

Masking in closed public spaces was especially used when transmission was theorized to be primarily droplet spread in an attempt to prevent COVID-19 transmission (Greenhalgh, 2021). Masking requirements were also maintained in some locations, and have also been maintained irrespective of community transmission rates and changes in understanding of disease transmission. However, masking appears to be minimally effective to largely ineffective. In contrast with masks, N95 respirators are theorized to be potentially helpful for select populations, such as high-exposure workers and workers with high personal risks, although recent evidence is challenging that theory (Loeb et al., 2022).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Moderate

Rationale

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 (Gupta et al., 2020). Another 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 (Bundgaard et al., 2020). A comparative trial among healthcare workers of masking compared with N95 respirators found lack of differences, which may be suggestive, but not dispositive of contradicting the theory of respiratory barriers producing measurable risk reductions (see also experimental filtering data reviewed below) (Loeb et al., 2022).

A large, low-quality cluster-randomized trial in Bangladesh reported an 11% reduction in risk of infection (Abaluck et al., 2022), and a follow-on interventional RCT by the same research group to improve mask wearing compliance (from 13% to 42%) found a 9% reduction in overall risk of infection (Abaluck et al., 2022). However, reanalysis of the data demonstrated a difference of only 20

symptomatic cases (1,106 v 1,086) with analytical evidence suggestive of ascertainment and other biases (Recht, 2021, Chikina et al., 2022). Since then, omicron and subsequent omicron subvariants have moved rapidly around the world irrespective of masking and/or physical distancing-business openness in countries and/or states. Multiple systematic reviews and metanalyses are mixing respiratory viruses (e.g., influenza), which may or may not be scientifically valid (Baier et al., 2022, Chou, 2022, Loeb et al., 2022).

Prior RCTs mostly involve influenza and influenza-like illness (Bartoszko et al., 2020, Li et al., 2020, Ippolito et al., 2020, Coclite et al., 2020, Jefferson et al., 2009, Liang et al., 2020, Long et al., 2020) and show somewhat conflicting results regarding efficacy to reduce risks of infections, particularly with use of respirators; there are more negative (Canini et al., 2010, Simmerman et al., 2011, Suess et al., 2012, MacIntyre et al., 2009, Jacobs et al., 2009) than positive trial results (Aiello et al., 2010, Cowling et al., 2008, Cowling et al., 2009). Equivalency has been reported between surgical mask use and N95 respirators (Radonovich et al., 2019, Loeb et al., 2009), although experimental evidence suggests superiority of respirators to reduce droplet and aerosols (Wilson et al., 2020, Darby et al., 2021, Asadi et al., 2020). Weak evidence suggests masking may be effective and that N95 respirator use may be superior to mask use in healthcare settings (MacIntyre et al., 2020, MacIntyre et al., 2017, MacIntyre et al., 2014, Chou et al., 2020). All of the epidemiological data have the benefits of being real-world data, but weaknesses include unclear compliance and masking techniques (Kolewe et al., 2020). Respirators performed better than masks in simulation studies (Noti et al., 2012); however, a simulation of SARS-CoV-2 found incomplete protection from masks and N95 respirators (Ueki et al., 2020).

Experimental data on filtering were as follows: N95 respirators, 99%; medical masks, 59%; 3-ply cotton, 51% vs. 47%; double-gaiter, 60%; face shield, 2% (Lindsley et al., 2021, Godoy et al., 2020). Surgical and cloth mask efficacies vary widely (Mueller et al., 2020). Experimental data thus suggest there should be markedly different rates of disease among those using N95s in comparison with medical masks; yet, that is not what the RCTs have shown.

Quality trials suggest a lack of significant efficacy of masks to alter risk of COVID-19 (Loeb et al., 2022, Gupta et al., 2020, Bundgaard et al., 2021) and an inability to either alter the rate of, or shape of epidemic curves. A low-quality randomized trial with multiple potential flaws (Chikina et al., 2022, Recht, 2021) assessed transmission of more remote and less transmissible strains in Bangladesh of SARS-CoV2, suggested an 11% reduction in risk with a total of 20 case differences between the two groups involving over 300,000 people (Abaluck et al., 2022). A Cochrane review came to similar conclusions (Jefferson T, 2023). Masks also provide communication barriers. Thus, in the absence of quality evidence of efficacy, universal masking is not recommended. Although there are no significant quality data for COVID-19, surgical-quality masks and N95 respirator use may be attempted to protect those with significant immunosuppressed states and the immediate contacts with such individuals (see Respirators).

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 using the following terms: Mask; Scarf; Bandana; reusability, reusable, reusable cloth, clothing, clothes, clothing, textiles, clothed Mask; Standard surgical mask; N-95; face shield; N95Respirators; 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 42 articles in PubMed, 175 in Scopus, 172 in CINAHL, 9 in Cochrane Library, 1,523 in Google Scholar, and 0 from other sources†. We considered for inclusion 0 from PubMed, 12 from Scopus, 0 from CINAHL, 1 from Cochrane Library, 20 from Google Scholar, and 0 from other sources. Of the 32 articles considered for inclusion, 1 randomized trial and 30 systematic reviews, and 1 background information, 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.

N95 RESPIRATORS FOR THE PREVENTION OF COVID-19 TRANSMISSION

Sometimes Recommended

Respirator use is primarily recommended for immunocompromised individuals or those with multiple risk factors for severe disease. Masking in closed public spaces was used when transmission was theorized to be primarily droplet spread in an attempt to prevent COVID-19 transmission. Masking in some locations has also been maintained irrespective of community transmission rates. However, masking appears ineffective potentially due to their inability to block aerosols (see Masking recommendation). In contrast with masks, N95 respirators provide a substantially higher level of protection against both droplets and aerosols and may be indicated for select populations (e.g., high-exposure workers, workers with high personal risks), although it is noteworthy that quality evidence of efficacy is also lacking (Loeb et al., 2022).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Most RCTs of masking to protect from respiratory viruses have been negative (see below). In the COVID-19 pandemic during 2021-2023, the omicron variant was identified and peaked throughout the world in ~2 months while producing nearly identical epidemic curves irrespective of population-based masking requirements, now followed by omicron subvariants which are reproducing this trajectory.
Efficacy of masking is reviewed in the masking recommendation. A comparative trial of masking compared with N95 respirators found lack of efficacy (Loeb et al., 2022). Prior RCTs mostly involve influenza and influenza-like illness (Li et al., 2020, Ippolito et al., 2020, Coclite et al., 2020, Jefferson et al., 2009, Liang et al., 2020, Long et al., 2020) and show somewhat conflicting results regarding efficacy to reduce risks of infections, particularly with use of respirators; there are more negative (Canini et al., 2010, Simmerman et al., 2011, Suess et al., 2012, MacIntyre et al., 2009, Jacobs et al., 2009) than positive trial results (Aiello et al., 2010, Cowling et al., 2008, Cowling et al., 2009). Equivalency has been reported between surgical mask use and N95 respirators (Radonovich et al., 2019, Loeb et al., 2009), although experimental evidence suggests superiority of respirators to reduce droplet and aerosols (Darby et al., 2021, Asadi et al., 2020) which is not borne out by a similar level of protection in epidemiological studies. Weak evidence suggests that N95 respirator use may be superior to mask use in healthcare settings (MacIntyre et al., 2020, MacIntyre et al., 2017, MacIntyre et al., 2014, Chou et al., 2020). All of the epidemiological data have the benefits of being real-world data, but weaknesses include unclear compliance and techniques (Kolewe et al., 2020). Respirators performed better than masks in simulation studies (Noti et al., 2012); however, a simulation of SARS-

CoV-2 found incomplete protection from masks and N95 respirators (Ueki et al., 2020) and a comparative trial found no differences in healthcare workers' risk of COVID-19 (Loeb 2022). Data on filtering were as follows: N95 respirators, 99%; medical masks, 59%; 3-ply cotton, 51% vs. 47%; double-gaiter, 60%; face shield, 2% (Lindsley et al., 2021, Godoy et al., 2020). Surgical and cloth mask efficacies vary widely (Mueller et al., 2020).

Quality trials suggest a lack of significant efficacy of masks to alter risk of COVID-19 (Loeb et al., 2022, Gupta et al., 2020)(Bundgaard et al., 2020) and an inability to either alter the rate of, or shape of epidemic curves. A low-quality randomized trial with multiple potential flaws (Recht, 2021, Chikina et al., 2022) assessed transmission of more remote and less transmissible strains in Bangladesh of SARS-CoV2, suggesting an 11% reduction in risk with a total of 20 case differences between the two groups involving over 300,000 people (Abaluck et al., 2022). A Cochrane review came to similar conclusions (Jefferson T, 2023). Masks also provide communication barriers. Thus, in the absence of quality evidence of efficacy, universal masking is not recommended. Although there are no significant quality data showing efficacy for COVID-19 as RCT data surprisingly showed no differences between masking and N95 respirators, N95 respirator use may be selectively recommended to attempt to protect those with significant immunosuppressed states and the immediate contacts with such individuals.

Evidence

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.

6. 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-in-place jurisdictions in the United States, the variants spread seemingly either without or with minimal regard to restrictions. Most individuals were permitted to continue to visit grocery stores despite lockdowns, which may have provided a means for continuing community spread despite masking requirements (e.g., walking through others' aerosol/vapor trails while using inadequate protection for a highly contagious aerosol).

Studies are being published concerning the efficacy of lockdowns. Most studies have reported some reductions in COVID-19 transmission after the implementation of a lockdown (433,434), although it has been reported that lockdowns were not effective in Europe (433). An ecological study suggested greater spread where restaurant dining was allowed (435).

However, an 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 (433). An analysis of all 50 US states failed to find that the degree of lockdown was related to reductions in excess mortality, while also reported associations with increased unemployment and reduced employment growth (215). A worldwide analysis also failed to find benefits of reductions in mortality based on non-pharmaceutical interventions (NPIs) (436). One analysis concluded there were benefits in the US, but failed to analyze for, and account for the differences by state (437).

Reports have questioned the cost-benefit efficacy of lockdowns (438,439)(5). Economic impacts of lockdowns were severe and damages to children's educations were stark (440,441)

Adverse mental health effects have been reported, including anxiety, depression and substance(s) abuse (442,443,444,445,446). The subject of lockdowns requires considerably greater research, especially as future surges attributed to variants are assured, and there is a potential for a more severe outbreak in a later wave The re-implementation of such lockdown policies for COVID-19 likely necessitates a stronger evidence base. Further study is also warranted to ascertain at what cutpoint a mortality rate may warrant consideration of lockdowns and restrictions for a different type of infection (e.g., avian influenza or 'bird flu').

Thus, the currently available evidence does not support lockdown measures as they:

- appear largely ineffective to slow the spread and impact of the SARS-CoV-2 virus and/or any of its variants during this pandemic;
- did not reduce overall mortality;
- appear to have contributed to increased problems with anxiety, depression, other mental health disorders and drug overdoses;
- increased job loss and unemployment;
- caused reduced economic growth, and
- were generally accompanied by cessation of in-classroom teaching at schools, for which there is now considerable evidence of both ineffectiveness and major academic harms (see Schools).

Lockdown measures are not recommended (5,447,215,448).

7. DIAGNOSTIC APPROACH

7.1. LABORATORY TESTS

COVID-19 has a widely varying clinical presentation. Depending on the extent of infection and the organ systems affected, any or all of the following may be found (58,59):

- 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 (60). 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 (61).

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 ± ribavirin) (62).

7.2. DIAGNOSTIC TESTING

Three main types of diagnostic tests are used for COVID-19:

- polymerase chain reaction (PCR) testing, typically using swabs (449);
- antigen testing, and
- antibody testing of blood serum.

PCR testing (e.g., nucleic acid amplification 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 (450). 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 (451). There are concerns with the accuracy of testing to detect newer variants, especially with false negative tests among those with early infections or mild symptoms and lower viral loads which have been particularly noted in studies of antigen tests, with one publication noting sensitivities of ~20-28% among 3,600 asymptomatic individuals (452,453).

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 (454). One study detected higher SARS-CoV-2 titers in saliva compared to nasopharyngeal swabs, with less longitudinal variability (455). A meta-analysis found similar sensitivities and lower costs for saliva sampling compared with nasopharyngeal swabs (456). Thus, saliva testing is increasingly replacing swabs to provide near universal sampling coverage for both symptomatic and asymptomatic patients (457). Yet, accuracy for omicron is similarly unclear.

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 (458).

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 (459). 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, thus use of PCR for travel restrictions is questionable.

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 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 continues to be important. The ability to widely perform COVID-19 testing is of particular importance during times of anticipated epidemic waves and regarding accuracy in detecting future variants.

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 (460,461):

- 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 (462).

PCR TESTING FOR THE DIAGNOSIS OF COVID-19

Recommended

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 (Domeracki et al., 2020) is ill-advised given that the risk of false-negative tests are 20–67% (Wiersinga et al., 2020). Thus, there is a strong indication to presumptively treat cases who test negative when disease is prevalent, which requires experienced medical judgment. Repeat testing may be indicated for those with a negative test but a high index of suspicion. However, as these tests amplify genetic material, they may remain positive 90 days after an infection, resulting in misleading individuals regarding cessation of infectivity; instead, antigen tests are advised if there are ongoing symptoms (Prevention, 2023).

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).
Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

ANTIGEN TESTING

Antigen tests detect viral proteins either on or within the virus. These have been FDA-approved and are also considered diagnostic (450). Antigen testing is popular as its main strength is rapid test results, which are provided in minutes compared with up to several days for PCR tests. It is also helpful for select circumstances (e.g., testing after a PCR test is positive but in the face of ongoing symptoms such as at 21-90 days after infection began).

One report has suggested lower sensitivity comparing four different rapid antigen tests (biotical, Panbio, Healgen, Roche) with one automated antigen detection test (VITROS) for the diagnosis of COVID-19; yet, the rapid results were felt to still confer an advantage for positive test results to detect infectious patients (463). Still, caution is warranted regarding omicron as sensitivities are lower.

ANTIGEN TESTING FOR THE DIAGNOSIS OF COVID-19

Recommended

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; data indicate low sensitivity at that time, resulting in a high potential for false-negative test results. However, the sensitivity among symptomatic persons is estimated to be approximately 80%. Thus, testing without experienced medical judgment is ill-advised (Domeracki et al., 2020), 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.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

ANTIBODY TESTING

Antibody testing attempts to detect the body's humoral response to the virus, whether post-vaccination or post-infection (464,465,466,467,468,469,470). 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 symptom onset), while the median seroconversion for IgG is 14 days (or 8 days after symptoms onset), although IgM may wane after 2–3 weeks, and IgG persists for a far longer period of time (471). A positive antibody test does not exclude the potential for the patient being infectious with COVID-19. The timing of the antibody testing is critical to accurate detection and interpretation: testing too soon after infection onset, or too late after infection resolution, can further increase risks of false-negative results. Similarly, immunity evidence wanes after vaccination.

Antibody testing may be performed for IgM or IgG to the spike protein, which will detect prior vaccination and/or prior infection. Antibody testing may also assess the viral nucleoprotein (which is not included in the mRNA vaccines), and which identifies prior COVID infection only.

It was aspirational that immune status testing (IgG, IgM) would eventually be the most important test for population-based risk assessments, such as herd immunity (472,473). This is no longer thought to be possible or true, whether considering post-vaccination or post-infection.

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% (474). 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 (475). Others have correlated titers with disease severity (464). 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 (476). Detectable immunity has been reported in more than 90% of patients at 5+ months (477), yet the total duration of immunity is still unclear. Duration of detectable immunity is naturally correlated with severity of infection (478,479).

Evidence also suggests immunoglobulins may not be measurable over time (480). 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 (481,482). Hence, a lack of measurable immunoglobulins may not indicate lack of immunity.

The CDC does not recommend antibody testing to determine immunity, risk of infection and/or use in decision-making for vaccination (470). The CDC advises use of these tests to include determining whether there are identifiable antibodies, assist in diagnosing multisystem inflammatory syndrome and monitor population immunity.

ANTIBODY TESTING FOR ASSESSING COVID-19 IMMUNE STATUS

Sometimes Recommended

Antibody testing is selectively recommended for determining whether there are identifiable antibodies, assisting in diagnosis of multisystem inflammatory syndrome, and monitoring population immunity. 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), time since last infection/vaccination, principles of testing, Bayes' theorem, and assessment of pre-test probability and post-test odds.

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

7.3. IMAGING

RADIOGRAPHS FOR THE DIAGNOSIS OF COVID-19

Recommended

Radiographs are recommended as part of the diagnostic evaluation of COVID-19. Radiographs are usually abnormal for individuals with pulmonary involvement. The prevalence of X-ray abnormalities peaks at 10–12 days after onset of symptoms (Rodriguez-Morales et al., 2020, Wong et al., 2020). 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 (Wong et al., 2020).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

COMPUTED TOMOGRAPHY (CT) FOR THE DIAGNOSIS OF COVID-19

Recommended

Computed tomography (CT) (including high-resolution CT) is recommended for the diagnostic evaluation of COVID-19 (Ishfaq et al., 2021).

Strength of evidence Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

CT abnormalities typically include bilateral patchy infiltrates and ground-glass opacities, and may progress to consolidation (Chan et al., 2020, Li et al., 2020, Li et al., 2020, Iwasawa et al., 2020, Liu et al., 2020) (Udugama et al., 2020, Sun, 2020). One report has suggested comparable sensitivity for screening in the emergency department for CT compared with ultrasound (Lieveld et al., 2020). One series reported 72% of cases with bilateral 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 (Xu et al., 2020). A large proportion of adult patients with COVID-19 who were hospitalized for care show persistent chest CT changes. A group of 80 patients with acute COVID-19 (mean age 59 yrs) who were discharged from the hospital between March and June 2020 were followed prospectively by symptoms and chest CT. At 3 months, 48% showed persistent ground-glass opacifications and 37% showed parenchymal bands. A follow-up chest CT at 1 year in 78% of those with 3-month CT abnormalities showed further improvement in 81% (Vijayakumar B, 2022). Another study showed that >50% of previously hospitalized survivors of COVID-19 infection show persistent chest CT abnormalities, including ground-glass opacities, parenchymal or subpleural bands, reticular abnormality and air trapping at 3 to 6 months post hospital discharge. Predictors of lung disease after COVID-19 include need for ICU admission, mechanical ventilation, higher inflammatory markers, longer hospital stay, and a diagnosis of ARDS (Solomon JJ, 2021).

8. TREATMENT RECOMMENDATIONS

8.1. OVERVIEW

Treatment is largely guided by randomized controlled trials (RCTs), and it continues to evolve as data are published. However, variants provide a significant challenge as each successive variant provides uncertainty regarding the translation of prior RCTs to application for treatment of the recent variant(s). There is a major need for RCT(s) that include comparative trials for therapeutics, especially for the very early phase of infection (24-48 hours after symptom onset) when use of effective treatments may obviate the need for hospitalization and prevent deaths. The design of at least one large, multi-armed RCT, including the available therapeutics with suggested efficacy (see below), is needed now to allow for enrollment at the beginning of the next variant surge. Results will determine which of several options is most effective, and used to calculate comparative efficacy. These trials are especially needed to prepare to treat the immunosuppressed populations, which may incur the worst outcomes in the subsequent variant waves.

There are numerous treatment guidelines available; although these guidelines tend to have similar recommendations, there are some differences regarding individual treatments (483,484,485,486,487,488,489,490,491,492,493,494). The FDA continues to provide unprecedented flexibility to accelerate the development of new drugs and testing.

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, some with evidence of efficacy and some without, have been used for treatment, including the following: ACE inhibitors, Adalimumab, anticoagulants, bamlanivimab, bebtelovimab, casirivimab/imdevimab, COVID-19 convalescent plasma, famotidine, fluvoxamine, low-molecular-weight heparin, molnupiravir, monoclonal antibodies, nirmatrelvir/ritonavir, azithromycin, baloxavir, baricitinib, chloroquine, colchicine, favipiravir, glucocorticosteroids, hydroxychloroquine, immunoglobulin, interferons, ivermectin, lopinavir/ritonavir, nitric oxide, paxlovid, ribavirin, remdesivir, sarilumab, siltuximab, statins, sotrovimab, thrombolytics, tocilizumab, zinc (495,496,497,498), vitamin C (499), and vitamin D (500,501,502,503). Many of these treatments have no quality evidence of efficacy, some had evidence of efficacy and became ineffective with subsequent (sub)variants, and some have evidence of a lack of efficacy. There is no clear evidence of lower risk of mortality with statin use (504). Vitamin D levels have been strongly correlated with COVID-19 disease severity (500,502,503); 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 (500).

Management of Hospitalized Adults with COVID-19

This ACOEM COVID-19 Guideline has transitioned to addressing topics including: 1) outpatient care, 2) occupationally relevant topics, and 3) preventive care. Hospitalized care is now beyond the scope of the guideline due primarily to the scarcity of affected workers who are hospitalized at this point with this endemic disease, rate of treatment evolution, and complexities involving select patient groups, such as patients who are pregnant. Interested readers are advised to consult the NIH guidelines for treatment of hospitalized patients (505).

There are five major therapeutic interventions for hospitalized patients: oxygen/respiratory support; anti-viral medications, anti-inflammatory/immune modulating medications, and anticoagulants. Some medications have varying recommendations depending on the severity of the disease (505).

Antiviral medications may have minimal roles in advanced pneumonia or ARDS, 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. Some antiviral medications are used for hospitalized patients, although several previously effective antiviral medications are particularly prone to becoming ineffective with subsequent waves of new variants. For example, bamlanivimab and casirivimab/imdevimab were previously approved; however, the omicron variant appears to evade these therapies. Thus, guidance for these medications continues to evolve.

Glucocorticosteroids are currently recommended among those requiring supplemental oxygen, as they have been shown in multiple quality trials to reduce mortality. Multiple agents have been studied to attempt to suppress the immune system, including the purported cytokine storm; most of the trials are centered around blocking interleukin-6 (IL-6). Yet, most quality data on IL-6 receptor antagonists have been negative. There is ongoing controversy regarding the contribution of cytokine storm to ARDS caused by COVID-19. Many cytokines are 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).

COVID-19 has a strong propensity towards procoagulant states, particularly among those severely affected and/or hospitalized; the degree of coagulopathy has been correlated with survival. Accordingly, treatment with anticoagulants, including as prophylaxis, with low-molecular weight heparin has been widely reported to be effective and is recommended in many patient groups (see NIH guideline) (505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520, 521,522,523,524).

Management of Adult Outpatients with COVID-19

A potential hierarchical approach for the treatment of outpatients with COVID-19 is as follows:

- Mild: No treatment unless high risk for progression to severe disease
- Moderate/severe:
    - Paxlovid (nirmatrelvir/ritonavir) *
    - Pegylated-lambda interferon*
    - Molnupiravir
    - Convalescent antibodies
    - Fluvoxamine
    - Vitamin D
    - Ivermectin
    - Hydroxychloroquine
    - Zinc

*these two treatments have quality evidence suggesting they have the strongest efficacy and are thus preferred over other potential treatments.

Additional treatments are being studied, including antiviral mouthwashes and nasal sprays (525,526)(527,528),(529,530)(531) melatonin (532,533,534,535,536,537,538), and others.

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 (58,539,540,541,542,543,544,545,546). See the ACOEM Guidelines on Anxiety and Depressive Disorders for recommendations on assisting with those issues. An association between adverse mental health and financial concerns has been noted (547). Data from a small autopsy study suggest findings similar to Alzheimer disease in the brains of those deceased from COVID-19 (548).

8.2. PAXLOVID

Paxlovid (nirmatrelvir/ritonavir) has been approved by the U.S. FDA through an emergency use authorization for the treatment of COVID-19 patients (63).

PAXLOVID (NIRMATRELVIR/RITONAVIR) FOR TREATMENT OF COVID-19

Recommended

Paxlovid (nirmatrelvir/ritonavir) is recommended for the treatment of patients with COVID-19, particularly within 3 days of symptom onset.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Outpatients with moderate to severe symptoms who are within 5 days, but ideally within 3 days of onset of symptoms (Mahase, 2021). Also indicated for those with mild symptoms and risks of adverse outcomes or those who are trending towards worsening of symptoms. The FDA EUA has not authorized use for treatment initiation among patients requiring hospitalization for severe or critical COVID-19 (Administration, 2022).

Benefits

89% reduction in the probability of hospitalization and/or death (Mahase, 2021).

Harms

Rebound cases may occur, with a large database electronic medical record study measuring symptoms recurrence as 2.3% and 5.9% at 7- and 30-days (Wang L, 2022). Adverse effects include diarrhea, altered taste/small, hypertension, myalgia, elevated hepatic transaminases, clinical hepatitis, jaundice. There are significant adverse drug-drug Interactions especially including those dependent on CYP3A for clearance. Drugs recommended to be not taken with paxlovid include alfuzosin, pethidine, piroxicam, propoxyphene, ranolazine, amiodarone, dronedarone, flecainide, propafenone, quinidine, colchicine, lurasidone, pimozide, clozapine, dihydroergotamine, ergotamine, methylergonovine, lovastatin, simvastatin, sildenafil for pulmonary arterial hypertension (PAH), triazolam, oral midazolam, apalutamide, carbamazepine, phenobarbital, phenytoin, rifampin, and St. John's Wort (Drugs.com, 2021).

Frequency/Dose/Duration

Paxlovid (nirmatrelvir/ritonavir) 300mg nirmatrelvir (2-150mg tablets)/100mg (1-100mg tablet) BID for 5 days (Administration, 2022).

Indications for discontinuation

Completion of a course of treatment, intolerance of adverse effects.

Rationale

A moderate-quality RCT found no deaths in the nirmatrelvir/ritonavir group (0 vs. 13 in the placebo group), while the risk of hospitalization was 9-fold higher in the placebo group (7.01% vs. 0.77%), with additional evidence of lower viral loads when used within 3 days of symptoms onset (Hammond et al., 2022, Mahase, 2021). A systematic review suggested efficacy (Reis S, 2022). Paxlovid (nirmatrelvir/ritonavir) is non-invasive, has considerable adverse effects, is high cost, has strong evidence in one trial of considerable efficacy and is selectively recommended for those non-hospitalized with at least moderate disease and/or risk of severe outcomes and/or having a worsening trend in symptoms.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 using the following terms: Paxlovid, Nirmatrelvir, Nirmatrelvir and Ritonavir Drug Combination, Nirmatrelvir and 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 0 articles in PubMed, 0 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 122 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, 2 from Google Scholar, and 0 from other sources. Of the 2 article considered for inclusion, 0 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.

8.3. INTERFERON

Interferon has been used both as sole therapy and combination therapy for the treatment of patients with COVID-19 (64) (65).

INTERFERON-PEGYLATED LAMBDA FOR COVID-19

Recommended

Early treatment of COVID-19 with pegylated interferon lambda is recommended.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Symptomatic COVID-19 disease, especially for those at risk of progression, hospitalization and mortality. The quality trial enrolled patients if they were within 7 days of symptoms onset and if they had at least one indicator of high risk for progression (50+ years of age, DM, HTN, cardiovascular disease, lung disease, smoking, BMI >30kg/m2, organ transplantation, chronic stage IV+ renal disease, immunosuppressive therapy including 10+mg of prednisone or equivalent, cancer diagnosis in the prior 6 months, receipt of chemotherapy for cancer) (Reis, 2023). This trial also enrolled those with severe symptoms but no risks for severe outcome.

Benefits

Reduced risk of hospitalization or emergency department visit (51% reduced risk) (Reis 2023). The deaths were non-significantly lower as well (0.1 vs. 0.4, RR=0.39) (Reis, 2023).

Harms

Fever, chills, headache, myalgia, nausea, vomiting. A total of 4.8% vs. 3.4% (placebo) risk of serious adverse event during treatment reported in the sole quality trial (Reis, 2023).

Frequency/Dose/Duration

One treatment course of 180ug of IV pegylated interferon lambda (Reis, 2023).

Rationale

One high-quality trial found the early treatment of outpatients who are either at high risk of severe outcomes or who had severe symptoms of COVID-19, incurred a reduced risk of hospitalization or emergency department visit (51% reduced risk) (Reis, 2023). The deaths were non-significantly lower as well (0.1 vs. 0.4, RR=0.39) (Reis, 2023). Pegylated interferon is invasive, has some adverse effects,

is high cost, and has evidence of considerable efficacy and thus is selectively recommended for those outpatients within 7 days of symptoms onset who are at increased risk of severe outcomes and/or having severe symptoms.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar from January 2019 to March 2023 using the following terms: Pegylated Interferon Lambda; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 2 articles in PubMed, 2 in CINAHL, 4 in Cochrane Library, 529 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 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.

8.4. MOLNUPIRAVIR

Molnupiravir has been approved by the U.S. FDA through an emergency use authorization for the treatment of COVID-19 patients (66,67,68,69)(70).

MOLNUPIRAVIR FOR THE TREATMENT OF COVID-19

Recommended

Molnupiravir is recommended for the treatment of patients with COVID-19, particularly within 3 days of symptom onset, especially if there is a reason nirmatrelvir/ritonavir (Paxlovid) cannot be administered.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Although there are no head-to-head comparative trials, outcomes data suggest stronger efficacy for nirmatrelvir/ritonavir (Paxlovid). However, regarding molnupiravir, patients with moderate to severe symptoms who are within 5 days, but ideally within 3 days, of onset of symptoms, may be candidates (Fischer et al., 2021, Painter et al., 2021, Khoo et al., 2021)(Jayk Bernal et al., 2022). Also indicated for those with mild symptoms and risks of adverse outcomes or those who are trending towards worsening of symptoms. The FDA EUA has not authorized use for treatment initiation among patients requiring hospitalization for severe or critical COVID-19 (Administration et al., 2022).

Data suggest lack of efficacy among those with known positive SARS-CoV-2 nucleocapsid antibody levels at baseline, with data favoring placebo (Jayk Bernal et al., 2022).

Benefits

One estimate is a 48% reduction in the probability of hospitalization and/or death (Jayk Bernal et al., 2022). However, a network analysis found evidence of publication bias with a third of global data missing, thus suggesting that reports indicating a reduced risk of hospitalization may not be accurate (Lawrence JM, 2023).

Harms

Adverse effects include diarrhea, nausea, dizziness. Not recommended for use during pregnancy, in children under 18 years of age due to potential altered bone/cartilage growth, and among women who are breastfeeding (Administration, 2022).

Frequency/Dose/Duration

Molnupiravir 800mg (4-200mg tablets) BID for 5 days (Administration, 2022).

Indications for discontinuation

Completion of a course of treatment, intolerance of adverse effects.

Rationale

One moderate-quality RCT reported a 48% reduction in risk of hospitalization and/or death; there also was 1 death with molnupiravir vs. 9 in the placebo group (Jayk Bernal et al., 2022). One trial among immunocompromised patients found marked reductions in hospitalization/death and improved inflammatory markers (Johnson et al., 2022, Johnson et al., 2023). However, another trial among "highly vaccinated" individuals found a lack of efficacy (Butler et al., 2023). Another RCT reported marked reductions in viral detection at 3 days of treatment with a dose of 800mg (2 vs 17%, p=0.02), while slower but superior clearance to placebo was shown with 400mg (Fischer et al., 2021). Another trial suggested faster viral clearance (Zou et al., 2022). Two early-phase trials in combination with the clinical trials suggest low toxicity and a dose of 800mg (Khoo et al., 2021, Painter et al., 2021, Fischer et al., 2021) (Jayk Bernal et al., 2022). Another trial suggested faster clinical resolution (Johnson et al., 2022). Some trials have suggested a lack of reduced risk of hospitalization (Butler et al., 2023, Khoo et al., 2023). A subanalysis of a randomized trial that assessed the immunosuppressed patients found evidence suggestive of potential efficacy for that select population (Johnson et al., 2023). Most RCTs suggest efficacy of molnupiravir to prevent hospitalization and/or death. It is non-invasive, has low adverse effects, is high cost, and is recommended, although generally after consideration of nirmatrelvir/ritonavir (Paxlovid) which has considerably strong evidence of efficacy.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 using the following terms: Molnupiravir, Lagevrio, EIDD-2801, MK-4482; 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 10 articles in PubMed, 141 in Scopus, 1 in CINAHL, 24 in Cochrane Library, 574 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 3 randomized trials and 1 systematic review met the inclusion criteria. There were no exclusion criteria.

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

8.5. REMDESIVIR

Remdesivir has been used to treat COVID-19 (71,72,73,74,75,76,77,78) and is recommended by other systematic reviews (79).

REMDESIVIR FOR THE TREATMENT OF COVID-19

Sometimes Recommended

Remdesivir is recommended as generally a second-line agent for selective use in the first 7 days of symptoms among patients at risk of progression.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Patients at least 60 years of age and/or at least one risk factor for disease progression (e.g., HTN, CV disease, DM, obesity (BMI>30mg/kg2), immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer or sickle cell disease) (Gottlieb RL, 2022).

Benefits

Reduced risk of hospitalization. Previously thought to reduce risk of death, but that has not been clearly demonstrated (Kaka et al., 2021).

Harms

Increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension. However, the largest RCT did not report significantly increased adverse events in any category (Beigel et al., 2020).

Frequency/Dose/Duration

Remdesivir 200 mg IV on day 1, then 100 mg QD on days 2 and 3 (Gottlieb RL, 2022).

Indications for discontinuation

Completion of a course, intolerance, adverse effect.

Rationale

An RCT found non-hospitalized patients at high risk given early remdesivir within 7 days of symptoms onset had an 87% lower risk of hospitalization or death (Gottlieb RL, 2022).

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 (Wang et al., 2020). A larger, moderate-quality NIH trial showed modest efficacy, including 31% shorter ICU stays and earlier clinical improvements, although the finding was discovered after the endpoint was changed. A RCT comparing remdesivir with standard care found a trend towards better results with a 5-day course of remdesivir (Spinner et al., 2020). However, other RCTs found a lack of efficacy (WHO, 2020) (Ader et al., 2021, Mahajan et al., 2021) and another found lack of efficacy to either speed viral clearance and/or improve mortality among hospitalized patients (Barratt-Due et al., 2021). One trial suggested reduced hospital stay but other outcomes were negative (Abd-Elsalam et al., 2021). None of the RCTs was able to show statistically improved survival, although the NIH trial trended toward improved survival (Beigel et al., 2020). One small trial found no significant differences between remdesivir and standard care both with glucocorticoids and heparin (Mahajan et al., 2021). There is one case series suggesting a fairly low death rate (13%) (Grein et al., 2020) and another non-randomized study suggesting potential efficacy (Antinori et al., 2020). A low-quality RCT found no difference between 5 and 10 days of treatment (Goldman et al., 2020). A trial suggested remdesivir plus interferon beta-1a was not superior to remdesivir alone among hospitalized COVID-19 patients with evidence of pneumonia and hypoxemia (Kalil et al., 2021), while another found baricitinib plus remdesivir superior to remdesivir alone for comparable patients (Kalil et al., 2021). There is evidence that remdesivir inhibits viral replication in vitro studies (Wang et al., 2020). It is possible that remdesivir is more effective if administered in the viral replication stage (Cubeddu et al., 2021, Glaus et al., 2020). Multiple systematic reviews largely confirm the above findings, particularly regarding the evidence supporting early use rather than use while ventilated (Consortium, 2022, Kaka, 2022, Tanni SE, 2022, Lee TC, 2022, Hung DT, 2022), while one review supported a reduction in mortality (Lee TC, 2022).

Remdesivir is invasive (IV), has minimal adverse effects, is high cost, has some evidence of efficacy for the early treatment of patients at risk of progression, and thus is selectively recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 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 471 articles in PubMed, 9083 in Scopus, 112 in CINAHL, 230 in Cochrane Library, 28800 in Google Scholar, and 0 from other sources†. We considered for inclusion 41 from PubMed, 3 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 47 articles considered for inclusion, 5 randomized trials and 21 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.

8.6. CONVALESCENT COVID-19 ANTIBODIES

Convalescent COVID-19 antibodies have been used to treat COVID-19 (549) (550) (551) (552) (553) (554) (555) (556) (557) (558) (559) (560) (561) (562) (563) (564) (565) (566) (567) (568). As the antibodies developed tend to be focused on that inciting variant, use in waves of subsequent variants would naturally need to be proven effective.

CONVALESCENT COVID-19 ANTIBODIES FOR TREATMENT OF COVID-19

Sometimes Recommended

Convalescent antibodies are selectively recommended for the early treatment of patients with COVID-19. Selective use may be recommended when both of: 1) the antibodies in the plasma address the same variant the patient has, and 2) when there is not another good alternative treatment available shown to be effective. There are alternate treatments that are easier to administer and may be more efficacious (e.g., Paxlovid).

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

COVID-19 patients with severe disease and symptoms, or patients at high risk of severe disease. Should generally have failed or be ineligible for a highly effective therapy (e.g., Paxlovid).

Benefits

Theoretically reduced severity and improved survival.

Harms

Allergic reactions. Rare and potentially serious adverse effects involving the lungs and heart.

Frequency/Dose/Duration

One transfusion over one hour by day 8.

Rationale

Two high-quality RCTs suggest lack of efficacy of convalescent antibodies for treatment of COVID-19 to prevent progression (Alemany A, 2022, Ortigoza MB, 2021). However, one sham-controlled RCT suggests efficacy of early outpatient treatment of COVID-19 within 7 days of symptoms onset, with a resulting 54% reduction in risk of hospitalization (Sullivan et al., 2020). This study was done before widespread emergence of the omicron variant. Thus, efficacy with current variants is unclear. Matching of the current variant to the donor variant would seem ideal if not essential, although that may have to be done by probability of the circulating variant(s).

There are many quality RCTs and nearly all reported lack of efficacy (Li et al., 2020, Simonovich et al., 2020, AlQahtani et al., 2020, Agarwal et al., 2020)(O'Donnell et al., 2021, Sekine et al., 2021, Devos et al., 2021, Horby et al., 2021, Gharbharan et al., 2020, Bennett-Guerrero et al., 2021, Balcells et al., 2021)(Bégin et al., 2021)(Körper et al., 2021)(Avendaño-Solà et al., 2020)(Duan et al., 2020)(Chen et al., 2021)(Gharbharan et al., 2021)(Tabarsi et al., 2021). One moderate-quality trial suggested potential reduction in the need for mechanical ventilation (Avendaño-Solà et al., 2020). A pilot study suggested efficacy (Bajpai et al., 2021). However, a retrospective cohort study suggested significantly lower mortality among hematological cancer patients administered convalescent plasma (Thompson, 2021).

Convalescent antibodies are invasive, have adverse effects, and are costly. Data conflict regarding survival benefits, with quality data suggesting treatment within 9 days is associated with efficacy and thus convalescent antibodies are selectively recommended. There are alternate treatments that are easier to administer and may be more efficacious (e.g., Paxlovid).

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 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; non-randomized controlled trials as topics. We found and reviewed 279 articles in PubMed, 10,212 in Scopus, 18 in CINAHL, 45 in Cochrane Library, 23,060 in Google Scholar, and 0 from other sources†. We considered for inclusion 17 from PubMed, 0 from Scopus, 0 from CINAHL, 1 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 20 articles considered for inclusion, 10 randomized trials and 10 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.

8.7. FLUVOXAMINE

Fluvoxamine has been used for the treatment of COVID-19 patients (80)(81)(82). Observational evidence suggests that two SSRI antidepressants, fluvoxamine and fluoxetine (but not other SSRIs), reduce mortality by 10% (83).

FLUVOXAMINE FOR THE TREATMENT OF COVID-19

Sometimes Recommended

Fluvoxamine is selectively recommended for the treatment of patients with COVID-19, particularly within 7 days of symptoms onset. However, other medications have better evidence of stronger efficacy and are thus recommended as first-line treatment (e.g., Paxlovid)

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Outpatients with moderate to severe symptoms who are within 7 days of onset of symptomatic disease (Lenze et al., 2020, Reis et al., 2022). Indicated for those with mild symptoms and risks of adverse outcomes or those who are trending towards worsening of symptoms. However, other medications have better evidence of stronger efficacy and are thus higher priorities (e.g., Paxlovid).

Benefits

Reduces probability of clinical deterioration, including hospitalization (Lenze et al., 2020, Reis et al., 2022).

Harms

Headache, nausea, diarrhea, dry mouth, dizziness, increased sweating, feeling nervous, restlessness, fatigue, insomnia.

Frequency/Dose/Duration

Fluvoxamine 100mg TID for 15 days (Lenze et al., 2020).

Indications for discontinuation

Completion of a course of treatment, intolerance of adverse effects, recovery

Rationale

One high-quality trial comparing ivermectin, metformin and fluvoxamine at an average 4.6-5 days after symptoms onset found none effective at reducing risk of hypoxemia, emergency department visit, hospitalization or death (Bramante, 2022) Two moderate-quality RCTs both suggest efficacy of fluvoxamine used within 7 days of symptoms onset to prevent clinical deterioration including hospitalization (Lenze et al., 2020, Reis et al., 2022). One trial found a 32% reduction in risk of hospitalization and/or going to the emergency room (Reis et al., 2022) and the other suggested fluvoxamine was associated with less clinical deterioration at 15 days compared with placebo (0% vs. 8.7%, p=0.009), although there also was no difference in the most severe symptom changes between the two groups (Lenze et al., 2020). Both trials suggest efficacy to prevent clinical worsening. A Cochrane review suggested evidence of efficacy but of low certainty (Nyirenda, 2022). Fluvoxamine is non-invasive, has low adverse effects, is low cost, and has conflicting evidence of efficacy, with inefficacy shown at 5 days, and thus is recommended for early use within 3 days of symptoms onset. However, other medications have better evidence of stronger efficacy and are thus higher priorities (e.g., Paxlovid).

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 using the following terms: Fluvoxamine, Fluvoxamine Maleate; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized

controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 6 articles in PubMed, 203 in Scopus, 9 in CINAHL, 7 in Cochrane Library, 1367 in Google Scholar, and 0 from other sources†. We considered for inclusion 3 from PubMed, 4 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 2 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.

8.8. HYDROXYCHLOROQUINE OR CHLOROQUINE

Hydroxychloroquine has been used for the treatment of COVID-19 (495,498,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,130). A meta-analysis of "early treatment" included studies well beyond the peak of viral replication (609).

There also are many in vitro studies suggesting antiviral activity (610,611,612,613,614,615,616,617,618). Chloroquine also has been used for the treatment of COVID-19 (619). Hydroxychloroquine has been used for prophylaxis for COVID-19, most typically among healthcare workers (606,620).

There are many quality trials suggesting lack of efficacy for later use in a clinical COVID course beyond approximately 3 days. Most data of early-use (e.g., especially in the first 48 hours) hydroxychloroquine (HCQ) suggest efficacy early in the symptomatic phase. Unfortunately, there are few studies and a high need for assessing the efficacy of antiviral medications within the first 1–2 days of symptom onset when viral replication is highest; there may be comparable parallels with influenza medications used within 48 hours of symptoms onset. Earlier use has been found to be more effective with other antiviral medication use (e.g., molnupiravir, remdesivir).

HYDROXYCHLOROQUINE FOR TREATMENT OF COVID-19 - USE IN FIRST 3 DAYS OF SYMPTOMS

Sometimes Recommended

Hydroxychloroquine (HCQ) is selectively recommended for use in the first 3 days of symptom onset. However, evidence of efficacy appears far stronger for nirmatrelvir/ritonavir (Paxlovid), and may also be stronger for molnupiravir. Thus, HCQ would at best be a third-line option in those not able to take the medications with stronger evidence of efficacy.

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

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.

Benefits

Benefits do not appear as strong as those associated with nirmatrelvir/ritonavir. However, there may be a reduced risk of hospitalization. Meta-analysis evidence of a 24% reduction in composite risk of COVID-19 infection, hospitalization, and death (Ladapo et al., 2020). Earlier clearance of pneumonia on CT scan (CHEN et al., 2020).

Harms

Negligible for most patients undergoing short-course use (Lofgren et al., 2020). Gastrointestinal symptoms occur above rates of placebo. Prior concerns about prolonged corrected QT intervals, and thus arrhythmias (Magagnoli et al., 2020, Chorin et al., 2020), 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 (Marmor et al., 2016).

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 (Carlucci et al., 2020). 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 (Yao et al., 2020).
- Hydroxychloroquine 400mg BID x 1 day, then 400mg QD for 4 day.
- Hydroxychloroquine 200mg BID x 5 days (CHEN et al., 2020)
- Hydroxychloroquine 200mg TID x 10 days (Gautret et al., 2020)
- Hydroxychloroquine 200mg TID x 10 days plus azithromycin 500mg x 1 day then 250mg QD x 4 days (Gautret et al., 2020)
- Hydroxychloroquine 600mg BID x 1 day, then 400mg QD for 4 days

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

Rationale

Late use of HCQ (>3 days) has been assessed in many quality RCTs among hospitalized and/or ICU patients. These trials consistently show late use of HCQ does not improve clinical outcomes, including mortality (Cavalcanti et al., 2020, Ulrich et al., 2020, Lyngbakken et al., 2020) (Self et al., 2020, Schwartz et al., 2021) (Johnston et al., 2021)(Reis et al., 2021, Axfors et al., 2021)(Beltran Gonzalez et al., 2022) or viral clearance (Barratt-Due et al., 2021). One trial of HCQ with and without AZT found no efficacy although there was a trend towards faster viral clearance with HCQ (Johnston et al., 2021). Another comparative trial found comparable (in)efficacy of HCQ and AZT (Brown et al., 2021). One trial with mostly late treatment patients found lack of benefit with Favipiravir with and without HCQ (Bosaeed et al., 2021). Two open-label trials reported worse outcomes with either HCQ or CQ (Réa-

Neto et al., 2021) or HCQ (Arabi et al., 2021). One trial reported a trend toward earlier viral clearance, but did not describe the stage of treatment and had many patients with significant disease (AlQahtani et al., 2022). There are observational studies suggesting more than doubling survival with combined HCQ/AZT among hospitalized patients on ventilators (Smith et al., 2021). Because there is reasonably consistent high- and 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. Early use of HCQ has been assessed in multiple studies that range from pre-diagnosis to within a few days of symptom onset (Ladapo et al., 2020). These trials are naturally individually underpowered for severe 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 (Ladapo et al., 2020). One other RCT trended towards reduced hospitalization and time to symptom resolution (Mitjà et al., 2021) and another showed earlier resolution of cough (Rodrigues et al., 2021). 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 (Lammers et al., 2020). A study of 1,274 outpatients in a propensity-matched cohort from New Jersey found a 31.2% reduced risk of hospitalization (Ip et al., 2021). An observational study found an 84% ($p<0.001$) reduction in risk of hospitalization and risk of death was also 80% ($p=0.12$) reduced among those treated early with HCQ, zinc, and AZT (Derwand et al., 2020). An RCT with patients averaging 4 days of symptoms onset comparing ivermectin plus zinc to HCQ, darunavir/ritonavir plus zinc found equivalency (Nimitvilai et al., 2022). A trial of mostly late symptoms onset (61.2% 4+ days) found a lack of efficacy (Avezum et al., 2022). A trial of mild/moderate COVID-19 patients without including reported symptoms onset found earlier viral clearance with favipiravir or hydroxychloroquine compared with standard of care (AlQahtani et al., 2022).

One early-use trial found non-significant reductions, with 20% being symptomatic at 14 days and a 60% reduced risk of death (Skipper et al., 2020). Another trial of HCQ used within 4 days of high-risk exposure found a 17% reduced risk of subsequent infection (Boulware et al., 2020). Another trial of once-weekly or twice-weekly HCQ as pre-exposure prophylaxis among HCWs found a non-significant 26–28% reduced risk of infection (Rajasingham et al., 2020). A randomized study among mild and asymptomatic patients with a median 4-5 days to enrollment found lack of efficacy and lack of viral load reduction (Nimitvilai et al., 2022). A large series of 2,111 hospitalized patients found HCQ plus AZT reduced mortality by 32% (Lagier et al., 2022). Because there is quality evidence of efficacy for the early use of HCQ, it is recommended for these select patients. However, evidence of efficacy appears far stronger for nirmatrelvir/ritonavir (Paxlovid), and may also be stronger for molnupiravir. Thus, HCQ would at best be a third-line option in those not able to take the medications with stronger evidence of efficacy.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2020 to October 2021 using the following terms: Hydroxychloroquine; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 153 articles in PubMed, 25,203 in Scopus, 1,779 in CINAHL, 18 in Cochrane Library, 10,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 11 from PubMed, 1 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 17 from Google Scholar, and 0 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 criteria. There were no exclusion criteria.

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

HYDROXYCHLOROQUINE FOR TREATMENT OF COVID-19 - USE BEYOND FIRST 3 DAYS OF SYMPTOMS

Not Recommended

Hydroxychloroquine (HCQ) is not recommended for the treatment of patients with COVID-19 after the first 3 days of symptoms (Oxford, 2020).

Strength of evidence Moderately Not Recommended, Evidence (B)
Level of confidence Moderate

Rationale

Late use of HCQ (>3 days) has been assessed in many quality RCTs among hospitalized and/or ICU patients. These trials consistently show late use of HCQ does not improve clinical outcomes, including mortality (Oxford, 2020, Cavalcanti et al., 2020, Ulrich et al., 2020, Lyngbakken et al., 2020, Abd-Elsalam et al., 2020, Horby et al., 2020) (Self et al., 2020, Schwartz et al., 2021) (Johnston et al., 2021)(Axfors et al., 2021, Reis et al., 2021)(Beltran Gonzalez et al., 2022) (WHO, 2022) or viral clearance (Barratt-Due et al., 2021). One trial of HCQ with and without AZT found no efficacy although there was a trend towards faster viral clearance with HCQ (Johnston et al., 2021). Another comparative trial found comparable (in)efficacy of HCQ and AZT (Brown et al., 2021). One trial with mostly late treatment patients found lack of benefit with Favipiravir with and without HCQ (Bosaeed et al., 2021). Two open-label trials reported worse outcomes with either HCQ or CQ (Réa-Neto et al., 2021) or HCQ (Arabi et al., 2021). There are observational studies suggesting more than doubling survival with combined HCQ/AZT among hospitalized patients on ventilators (Smith et al., 2021) and other hospitalized patients (Lagier et al., 2022). Because there is reasonably consistent high- and 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.

Early use of HCQ has been assessed in multiple studies that range from pre-diagnosis to within a few days of symptom onset (Ladapo et al., 2020). These trials are naturally individually underpowered for severe 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 (Ladapo et al., 2020). One other RCT trended towards reduced hospitalization and time to symptom resolution (Mitjà et al., 2021) and another showed earlier resolution of cough (Rodrigues et al., 2021). 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 (Lammers et al., 2020). A study of 1,274 outpatients in a propensity-matched cohort from New Jersey found a 31.2% reduced risk of

hospitalization (Ip et al., 2021). An observational study found an 84% (p<0.001) reduction in risk of hospitalization and risk of death was also 80% (p=0.12) reduced among those treated early with HCQ, zinc, and AZT (Derwand et al., 2020).

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: Hydroxychloroquine; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 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 criteria. There were no exclusion criteria.

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

CHLOROQUINE FOR TREATMENT OF COVID-19 - USE IN FIRST 3 DAYS OF SYMPTOMS

No Recommendation

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)
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 (Lammers et al., 2020). Thus, there is no recommendation for use of chloroquine for early treatment of COVID, and, by analogy to hydroxychloroquine, chloroquine is not recommended for late treatment or for 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 October 2021 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 766 articles in PubMed, 18,961 in Scopus, 33 in CINAHL, 1,279 in Cochrane Library, 9,500 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. Of the 0 articles considered for inclusion, 0 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.

CHLOROQUINE FOR TREATMENT OF COVID-19 - USE BEYOND FIRST 3 DAYS OF SYMPTOMS

Not Recommended

Chloroquine is not recommended for the treatment of patients with COVID-19 after the first 3 days of symptoms (Oxford, 2020).

Strength of evidence Not Recommended, Evidence (C)
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 (Lammers et al., 2020). Thus, by analogy to hydroxychloroquine, chloroquine is not recommended for treatment of hospitalized COVID-19 patients or patients after 5 days of symptoms. 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 October 2021 using the following terms: Chloroquine, Prophylaxis; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 766 articles in PubMed, 18,961 in Scopus, 33 in CINAHL, 1,279 in Cochrane Library, 9,500 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. Of the 0 articles considered for inclusion, 0 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.

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

One systematic review and meta-analysis concluded a benefit of hydroxychloroquine could not be ruled out and the trials for prophylaxis had been prematurely terminated (García-Albéniz, 2022).

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 (Boulware et al., 2020); thus, underpowering is possible. One large RCT found a 21% reduction in risk of COVID-19 (Seet et al., 2021). A cluster-randomized trial found a nonsignificant 8.1% reduction in PCR-confirmed COVID (Mitja, 2020). Some RCTs found lack of efficacy for prophylaxis among healthcare workers (Abella et al., 2020) (Syed et al., 2021), whereas two others trended towards modest efficacy (Rojas-Serrano et al., 2021, Naggie et al., 2021). Other RCTs found lack of efficacy (Barnabas et al., 2021)(Mitjà et al., 2021). An underpowered RCT with 11 vs. 12 cases found no differences (Vijayaraghavan et al., 2022).

A meta-analysis was performed with multiple RCTs that included early use of HCQ, ranging from pre-diagnosis to within a few days of symptoms onset (Ladapo et al., 2020). 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 (Ladapo et al., 2020). A systematic review found weak and conflicting evidence (Hernandez et al., 2020). As evidence for widespread prophylactic use is weak and somewhat conflicting, 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: 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 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; non-randomized 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 non-randomized trial, and 2 systematic review met the inclusion criteria. There were no exclusion criteria.

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

8.9. IVERMECTIN

Ivermectin has been used for the treatment of COVID-19 (84)[(85) (86) (87) (88) (89) (90) (91). There is experimental evidence of its ability to inhibit viral replication (92).

IVERMECTIN FOR THE TREATMENT OF COVID-19 - LATE ONSET OF SYMPTOMS

Not Recommended

Ivermectin is not recommended for late treatment of COVID-19 (Podder et al., 2020, Chaccour et al., 2020, Krolewiecki et al., 2020, Niaee et al., 2021, Chowdhury et al., 2020, Hashim et al., 2020, Ahmed et al., 2020, Alam et al., 2020, Behera et al., 2020, Cadegiani et al., 2020, Camprubí et al., 2020, Gorial et al., 2020, Heidary et al., 2020, Ortiz-Muñoz et al., 2020, Padhy et al., 2020, Rajter et al., 2020, Soto-Becerra et al., 2020).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are many RCTs assessing ivermectin, with most assessing the treatment of late symptoms. Trials used different dose regimens (including single dose), in patients of varying symptoms duration. One metanalysis of controlled studies reported 61% reductions in mortality, time to recovery, and time to viral clearance (Marik et al., 2021).

There are no quality trials for the early treatment (within 1-2 days of symptoms onset). There are several trials assessing the use of ivermectin for intermediate-term treatment (e.g., within 3-5 days of the onset of symptoms).

One high-quality trial comparing ivermectin, metformin and fluvoxamine at an average 4.6-5 days after symptoms onset found none effective at reducing risk of hypoxemia, emergency department visit, hospitalization or death (Bramante, 2022). One high-quality trial of a combination of a single dose of ivermectin 12 mg and doxycycline 100mg BID for 5 days found 51% reduced risk of progression to serious disease and recovery averaged 2 fewer days (Mahmud et al., 2021). One comparative trial found superiority of ivermectin 12mg to Ivermectin 6 mg to lopinavir/ritonavir for viral clearance (Babalola et al., 2021). Another high-quality trial found a non-significant 33% reduced risk of hospitalization among those treated with weight-dependent dosing of Ivermectin (e.g., among 80-110kg, 18mg and another 18mg at 24 hrs) at 3-6 days of symptoms (Vallejos et al., 2021). Another RCT found lack of efficacy (Lim et al., 2022), while another found efficacy (Babalola et al., 2021)(Babalola 2021). Three RCTs of treatment within 5 days of symptoms onset showed an association of ivermectin with subsequently lower viral loads (Chaccour et al., 2020, Krolewiecki et al., 2020)(Biber et al., 2021), although one trial of a single dose of Ivermectin 12mg or 24mg failed to accelerate viral clearance (Mohan et al., 2021). Thus, most studies of early use of Ivermectin found efficacy. As Ivermectin is non-invasive, has low adverse effects, is low cost and there is evidence of efficacy, it is recommended for treatment of early COVID-19 cases.

Late treatment (>5 days) with Ivermectin has been assessed in multiple RCTs). There is one moderate-quality RCT comparing usual care to usual care plus ivermectin, which found no benefits (Podder et al., 2020). Another with mostly late treatment found lack of efficacy (Reis et al., 2022). Another found a lack of benefit when started an average 5 days after symptom onset (López-Medina et al., 2021). Another trial found lack of benefits (Beltran-Gonzalez et al., 2021). However, one trial found improvements in duration of symptoms and reduced hospitalization (Shahbaznejad et al., 2021). Another RCT reported faster recovery and reduced mortality when Ivermectin was added to HCQ/AZT/Favipiravir (Okumuş et al., 2021). One trial found lack of statistical significance for viral clearance, although there were 0 deaths in the ivermectin vs. 4 in the placebo groups; there were 100% discharges in the Ivermectin vs. 93% in the placebo groups, p=0.045 (Ravikirti et al., 2021). There are some RCTs treating patients of unclear symptoms duration. A comparative trial of HCQ, CQ and Ivermectin among hospitalized, severely-affected patients of unclear symptoms duration found lack of significant differences. One trial suggested no differences in duration of hospitalization (Marques et al., 2022). One trial suggested accelerated viral clearance . A trial among patients of unclear severity (severely affected per abstract, mildly affected per Table) found lack of efficacy (Saxena et al., 2021).

As most data suggest a lack of efficacy, ivermectin is not recommended for the treatment of late COVID-19 disease.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2020 to October 2021 using the following terms: Ivermectin; 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 72 articles in PubMed, 1 in Scopus, 22 in CINAHL, 711 in Cochrane Library, 7730 in Google Scholar, and 26 from other sources†. We considered for inclusion 13 from PubMed, 0 from Scopus, 0from CINAHL, 0 from Cochrane Library, 14 from Google Scholar, and 0 from other sources. Of the 28 articles considered for inclusion, 13 randomized trials and 14 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.

IVERMECTIN FOR THE TREATMENT OF COVID-19 - WITHIN 3 DAYS OF SYMPTOM ONSET

No Recommendation

There is no recommendation for or against the use of Ivermectin for early treatment of COVID-19, within 3 days of symptom onset. However, there is quality evidence of strong efficacy for other treatments that should be a higher priority when possible (e.g., Paxlovid). Ivermectin is not recommended for late treatment of COVID-19 (Podder et al., 2020, Chaccour et al., 2020, Krolewiecki et al., 2020, Niaee et al., 2021, Chowdhury et al., 2020, Hashim et al., 2020, Ahmed et al., 2020, Alam et al., 2020, Behera et al., 2020, Cadegiani et al., 2020, Camprubí et al., 2020, Gorial et al., 2020, Heidary et al., 2020, Ortiz-Muñoz et al., 2020, Padhy et al., 2020, Rajter et al., 2020, Soto-Becerra et al., 2020).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Rationale

There are many RCTs assessing ivermectin. Trials are fairly heterogenous, and used different dose regimens (including single dose), in patients of varying symptoms duration. One metanalysis of controlled studies reported 61% reductions in mortality, time to recovery, and time to viral clearance (Marik et al., 2021). However, there are few trials assessing use of ivermectin solely for early treatment (e.g., within 3 days). One high-quality trial involving patients at symptoms day 3-5 at enrollment with a combination of a single dose of ivermectin 12 mg and doxycycline 100mg BID for 5 days found 51% reduced risk of progression to serious disease and recovery averaged 2 fewer days (Mahmud et al., 2021). Another high-quality trial found a non-significant 33% reduced risk of hospitalization among those treated with weight-dependent dosing of Ivermectin (e.g., among 80-110kg, 18mg and another 18mg at 24 hrs) at 3-6 days of symptoms (Vallejos et al., 2021). Three RCTs of treatment within 5 days of symptoms onset showed an association of ivermectin with subsequently lower viral loads (Chaccour et al., 2020, Krolewiecki et al., 2020)(FDA, 2022), although one trial at a median of symptoms days 4-5 (3-7) with a single dose of Ivermectin 12mg or 24mg failed to accelerate viral clearance (Mohan et al., 2021). One high-quality trial comparing ivermectin, metformin and fluvoxamine at an average 4.6-5 days after symptoms onset found none effective at reducing risk of hypoxemia, emergency department visit, hospitalization, or death (Bramante, 2022). An RCT with patients averaging 4 days of symptoms onset comparing ivermectin plus zinc to HCQ, darunavir/ritonavir plus zinc found equivalency (Nimitvilai et al., 2022). Thus, most studies of early use of ivermectin within 3 days found efficacy.

As ivermectin has low adverse effects, is low cost, and as the studies of early use are both sparse and conflict regarding efficacy, there is no recommendation. However, there is quality evidence of strong efficacy of other treatments that should be a higher priority when possible (e.g., Paxlovid).

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2020 to October 2021 using the following terms: Ivermectin; 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 72 articles in PubMed, 1 in Scopus, 22 in CINAHL, 711 in Cochrane Library, 7730 in Google Scholar, and 26 from other sources†. We considered for inclusion 13 from PubMed, 0 from Scopus, 0from CINAHL, 0 from Cochrane Library, 14 from Google Scholar, and 0 from other sources. Of the 28 articles considered for inclusion, 13 randomized trials and 14 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.

IVERMECTIN FOR THE TREATMENT OF COVID-19 - PROPHYLAXIS

No Recommendation

There is no recommendation for ivermectin prophylaxis.

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Indications

Outpatients with COVID-19 and less than 5 days of symptoms.

Benefits

Reduced risk of progression, shorter recovery, reduced hospitalization and faster viral clearance.

Harms

Dizziness, loss of appetite, nausea, vomiting, stomach pain, diarrhea, constipation, weakness, headache, myalgias, rash.

Frequency/Dose/Duration

Single dose of ivermectin 12 mg and doxycycline 100mg BID for 5 days (Mahmud et al., 2021).

Indications for discontinuation

Completion of course, adverse effects, intolerance

Rationale

There are few studies of the use of ivermectin as a prophylactic for those close contacts exposed to COVID cases. One trial found 7.4% developed COVID compared with 58.4% of controls (Shoumann et al., 2021). Another trial assessed a combination of high-dose ivermectin (12mg/day for 7 days) and inhaled iota-carrageenan, finding 3.4% developed COVID vs. 21.4% of controls; those with moderate and severe symptoms were solely in the control group (Chahla et al., 2021). There are insufficient studies for a recommendation for prophylactic use of ivermectin, although the current studies suggest a potential for benefit and more studies are needed.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2020 to October 2021 using the following terms: Ivermectin; 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 72 articles in PubMed, 1 in Scopus, 22 in CINAHL, 711 in Cochrane Library, 7730 in Google Scholar, and 26 from other sources†. We considered for inclusion 13 from PubMed, 0 from Scopus, 0from CINAHL, 0 from Cochrane Library, 14 from Google Scholar, and 0 from other sources. Of the 28 articles considered for inclusion, 13 randomized trials and 14 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.

8.10. AZITHROMYCIN

Azithromycin has been suggested to inhibit the growth of both the Zika and Ebola viruses, as well as prevent severe lower respiratory tract infections (93,94,95,96). Azithromycin has been used for treatment of COVID-19, as both stand-alone and combined therapy (97,98,99).

AZITHROMYCIN FOR TREATMENT OF COVID-19 - USE IN FIRST 3 DAYS OF SYMPTOMS

No Recommendation

There is no recommendation for or against the use of azithromycin in the first 3 days of COVID-19 symptoms.

Strength of evidence No Recommendation, Insufficient Evidence (I)
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 (Lau et al., 2020). 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 (Sekhavati et al., 2020).

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 (Gautret et al., 2020), 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 (CHEN et al., 2020).

Benefits

Theoretical reduced need for a ventilator or ICU stay.

Harms

Negligible for most patients undergoing short-course use. There are concerns about the potential for prolonged corrected QT intervals when used in combination therapy, and thus arrhythmias. ECG monitoring is particularly indicated in those undergoing adjunctive treatment with HCQ/CQ with underlying cardiovascular disease, history of prolonged QT, unexplained syncope, family history of premature sudden cardiac death, electrolyte abnormalities, renal insufficiency, and use of other drugs reported to prolong QT intervals, including when there is planned adjunctive use with hydroxychloroquine/chloroquine.

Frequency/Dose/Duration

The regimen used for treatment of COVID is azithromycin 500mg on day 1 and then 250 mg/day for 4 days (Gautret et al., 2020, Gautret et al., 2020).

Indications for discontinuation

Completion of a course, intolerance, adverse effect, prolongation of QT interval.

Rationale

Late administration of AZT has been assessed in multiple RCTs and been found to be mostly ineffective (Sivapalan et al., 2021, Horby, 2021, Johnston et al., 2021, Hinks et al., 2021, Butler et al., 2021) (Gyselinck I, 2022), which has also been confirmed by systematic reviews (Ayerbe L, 2021, Kamel AM, 2022). One trial of HCQ/AZT and another of AZT alone that included patients who were mostly beyond the early stage found a lack of efficacy (Rodrigues et al., 2021, Oldenburg et al., 2021). Another comparative trial found comparable (in)efficacy of HCQ and AZT (Brown et al., 2021). One RCT has suggested no difference between AZT, HCQ, and the combination for treatment of hospitalized patients (Cavalcanti et al., 2020). Thus, as the data are mostly consistent, Azithromycin is not recommended for late treatment of COVID-19.

One trial of uncertain symptom duration among patients with mild COVID-19 suggested faster resolution of symptoms with AZT (Rashad et al., 2021).

Most non-randomized but controlled studies have suggested some evidence of efficacy, particularly for early adjunctive use when combined with HCQ (Gautret et al., 2020, Gautret et al., 2020, Lagier et al., 2020, Arshad et al., 2020, Guérin et al., 2020), although some other studies have suggested a lack of efficacy (Rosenberg et al., 2020, Sbidian et al., 2020). Thus, there is no recommendation for use of AZT in the early phase of COVID-19.

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: 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 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.

AZITHROMYCIN FOR TREATMENT OF COVID-19 - USE BEYOND FIRST 3 DAYS OF SYMPTOMS

Not Recommended

Azithromycin is not recommended for the late treatment of patients with COVID-19.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

Late administration of AZT has been assessed in multiple RCTs and been found to be mostly ineffective (Sivapalan et al., 2021, Johnston et al., 2021, Hinks et al., 2021, Butler et al., 2021)(Horby, 2021). One trial of HCQ/AZT and another of AZT alone that included patients who were mostly beyond the early stage found a lack of efficacy (Rodrigues et al., 2021, Oldenburg et al., 2021). Another comparative trial found comparable (in)efficacy of HCQ and AZT (Brown et al., 2021). One RCT has suggested no difference between AZT, HCQ, and the combination for treatment of hospitalized patients (Cavalcanti et al., 2020). Thus, as the data are mostly consistent, Azithromycin is not recommended for late treatment of COVID-19.

One trial of uncertain symptom duration among patients with mild COVID-19 suggested faster resolution of symptoms with AZT (Rashad et al., 2021).

Most non-randomized but controlled studies have suggested some evidence of efficacy, particularly for early adjunctive use when combined with HCQ (Gautret et al., 2020, Gautret et al., 2020, Lagier et al., 2020, Arshad et al., 2020, Guérin et al., 2020) (Lagier et al., 2022), although some other studies have suggested a lack of efficacy (Rosenberg et al., 2020, Sbidian et al., 2020). Thus, there is no recommendation for use of AZT in the early phase of COVID-19.

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: 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 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.

8.11. VITAMIN D

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 (100) (101) (102) (103) (104) (105) (106) (107) (108) (109) (110) (111) (112) (113) (114) (115) (116). It has also been used in patients with COVID-19 to maintain bone health.

VITAMIN D FOR THE TREATMENT OF COVID-19

Recommended

Vitamin D is recommended at RDA doses 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. Brief, high-dose use may be selectively considered for those with onset of COVID-19 disease. Also recommended for those with vitamin D deficiency and/or risks for deficiency.

Benefits

Theoretical potential to reduce disease severity

Harms

Negligible

Frequency/Dose/Duration

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). Use above 100% RDA is not advised without supportive medical advice. Another trial of high-dose administration used 400,000 IU cholecalciferol.

Indications for discontinuation

After cessation of the epidemic.

Rationale

One trial of 10ug of vitamin D for 6 months did not prevent COVID-19 or other respiratory infections (Brunvoll et al., 2022). Another trial found vitamin D supplementation among deficient individuals did not affect COVID-19 infection rates or immunogenicity (Jolliffe et al., 2022, Jolliffe et al., 2022). However, another trial found vD supplementation among health care workers resulted in prevention of COVID-19 ((Villasis-Keever et al., 2022). One RCT for treatment of asymptomatic or mildly symptomatic but vitamin D deficient individuals treated with vitamin D supplementation cleared virus sooner and with reduced fibrinogen levels (Rastogi et al., 2020). Another RCT found a 32% reduction in symptoms duration associated with vitamin D 5000 IU vs. 1000 IU for 2 weeks (Sabico et al., 2021).

Other trials have evaluated use among hospitalized patients. One trial suggested lack of efficacy to prevent worse outcomes (Mariani 2022). 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 (Entrenas Castillo et al., 2020). 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) (Murai et al., 2020). Another trial of a single bolus of 100,00 IU of cholecalciferol on hospital admission was ineffective (Cannata-Andía et al., 2022). Another trial reported beneficial effects of short-term high dose treatment among hospitalized patients (Cervero et al., 2022). A single high dose administration (200,000 IU) was found ineffective for short- and long-term among hospitalized patients (Fernandes et al., 2022, Fernandes et al., 2022). Another trial found calcitriol reduced exogenous oxygen requirements (Elamir et al., 2022). Another trial found improvements in inflammatory markers (Torres et al., 2022). A trial found high dose vD resulted in improved inflammatory markers (Sarhan et al., 2022). Another trial found cholecalciferol supplementation was associated with a reduction in hospitalization days, however the group mean ages differed (Karonova et al., 2022). Another trial also suggested a reduction in length of hospital stay (De Niet et al., 2022). ICU mortality was not affected in a trial among severely affected, ICU patients (Bychinin et al., 2022). Another trial suggested early administration of vitamin D was associated with reduced mortality (Annweiler et al., 2022).

Vitamin D levels have been strongly correlated with COVID-19 disease severity (Lau et al., 2020, D'Avolio et al., 2020), however, they are at minimum a colinear variable with other morbidity

measures such as debility that affect both disease severity and survival, resulting in vitamin D being both a probable confounder and effect modifier, resulting in a challenging scientific problem to disentangle. The available literature substantially conflicts regarding the prevention of disease and/or early amelioration of symptom severity. Yet, supplementation at RDA levels has negligible (if any) adverse effects.

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. Thus, vitamin D supplementation is selectively recommended, particularly for those with vitamin D deficiency.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 using the following terms: Vitamin D, Vitamin D Supplementation; 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 185 articles in PubMed, 14,869 in Scopus, 68 in CINAHL, 7 in Cochrane Library, 13,400 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 3 from Scopus, 0 from CINAHL, 2 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 43,843 articles considered for inclusion, 2 randomized trials and 7 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.

8.12. ZINC

Zinc serum levels have been found to be low in those with more severe COVID-19 disease (117) (118) (119). Zinc supplementation has been used typically as adjunctive treatment to reduce severity of COVID-19 (120) (121).

ZINC FOR THE TREATMENT OF COVID-19

Recommended

Zinc is recommended at RDA doses 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.

Frequency/Dose/Duration

10-15 mg/day (>100% Recommended Daily Allowance).

Indications for discontinuation

After cessation of the epidemic.

Rationale

There are multiple RCTs, but few test the value of zinc alone (Derwand et al., 2020, Skalny et al., 2020, Finzi, 2020, Carlucci et al., 2020). One pilot RCT suggested a non-significant inverse correlation between zinc levels and oxygenation requirements (Patel et al., 2021). There is one low-quality study suggesting lack of efficacy of zinc added to HCQ (Abd-Elsalam et al., 2020) and another low-quality trial found lack of efficacy of high-dose zinc and ascorbic acid added to usual care (Thomas et al., 2021). 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 (Derwand et al., 2020). 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 (Carlucci et al., 2020). This is supported by evidence that hydroxy/chloroquine are zinc ionophores, which increase intracellular zinc and reduce or prevent viral replication in laboratory studies (te Velthuis et al., 2010, Xue et al., 2014). A meta-analysis found evidence of reduced mortality (Tabatabaeizadeh, 2022).

Zinc supplementation has negligible adverse effects and has been associated with improved outcomes in non-randomized studies; thus, it is recommended with insufficient evidence.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 using the following terms: Zinc, Zinc Compounds; 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 17 articles in PubMed, 20 in Scopus, 6 in CINAHL, 114 in Cochrane Library, 17000 in Google Scholar, and 0 from other sources†. We considered for inclusion 2 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 1 randomized trial 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.

8.13. GLUCOCORTICOSTEROIDS

GLUCOCORTICOSTEROIDS FOR THE TREATMENT OF COVID-19

Recommended

Glucocorticosteroids are recommended for the treatment of COVID-19. There are other indications for use that may occur in the context of treatment of COVID-19 (e.g., asthma, COPD).

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. Use is also indicated in outpatients at risk of hospitalization which includes the use of inhaled steroids.

Benefits

A meta-analysis estimated a 36% reduction in mortality with dexamethasone, 31% reduction with hydrocortisone, and 9% reduction with methylprednisolone (Sterne et al., 2020). 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. Inhaled steroid reportedly reduce illness duration by 3 days among those at higher risk (Yu et al., 2021).

Harms

Hyperglycemia, risk of secondary infection, higher blood pressure.

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 (Angus et al., 2020)

Two trials have suggested efficacy of budesonide 2 puffs BID, with use including outpatients (Ramakrishnan et al., 2021, Yu et al., 2021).

Indications for discontinuation

Completion of a course, intolerance, adverse effect.

Rationale

There are multiple RCTs, with all larger sized studies suggesting efficacy (Angus et al., 2020, Tomazini et al., 2020, Horby et al., 2020, Edalatifard et al., 2020, Jeronimo et al., 2020), while the negative studies were small sample sizes and appear tended to trend towards efficacy (Abd-Elsalam et al., 2020, Dequin et al., 2020)(Tang et al., 2021, Jamaati et al., 2021, Ghanei et al., 2021). A meta-analysis estimated a 36% reduction in mortality with dexamethasone, 31% reduction with hydrocortisone, and 9% reduction with methylprednisolone (Sterne et al., 2020). A comparative trial suggested superiority of methylprednisolone 2mg/kg/day to dexamethasone 6mg/kg/day, which is a lower steroid dose of the methylprednisolone (Ranjbar et al., 2021). Two studies of inhaled budesonide suggest modest efficacy (Yu et al., 2021, Ramakrishnan et al., 2021), with one suggesting shortening of recovery by ~3 days (Yu et al., 2021). A comparative trial found dexamethasone superior to tocilizumab (Rashad et al., 2021).

A large RCT found mortality reductions with dexamethasone (Horby et al., 2020, Oxford, 2020, Ledford, 2020). 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 (Tomazini et al., 2020). Another RCT found superiority of glucocorticosteroid (Angus et al., 2020). Two RCTs of modest size found no significant benefits, but appear underpowered (Dequin et al., 2020, Abd-Elsalam et al., 2020). Another negative study used a low dose of hydrocortisone (Dequin et al., 2020). Because glucocorticosteroids have moderate adverse effects, low costs, and have significant efficacy in reducing mortality based on meta-analyses, they are moderately and selectively recommended for treatment of COVID-19 patients who are hospitalized and hypoxemic and/or needing cardiopulmonary support.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 using the following terms: Glucocorticoids, Glucocorticoid Steroid, Prednisone, Dexamethasone, Hydrocortisone; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 364 articles in PubMed, 939 in Scopus, 32 in CINAHL, 20 in Cochrane Library, 11980 in Google Scholar, and 0 from other sources†. We considered for inclusion 30 from PubMed, 4 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 5 from Google Scholar, and 0 from other sources. Of the 39 articles considered for inclusion, 12 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.

8.14. FAVIPIRAVIR

Favipiravir, a guanine analogue to inhibit RNA-dependent RNA polymerase, has been used to treat influenza. Favipiravir has now been used to treat mostly severely affected COVID-19 patients (122,123,124,125,126,127,128,129).

FAVIPIRAVIR FOR THE TREATMENT OF COVID-19

Not Recommended

Favipiravir is not recommended for treatment of COVID-19.

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

A trial of favipiravir for treatment of COVID-19 within 5 days of symptoms onset found a lack of efficacy (Golan et al., 2022). A high-quality trial found no differences in viral loads between favipirivir plus lopinavir/ritonavir vs. either drug alone or vs. both placebos (Lowe et al., 2022), suggesting lack of efficacy RCTs among those who were treated late and/or who initiated treatment while hospitalized are also mostly negative. One trial with mostly late treatment patients found lack of benefit with favipiravir with and without HCQ (Bosaeed et al., 2021). 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 (Khamis et al., 2020). A comparative trial found no differences between favipiravir and lopinavir/ritonavir (Solaymani-Dodaran et al., 2021). A moderate-quality RCT found no evidence of benefit of favipiravir for viral clearance, although there was faster defervescence (Doi et al., 2020), while another low-quality study found faster viral clearance (Zhao et al., 2021). Another trial of many combinations found accelerated viral clearance but more deaths with favipiravir plus lopinavir-ritonavir (Atipornwanich et al., 2021). A trial of mild/moderate COVID-19 patients without including reported symptoms onset found earlier viral clearance with favipiravir or hydroxychloroquine compared with standard of care (AlQahtani et al., 2022).

There are two RCTs that appear to have included both early and late patients, with one reporting Favipiravir was associated with shortening of symptoms by 3 days compared with placebo (Shinkai et al., 2021), while another reported a trend towards earlier viral clearance (Udwadia et al., 2021).
An RCT evaluating favipiravir use within 5 days of symptoms found a lack of efficacy (Golan et al., 2022).

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 (Chen et al., 2020). A low-quality RCT of baloxavir, marboxil, and favipiravir found no evidence that favipiravir accelerated viral clearance (Lou et al., 2020). One non-randomized controlled trial suggested acceleration of viral clearance compared with lopinavir-ritonavir (Cai et al., 2020). A systematic review reported some evidence of efficacy for use among hospitalized, but not non-hospitalized patients (Hung DT, 2022).

There is limited evidence that early treatment may be associated with modestly superior outcomes, although most studies do not assess use in the first 2 days of symptoms. Thus, there is a selective recommendation for use among COVID-19 patients in the first 3-5 days of disease.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 using the following terms: Favipiravir, Amides, Pyrazines, T-705 cpd, 6-fluoro-3-hydroxy-2-pyrazinecarboxamide, Avigan; 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 105 articles in PubMed, 4023 in Scopus, 28 in CINAHL, 118 in Cochrane Library, 13190 in Google Scholar, and 0 from other sources†. We considered for inclusion 23 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 10 from Google Scholar, and 0 from other sources. Of the 37 articles considered for inclusion, 10 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.

8.15. LOPINAVIR/RITONAVIR

Lopinavir-ritonavir has been used for the treatment of COVID-19 (130,131,132,133,134,135,136,137,138,139).

LOPINAVIR/RITONAVIR FOR THE TREATMENT OF COVID-19 - COMBINATION THERAPY

Not Recommended

Lopinavir-ritonavir is not recommended either stand alone or in combination therapy for treatment of COVID-19 (Hung et al., 2020).

Strength of evidence Not Recommended, Evidence (C)
Level of confidence Low

Rationale

A high-quality trial found no differences in viral loads between favipirivir plus lopinavir/ritonavir vs. either drug alone or vs. both placebos (Lowe et al., 2022). 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 (Hung et al., 2020). 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) (Rahmani et al., 2020), which could suggest that the only medication effective in the triple therapy is the interferon beta-1b. Another RCT found lack of efficacy and trends towards worse outcomes with Lopinavir-ritonavir (Arabi et al., 2021).

Lopinavir-ritonavir as a stand-alone antiviral treatment has been trialed in five RCTs, all of which showed a lack of efficacy compared with standard care (WHO, 2020, Cao et al., 2020, Li et al., 2020, Horby et al., 2020) (Reis et al., 2021). Another double-blind RCT also suggested lack of efficacy, although it may have been underpowered (Li et al., 2020). 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. One trial with unclear symptom durations and baseline outcomes differences suggesting possible randomization failure nevertheless suggested potentially faster PCR negative results in 3 days with various combinations of drugs (either lopinavir/ritonavir-doxycycline; lopinavir/ritonavir-azithromycin; or azithromycin-HCQ)

(Purwati et al., 2021). Lopinavir-ritonavir has also been suggested to be inferior to favipiravir in a non-randomized comparative trial [(Cai et al., 2020). Another comparative trial found no significant difference between lopinavir/retinovir and umifenovir (Darazam et al., 2021).

Studies of combination therapy conflict. The highest quality trial found a lack of efficacy, and most studies suggest lopinavir in combination is not associated with improved outcomes. Thus, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 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 256 articles in PubMed, 0 in Scopus, 0 in CINAHL, 213 in Cochrane Library, 19300 in Google Scholar, and 0 from other sources†. We considered for inclusion 23 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 25 articles considered for inclusion, 5 randomized trials and 17 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.

8.16. ADALIMUMAB

ADALIMUMAB FOR THE TREATMENT OF COVID-19

Not Recommended

Adalimumab is 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 lack of efficacy (Fakharian et al., 2021). Thus, adalimumab is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar from January 2019 to March 2023 using the following terms: Adalimumab; 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, 0 in CINAHL, 4 in Cochrane Library, 20400 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 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.

8.17. BAMLANIVIMAB PLUS ETESEVIMAB

Bamlanivimab is a neutralizing monoclonal IgG1 antibody that targets the receptor-binding domain of the spike protein of SARS-CoV-2 and was used to treat COVID-19, often with etesevimab. FDA emergency use authorization was revoked after evidence it was unlikely to be effective against omicron (140) (141) (142).

BAMLANIVIMAB PLUS ETESEVIMAB FOR THE TREATMENT OF COVID-19

Not Recommended

Bamlanivimab plus etesevimab is not recommended for the treatment of patients with COVID-19 (IDSA, 2021).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

RCTs involve variants prior to omicron. However, subsequent evidence suggests lack of efficacy against omicron. 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 (Gottlieb et al., 2021). Another moderate-quality RCT that also combined treatment with etesevimab found 67% reduced risk of hospitalization and 0 vs 10 deaths in the placebo group (Dougan et al., 2021). Data provided to the FDA suggest a reduction of 68–84% in the risk of combined 28-day hospitalization, emergency department visit, or death (NIH, 2020). Another study suggested a 72% reduction in the risk of hospitalization among those at high risk (NIH, 2020).

An RCT found no difference in recovery time from a combination of bamlanivimab and remdesivir among hospitalized patients (Lundgren et al., 2022). Another small hospital-based dose-ranging RCT did not report statistical outcomes data (Chen et al., 2021). Thus, bamlanivimab is not recommended among hospitalized or late cases.

One moderate-quality RCT suggested 44% reduced risk of skilled nursing home residents and staff contracting COVID-19 within 8 weeks of randomization; there were 5 vs. 0 deaths with all deaths in the placebo group (Cohen et al., 2021).

The combination of bamlanivimab/etesevimab is invasive, has some adverse effects, is high cost, has past evidence of efficacy, is not anticipated to have significant efficacy against omicron ((NIH), 2022) and thus is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021using 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 41 articles in PubMed, 345 in Scopus, 10 in CINAHL, 0 in Cochrane Library, 1520 in Google Scholar, and 0 from other sources†. We considered for inclusion 11 from PubMed, 1 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 14 articles considered for inclusion, 10 randomized trials and 4 systematic reviews met the inclusion criteria. There were no exclusion criteria.

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

8.18. BARICITINIB

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 FOR THE TREATMENT OF COVID-19

No Recommendation

There is no recommendation regarding baricitinib for the treatment of outpatients and/or for prophylaxis of COVID-19 (Kalil et al., 2020). There is FDA emergency use authorization for hospitalized patients (FDA, 2022) and for combination with remdesivir (FDA, 2023).

Strength of evidence No Recommendation, Insufficient Evidence (I)
Level of confidence Low

Indications

The U.S. FDA issued an emergency use authorization for use in combination with remdesivir (Administration, 2020, Administration, 2020) and another EUA for hospitalized patients in 2022 (FDA, 2022). 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).

Rationale

Baricitnib plus remdesivir was superior to remdesivir alone (Kalil et al., 2021). Caution is warranted as RCTs address variants prior to omicron. Regardless, one RCT found lack of efficacy (Marconi et al., 2021). Another 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 (Kalil et al., 2020, Administration, 2020, Administration, 2020).

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 (Rodriguez-Garcia et al., 2020). A comparative consecutive case series suggested significant benefits, such as eliminating ICU transfers and 58% vs. 8% discharge at 2 weeks (Cantini et al., 2020).

Baricitinib is invasive, has some adverse effects, is costly, and does not have quality evidence of efficacy for treatment of outpatients or for prophylaxis and thus there is no recommendation. There are FDA EUAs for hospitalized patients (FDA, 2020) (FDA, 2022).

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.

8.19. BEBTELOVIMAB

BEBTELOVIMAB FOR THE TREATMENT OF COVID-19

Not Recommended

Bebtelovimab is not recommended for treatment of COVID-19 as it is no longer believed to be active against omicron, although it was previously approved under the FDA Emergency Use Authorization process (February 11, 2022).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Preliminary data (Administration, 2022)(Administration, 2022) on which the FDA initially issued its Emergency Use Authorization were subsequently overturned by evidence suggesting lack of efficacy against omicron (NIH, 2022). Bebtelovimab is minimally invasive, has low adverse effects, but is high cost and is not believed to be effective against omicron. Thus, it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 using the following terms: bebtelovimab, LY-CoV1404; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 1 articles in PubMed, 0 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 8 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, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 0 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.

8.20. CASIRIVIMAB PLUS IMDEVIMAB (REGENERON)

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 were previously approved for use by FDA under the emergency use authorization provision (143).

CASIRIVIMAB PLUS IMDEVIMAB (REGENERON) FOR THE TREATMENT OF COVID-19

Not Recommended

The combination of casirivimab plus imdevimab (Regeneron) is not recommended for the treatment of patients with mild to moderate COVID-19 at risk of severe disease, as this combination is not efficacious against the omicron variant ((NIH), 2022).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

The combination of casirivimab/imdevimab is not efficacious against omicron (National Institutes of Health, 2022). The RCTs addressed prior variants before omicron. A moderate-quality RCT found significant reductions in viral load among those infected, with greater reductions including among those with higher viral loads (Weinreich et al., 2021). Data provided to the FDA suggest a reduction of

67% in the risk of hospitalization (9% vs. 3%) (NIH, 2020). A prophylaxis trial of subcutaneous administration found development of symptomatic infection in 1.5% vs. 7.8% among controls (O'Brien et al., 2021). An open label trial among those hospitalized found a 20% reduction in risk of mortality at 28 days (Horby et al., 2021).

The combination of Casirivimab/imdevimab is invasive, has some adverse effects, is high cost, has past evidence of efficacy, but is not efficacious against omicron (NIH, 2022), and thus it is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, andGoogle Scholar from January 2019 to October 2021 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 27 articles in PubMed, 393 in Scopus, 4 in CINAHL, 15 in Cochrane Library, 1,682 in Google Scholar, and 0 from other sources†. We considered for inclusion 0from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 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.

8.21. SOTROVIMAB

Sotrovimab is a neutralizing monoclonal IgG antibody that targets an evolutionarily-conserved epitope that is not on the rapidly evolving receptor-binding domain of the spike protein of SARS-CoV-2 and has been used to treat COVID-19. It was approved for use by the U.S. FDA under the emergency use authorization provision (144)(145)(146). However, that was withdrawn April 5, 2022 due to lack of efficacy against omicron variants (147).

SOTROVIMAB FOR THE TREATMENT OF COVID-19

Not Recommended

Sotrovimab is not recommended for the treatment of patients with COVID-19 (Administration, 2021, Administration et al., 2022).

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

While sotrovimab had prior evidence of efficacy, it was ineffective against omicron and the FDA withdrew its approval April 5, 2022. Thus, sotrovimab is no longer recommended for the treatment of any stage, and any severity of COVID-19.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 using the following terms: Sotrovimab; 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 8 articles in PubMed, 90 in Scopus, 1 in CINAHL, 8 in Cochrane Library, 377 in Google Scholar, and 0 from other sources†. We considered for inclusion 3 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0from other sources. Of the 4 articles considered for inclusion, 2 randomized trials and 1 systematic review met the inclusion criteria. There were no exclusion criteria.

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

8.22. TIXAGEVIMAB PLUS CILGAVIMAB (EVUSHELD)

Tixagevimab plus cilgavimab is a monoclonal antibody combination that has been used as a combination for the pre-exposure prophylaxis, as well as early treatment of SARS-CoV-2 (148,149,150,151,152,153,154,155,156,157).

TIXAGEVIMAB-CILGAVIMAB FOR THE TREATMENT OF COVID-19

Not Recommended

Tixagevimab-cilgavimab is not recommended for treatment of COVID-19 or for prophylaxis.

Strength of evidence Not Recommended, Insufficient Evidence (I)
Level of confidence Low

Rationale

Some RCTs have suggested prior efficacy of tixagevimab-cilgavimab against prior variants (Group, 2022, Montgomery et al., 2022, Levin et al., 2022, Levin et al., 2022, Ignacio et al., 2022, Jondreville et al., 2022). However, with the development of subsequent variants, tixagevimab-cilgavimab is no longer projected to have efficacy (FDA, 2023). Thus, tixagevimab-cilgavimab is not recommended.

Evidence

A comprehensive literature search was conducted using PubMed, CINAHL, Cochrane Library, and Google Scholar from January 2019 to March 2023 using the following terms: Tixagevimab,Cilgavimab; 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 32 articles in PubMed, 3 in CINAHL, 23 in Cochrane Library, 2513 in Google Scholar, and 0 from other sources†. We considered for inclusion 4 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 4 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.

8.23. RIBAVIRIN

RIBAVIRIN FOR THE TREATMENT OF COVID-19

Recommended

Adjunctive use of ribavirin is recommended for the treatment of selected patients with COVID-19. There are other treatments with demonstrated strong efficacy (e.g., Paxlovid).

Strength of evidence Recommended, Evidence (C)
Level of confidence Low

Indications

Adjunctive use with lopinavir-ritonavir and interferon beta-1b in moderately and severely affected patients with COVID-19 (Hung et al., 2020). 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 (Hung et al., 2020).

Benefits

Faster symptom resolution, viral clearance, and hospital discharge. Reduced need for a ventilator or ICU stay.

Harms

Nausea, diarrhea, hepatitis.

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 (Hung et al., 2020).

Indications for discontinuation

Completion of a course, intolerance, adverse effect, prolongation of QT interval.

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 (Hung et al., 2020). Two other RCTs were underpowered for meaningful clinical differences (Huang et al., 2020, Abbaspour Kasgari et al., 2020). One trial of adjunctive use also did not define the timing of treatment vs. symptoms onset (Panda et al., 2021).

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 selectively recommended (Hung et al., 2020). However, there are other treatments with demonstrated strong efficacy which should generally be preferentially used (e.g., Paxlovid).

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to October 2021 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 103 articles in PubMed, 7,064 in Scopus, 10 in CINAHL, 977 in Cochrane Library, 16,570 in Google Scholar, and 0 from other sources†. We considered for inclusion 7 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 8 articles considered for inclusion, 1 randomized trial and 7 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.

9. REHABILITATION

9.1. OVERVIEW

Although most patients with COVID-19 completely recover, some cases may experience a multitude of disorders (621) and some develop chronic symptoms. It is beyond the scope of this guideline to address every possible presentation, combination, and permutation (86). 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" (392), "post-acute sequalae of COVID," and "long COVID"; definitions for these other terms vary and sometimes conflict.

A key part of rehabilitation includes an assessment of, and planning return to work (RTW). The RTW process should include an assessment of both the patient's abilities and the job tasks with its requirements. The patient's assessment should ascertain any physical and/or cognitive impairments, preferably with quantification (622). The job assessment should include its quantified physical requirements, cognitive demands and safety critical requirements. The rehabilitation plan developed must target any gap(s) between the patient's current capabilities and the job demands, as the success of the rehabilitation process is optimized when it addresses those specific gaps instead of generic abilities.

The severity of the COVID-19 infection has been associated with the risk of long-term symptoms and impairments (623), although it may affect adults of any age and severity. For example, approximately two-thirds of outpatients diagnosed with COVID-19 return to normal health by the fourth week (624). In contrast, of those who were evaluated in an emergency department (66% hospitalized), 50.9% developed chronic COVID-19 symptoms (625). 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.

Some findings among those with chronic/long COVID include: exertional intolerance with reduced VO_{2max} (412), inflammatory biomarkers and viral antigen in cerebrospinal fluid (626,627), neural dysregulation (394), prolonged gut viral antigen presence (393). A potentially important pre-morbid finding reported was a history of antecedent psychological distress that predicted increased risk of persistent post-infection symptoms (628).

Evidence also suggests that symptoms improve over time. Overall, 5–51% of patients have symptoms persisting up to 12 weeks (397,629,630,631), whereas 2–15% have symptoms beyond 12 weeks after onset (625,629,631,632,633). Long-term symptoms have wide-ranging estimates of prevalence and include fatigue (17–98%) (397,625,629,630,631,634,635,636), dyspnea (17–93%) (397,625,629,630,631,634,635,636), cough (29–43%), chest pain (44–88%) (397,625,629,630,635), back pain, muscle pain, and headache (38–91%) (625). Cognitive changes, such as impaired memory, concentration, and multitasking ability, are also reportedly common. Cerebrospinal fluid abnormalities have been associated with cognitive impairment (626). Risk factors for chronic COVID-19 beyond severity of the initial disease appear to include increased age, having more comorbidities, and psychological disorders (631,637). However, others report younger age as a risk factor after SARS-COV-2 infection (638).

A multi-national study of 1.2 million individuals who had had a symptomatic SARS-CoV-2 infection were assessed for ongoing problems beyond 3 months post-infection (396). Estimates include that

3.2% persistent fatigue with bodily pain or mood swings, 3.7% had ongoing respiratory problems and 2.2% had cognitive problems. The average long COVID symptom cluster duration was 9 months among those hospitalized and 4 months among the non-hospitalized patients. An estimated 15.1% of those with symptoms lasting 3 months were still experiencing symptoms at 12 months.

Acute mental health disorders are common and reportedly affect 55% of those having visited an emergency department (75% were hospitalized) in the first month (639). New-onset psychiatric illness was reported in 5.8% [801]. Of these, 4.7% were anxiety disorders and 2% were depression (640). One report noted persistence of post-traumatic stress among survivors (641). 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 (623).

Some rehabilitation protocols are heavily multidisciplinary, reportedly including pulmonologists, physiatrists, neurologists, cardiologists, physical therapists, occupational therapists, psychologists, neuropsychologists, psychiatrists, speech therapists, and nutritionists (642,643)(644). Some patients are sufficiently complex and/or severe that inpatient rehabilitation is necessary and effective.; further there is evidence, although non-randomized, that earlier rehabilitation in hospitalized patients results in lower mortality (645).Telemedicine has been used for rehabilitation of COVID-19 patients (643,646). There are no quality trials to assess the various disciplines on rehabilitation teams, comparative trials of different treatment regimens, and/or efficacy of telemedicine regimens. There is evidence that telehealth approaches are effective (647).

9.2. 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 (648,649) (623)(650). The most common spirometric abnormalities after initial recovery are reduced diffusion capacity and restrictive ventilatory defects (651,652). Risk and severity of spirometric abnormalities are correlated with COVID-19 severity (652).

Pulmonary rehabilitation is used for COVID-19 (653) (654) and has been shown to be successful for functional improvements in individuals with non-COVID-related pulmonary deficits (655,656), including those from pneumonia (657), interstitial lung disease (658), and SARS (659). It commonly includes behavioral components (660). Consensus guidelines have also been produced (650).

An estimated 3.7% of 1.2 million individuals who had had a symptomatic SARS-CoV-2 infection had respiratory problems lasting more than 3 months (661). Multiple studies have been reported on pulmonary rehabilitation of COVID patients. Systematic reviews and metanalyses found evidence of efficacy including for symptoms of dyspnea, exercise capacity, lung function and fatigue (662). European guidelines are supportive of pulmonary rehabilitation (663).

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, Evidence (C)
Level of confidence Moderate

Indications

Indicated for COVID-19 affected patients with pulmonary dysfunction, exercise intolerance, and/or dyspnea, especially when combined with activity reductions or exercise intolerances attributed to the infection's pulmonary complications. Important targets are gaps between current function and job demands (esp. objectively measured). Earlier institution of exercises, as tolerated, is advised to counter the debility associated with the disease and accelerate recovery (Spruit et al., 2013). Careful cardiac evaluation (e.g., 24-hr ECG, echocardiogram, exercise testing, MRI (Barker-Davies et al., 2020)) 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, activity tolerance and stamina/endurance.

Harms

A randomized crossover trial interpreted their data from 10 patients as showing post-hospitalized patients having had severe COVID can undergo high-intensity exercise training (Foged et al., 2021). However, a population of 10 cannot be used to infer safety unless a highly common adverse effect. 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.

Frequency/Dose/Duration

An individualized but interdisciplinary treatment regimen is usually formulated based on a comprehensive baseline assessment (Dowman et al., 2021, Spruit et al., 2020). Careful cardiac evaluation (e.g., 24-hr ECG, echocardiogram, exercise testing, MRI (Barker-Davies et al., 2020)) 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" (Spruit et al., 2020), 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 (Barker-Davies et al., 2020). 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 (Alawna et al., 2020). Program duration is typically at least 4 weeks.

Indications for discontinuation

Completion of a treatment course, noncompliance, reaching a plateau in recovery.

Rationale

An RCT suggested improved symptoms with inspiratory muscle training (McNarry et al., 2022). A 6-week post-discharge rehabilitation protocol was found to be effective (Li et al., 2022). An RCT assessing a virtual reality-based program found improvements in 6-min walk test and dyspnea; improvements in quality of life were greater in the aqua-Pilates group (Rutkowski et al., 2022). A telehealth exercise protocol was found superior to a control for treatment of post-hospitalized

patients (Bagherzadeh-Rahmani et al., 2022). Another trial found improvements in quality of life from an 8-week protocol, but was one of the few studies to fail to find improvements in exercise tolerance (Del Corral et al., 2022). A low quality 8-weeks trial of Pilates and aqua-Pilates were found superior to control for improving FEV1, FVC and FEV1/FVC% (Bagherzadeh-Rahmani et al., 2022). A low-quality, quasi-randomized trial also suggested evidence of efficacy of a 6-week pulmonary rehabilitation program (Liu et al., 2020).

There are few quality trials for treatment of COVID-19, but there are many trials documenting efficacy for other pulmonary conditions (McCarthy et al., 2015, Hill, 2006, Cheng et al., 2018, Dowman et al., 2021, Lau et al., 2005). A home-based respiratory program was found to be effective (Del Corral et al., 2022). A virtual reality based pulmonary rehabilitation program was found to be ineffective (Rutkowski et al., 2022). Inspiratory muscle control has been suggested as effective (McNarry et al., 2022). Another trial round respiratory rehabilitation to be effective among elderly patients (Liu et al., 2020). Pulmonary rehabilitation has negligible adverse effects, is moderate to high cost depending on number of treatments and durations required, has some heterogeneous evidence of efficacy, 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 14 from PubMed, 4 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 18 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.

9.3. CARDIAC REHABILITATION

Cardiomyopathy, cardiac muscle damage, and arrhythmias have been reported to affect 30–78% of patients (409), and cardiac problems contribute to COVID-19 fatalities (409,410,411,413). Reduced VO_2 max has been reported among those having had mild COVID-19 symptoms, but having persistent exertional intolerance (412). Vascular inflammation, hypotension, and direct muscle damage are all potential mechanisms (664,665). 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 (664,665), although ongoing, subclinical cardiac problems have been detected among recovered patients (413,666).

Cardiac rehabilitation is used for COVID-19 (667) and has been shown to be successful for functional improvements in individuals with non-COVID-related cardiac deficits (668,669,670,671,672), including those from myocardial infarction (664), 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 (Barker-Davies et al., 2020), although there is no quality evidence to support the expert consensus. Important targets are gaps between current function and job demands (esp. objectively measured).

Benefits

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, activity tolerance, and stamina/endurance (Piquet et al., 2021).

Harms

A randomized crossover trial interpreted their data from 10 patients as showing post-hospitalized patients having had severe COVID can undergo high-intensity exercise training (Foged et al., 2021); however, a population of 10 cannot be used to infer safety unless a highly common adverse effect. 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.

Frequency/Dose/Duration

An individualized but multidisciplinary treatment regimen is usually formulated based on a comprehensive baseline assessment (Hevey et al., 2003, Price et al., 2016). Careful cardiac evaluation (e.g., 24-hr ECG, echocardiogram, exercise testing, MRI (Barker-Davies et al., 2020)) 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 (Linden, 2000). 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 (Price et al., 2016). 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 (Price et al., 2016). 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 (Barker-Davies et al., 2020).

Indications for discontinuation

Completion of a treatment course, noncompliance, reaching a plateau in recovery.

Rationale

There is one low-quality pilot study suggesting efficacy for treatment of COVID-19 patients (Liu et al., 2020), but no quality trials. There are many trials documenting efficacy for other 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.

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 14 from PubMed, 4 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 18 articles considered for inclusion, 1 randomized trial and 8 systematic reviews met the inclusion criteria. There were no exclusion criteria.

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9.4. EXERCISE THERAPY

Research has supported rehabilitation for hospital-associated deconditioning prior to the COVID pandemic (158,159,160). Early mobilization of COVID-19 patients has been encouraged, and yet others suggest delaying until after the acute COVID-related symptoms have been resolved for 2-3 weeks (161)(162). Early therapy has also been used in the ICU and pre-discharge for COVID patients (163,164,165). A review of physical therapy suggests that there will eventually be efficacy, but currently the available literature is sparse and mostly low quality (166)(167).

For those with fibromyalgia, please refer to the ACOEM Chronic Pain Guideline. Also consider chronic fatigue syndrome and myalgic encephalomyelitis (168).

EXERCISE THERAPY FOR PHYSICAL DEBILITY AND/OR CHRONIC FATIGUE ASSOCIATED WITH COVID-19

Recommended

A titrated return to physical activity/exercise therapy is recommended for the treatment of physical debility and/or chronic fatigue associated with COVID-19 (Vickory et al., 2021).

Strength of evidence Recommended, Evidence (C)
Level of confidence Moderate

Indications

Indicated for COVID-19 affected patients with debility, poor exercise tolerance, and/or chronic fatigue attributed to the COVID-19. Important targets are gaps between current function and job demands (esp. objectively measured). 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. A randomized crossover trial interpreted their data from 10 patients as showing post-hospitalized patients having had severe COVID can undergo high-intensity exercise training (Foged et al., 2021); however, a population of 10 cannot be used to infer safety unless a highly common adverse effect. Those with evidence of thrombotic tendencies and/or multi-system involvement may have greater risk of harm from aggressive exercise regimens.

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) and should be tracked and easily increased as indicated. When there is a lack of further improvement, the course of treatment should be discontinued. Web-based programs are also possible.

Indications for discontinuation

Completion of course of treatment, noncompliance, reaching a plateau in recovery.

Rationale

There are a few quality trials of exercise therapy for the treatment of physical debility, activity intolerance, and/or chronic fatigue attributed to COVID. The studies differed considerably in the intervention(s) trialed, patient clinical variance, and outcome measures. Trials suggested efficacy of various exercise rehabilitation strategies (Li et al., 2022, Foged et al., 2021). Telehealth supervised exercise has also been suggested as effective (Amaral et al., 2022). Titrated return to activity and exercise programs have 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 14 from PubMed, 4 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 18 articles considered for inclusion, 1 randomized trial and 8 systematic reviews met the inclusion criteria. There were no exclusion criteria.

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9.5. MEMORY AND COGNITION

Memory issues are also potentially problematic for some workers who have had COVID (673,674,675,676,677,678,679,680,681,682,683,684,685). 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 (623), 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 (686,687,688)(290,289). Cognitive rehabilitation has been successfully used for various infectious disease complications, especially for HIV (689) and severe malaria (690). One guideline recommended cognitive screening, assessment of contributing other conditions, imaging, testing, and consensus statements on treatment options (691).

A potentially important pre-morbid finding reported was a history of antecedent psychological distress that predicted increased risk of persistent post-infection symptoms (628). The importance of that finding is that it significantly increases the probability that cognitive behavioral therapy is likely to be proven effective for the treatment of cognitive dysfunction caused by COVID-19.

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. Important targets are gaps between current function and job demands (especially when objectively measured). 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

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 (Faria et al., 2016, Bunketorp-Käll et al., 2017, Cho et al., 2019) are also possible. There is some evidence in stroke patients that combining cognitive rehabilitation with aerobic exercise results in superior outcomes (Yeh et al., 2019).

Indications for discontinuation

Completion of course of treatment, noncompliance, reaching a plateau in recovery.

Rationale

There is one pilot study suggesting trends towards efficacy of depression and anxiety measures when used to treat COVID-19 patients (Liu et al., 2020), but no other quality trials. 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 14 from PubMed, 4 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 18 articles considered for inclusion, 1 randomized trial and 8 systematic reviews met the inclusion criteria. There were no exclusion criteria.

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9.6. JOINT PAIN

Joint pain is common in subacute and chronic COVID (169,170,171), with 27.3% reporting joint pain at 2 months after COVID onset (169). Detailed guidance is available by body part in other ACOEM guidelines (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).

9.7. MENTAL HEALTH

Treatments for mental health disorders that result from COVID-19 have undergone limited numbers of randomized trials for efficacy. Mostly low-quality trials have thus far been reported (172,173,174,175,176). Various systematic reviews have suggested efficacy of cognitive behavioral therapy (CBT). However, there are increasing numbers of moderate-quality RCTs reported. Multiple RCTs have suggested efficacy of CBT. One trial combined anxiety, depression, and stress, reporting that cognitive behavioral therapy (CBT) was effective (177). Another trial found progressive muscle relaxation helpful for anxiety and sleep quality (178). Another trial found an internet-based intervention on depression and anxiety to be effective (179).

Aside for CBT for which there is evidence of efficacy, in the absence of quality evidence specific to COVID-19, analogy to existing quality evidence and evidence-based guidance is recommended for other 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 Posttraumatic Stress Disorder Guideline.

COGNITIVE BEHAVIORAL THERAPY FOR TREATMENT OF PSYCHOLOGICAL DISORDERS RELATED TO COVID-19

Recommended

Cognitive behavioral therapy (CBT), including internet-based therapy, is recommended for treatment of psychological disorders associated with COVID-19, such as anxiety, depression, stress, and posttraumatic stress disorder (PTSD).

Strength of evidence Moderately Recommended, Evidence (B)
Level of confidence Moderate

Indications

All COVID-19 patients who have need of treatment for anxiety, depression, stress and/or PTSD.

Benefits

Improved in psychological conditions.

Harms

Negligible

Frequency/Dose/Duration

Various regimens were utilized in the quality trials. Durations of trial CBT interventions were typically 3-6 weeks.

Indications for discontinuation

Completion of a course of treatment, resolution of symptoms, non-compliance.

Rationale

There are multiple moderate quality RCTs of CBT, with nearly all suggesting efficacy. Conditions treated were most often depression, anxiety, stress, and PTSD (Li et al., 2020, Al-Alawi et al., 2021, Egan et al., 2021, Aminoff et al., 2021). Internet or online treatment options also were shown to be effective (Wahlund et al., 2021, Shabahang et al., 2021, Liu et al., 2021). Narrative exposure therapy has also been shown to be effective (Fan et al., 2021). CBT is non-invasive, has negligible adverse effects, is low cost especially when online, and has many trials suggesting efficacy; thus, it is recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to March 2023 using the following terms: cognitive behavioral therapy, CBT; 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 241 articles in PubMed, 65 in CINAHL, 265 in Cochrane Library, 39900 in Google Scholar, and 0 from other sources†. We considered for inclusion 9 from PubMed, 0 from CINAHL, 0 from Cochrane Library, 6 from Google Scholar, and 0 from other sources. Of the 15 articles considered for inclusion, 15 randomized trials and 0 systematic reviews met the inclusion criteria. There were no exclusion criteria.

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10.2. CONFLICT OF INTEREST DISCLOSURES

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National, Regional, Local Committee Affiliations—Board of Trustees (2003-12) and Chair (2010-12), American Board of Preventive Medicine; Chair, Federal Motor Carrier Safety Administration's Medical Review Board (2006-2010); Member, *Journal of Occupational and Environmental Medicine* Editorial Board

Other Guidelines Related Professional Activities—Chair, Evidence-based Practice Committee, ACOEM (2006-present)

Research Grants/Other Support—NIOSH (CDC) Training grants and research grants primarily on the epidemiology of musculoskeletal disorders (e.g., CTS, shoulder tendinosis, LBP) and truck driver safety.

Financial/Non-Financial Conflict of Interest—Consultant, Reed Group (ACOEM Guidelines Editor-in-Chief); Consulting with companies, unions and insurers

Clayton T. Cowl, MD, MS, FACOEM (Panel Member)

Associate Professor of Medicine, Mayo Clinic

National, Regional, Local Committee Affiliations—Past President, American College of Chest Physicians

Other Guidelines Related Professional Activities—None

Research Grants/Other Support—Co-Co-Principal Investigator, U.S. Department of Labor RETAIN Grant

Financial/Non-Financial Conflict of Interest—None

Philip Harber, MD, MPH, FACOEM, ATSF, FCCP (Panel Member)

Adjunct Professor of Public Health, Mel and Enid Zuckerman College of Public Health, University of Arizona; Professor Emeritus, UCLA; Dr Philip Harber PLLC

National, Regional, Local Committee Affiliations— Member, ACOEM Council on Scientific Affairs; ISO (respirators)

Other Guidelines Related Professional Activities—Member, ACOEM Evidence-based Practice Asthma Panel

Research Grants/Other Support— National Library of Medicine (NIH)

Financial/Non-Financial Conflict of Interest—None

Mark H. Hyman, MD, FACP, FAADEP

HymanHealth; Internal Medicine, Emeritus Associate Clinical Professor of Medicine at UCLA

National, Regional, Local Committee Affiliations— Veritas Medicus Board Officer (2017-2020); Director/Chairman, International Academy of Independent Medical Evaluators (2008-2015); Member, ACOEM Public Safety Medicine Section; American College of Physicians Governor's Advisory Council (2008-2013)

Other Guidelines Related Professional Activities—Evidence-based Practice Occupational Asthma Panel, ACOEM; Medical Advisory Board, *The Medical Disability Advisor*, 6th Edition; Advisory Committee, American Medical Association (AMA) *Guides to the Evaluation of Permanent Impairment*; Editorial Board, AMA *Guides Newsletter*

Research Grants/Other Support—None

Financial/Non-Financial Conflict of Interest— Honoraria: Teaching honoraria from various courses, ACOEM and IAIME related

Karin A. Pacheco, MD, MSPH, FAAAAI (Panel Member)

Staff Physician, Division of Environmental and Occupational Health Sciences, National Jewish Medical and Research Center; Assistant Professor, Preventive Medicine and Allergy/ Immunology, University of Colorado Health Sciences Center

National, Regional, Local Committee Affiliations—Reviewer/contributor to AMA Guides, 5th Edition and 6th edition; Chair of EORD Interest Section, American Academy of Allergy, Asthma & Immunology; Member of Occupational Disease Committee, American Academy of Allergy, Asthma & Immunology**;** Reviewer for American Journal of Respiratory and Critical Care Medicine, Allergy and Clinical Immunology, Annals of Allergy, European Respiratory Journal, and Clinical Experimental Allergy, Chest, and Allergy

Other Guidelines Related Professional Activities—Occupational Asthma Committee (Contributing Author), American College of Chest Physicians: "An Evidence-based Guide for the Diagnosis and Management of Occupational Asthma;" "Contact Dermatitis Practice Parameters Update" for American Academy of Allergy,

Asthma & Immunology/American College of Allergy, Asthma and Immunology/Joint Council of Allergy, Asthma and Immunology

Research Grants/Other Support—Colorado Bioscience: Development of diagnostic tests for metal allergy, Colorado Challenge: Mechanisms and diagnosis of metal sensitization

Financial/Non-Financial Conflict of Interest—None

Thomas Winters, MD, FACOEM, FACPM, FACP (Panel Member)

Chief Medical Officer & Principal, OEHN; Visiting Scientist, Occupational and Environmental Health, Harvard School of Public Health; Visiting Lecturer, Harvard Medical School

National, Regional, Local Committee Affiliations—Member, Residency Advisory Committee, Occupational/Environmental Health, Harvard School of Public Health

Other Guidelines Related Professional Activities—Member, ACOEM Evidence-based Practice Opioids Panel

Research Grants/Other Support—None

Financial/Non-Financial Conflict of Interest—Consultations: healthcare and business organizations

Eric M. Wood, MD, MPH, FACOEM (Panel Member)

Occupational Medicine Program Director and Residency Program Director in Occupational and Environmental Medicine, Rocky Mountain Center for Occupational and Environmental Health, University of Utah; Associate Professor (Clinical), School of Medicine, University of Utah; Department of Family and Preventive Medicine, University of Utah

National, Regional, Local Committee Affiliations—Vice-Chair, Occupational Medicine, American Board of Preventive Medicine; Member, ACOEM Maintenance of Certification Committee; Member, ACOEM Council on Education and Academic Affairs; Co-Chair, NIOSH, National Occupational Research Agenda, TWU Sector; Chair, American Board of Preventive Medicine Occupational Medicine Examination Committee; Member, Education Committee, Department of Family and Preventive Medicine, University of Utah; Residency Advisory Committee, Rocky Mountain Center for Occupational and Environmental Health, University of Utah

Guidelines Related Professional Activities— Hospital committee guideline for clinical practice; occupational medicine outpatient clinic guidelines

Research Grants/Other Support— NIOSH (CDC) Training grants and research grants primarily on the epidemiology of musculoskeletal disorders (e.g., CTS, shoulder tendinosis, LBP) and preventing work injuries and chronic illnesses in truck drivers

Financial/Non-Financial Conflict of Interest—Honoraria: Teaching honoraria from various courses, mostly ACOEM-related; Clinical: Primary, secondary and tertiary clinical management of occupational injuries and diseases

Steven Mandel, MD, FAAN, FACOEM, FABQAURP (Panel Consultant)

Clinical Professor of Neurology, Zucker School of Medicine at Hofstra/Northwell; Adjunct Professor of Medicine NY Medical College; Adjunct Professor of Podiatry at Temple University and NY College of Pediatric Medicine; Steven Mandel MD PC

National, Regional, Local Committee Affiliations—Medical Review Officer; Certified Medical Examiner; Reviewer, Journal of Voice; Expert Opinion Editor, Practical Neurology; Past President, NY Occupational and Environmental Medical Association; Diversity and Inclusion Committee, NY State and NY County Medical Society; Wellness Committee, NY State and NY County Medical Society; AMA Ambassador; NY State Liaison of the Senior Physician Section, AMA

Other Guidelines Related Professional Activities—Member, ACOEM Evidence-based Practice Traumatic Brain Injury Panel; Member, ACOEM Evidence-based Practice Ankle/Foot Panel; Member, ACOEM Evidence-based

Practice Opioids Panel; Member, ACOEM Evidence-based Practice Disability Prevention and Treatment Panel; Member, Sports Concussion, American Academy of Neurology

Research Grants/Other Support—None

Financial/Non-Financial Conflict of Interest—None

William Niehaus, MD (Panel Consultant)

Assistant Professor, University of Colorado School of Medicine; Associate Program Director, CU PM&R Residency Program; President and Founder, Free Rehabilitation Services Volunteer Partnership Clinic; Co-Founder, Combined Neuro Therapy Clinic; Medical Director, Outpatient PM&R Services

National, Regional, Local Committee Affiliations—Social Media Editor, Physical Medicine & Rehabilitation Journal; Reviewer, PM&R Journal; Founder and Physician Lead for UCH Proactive Rehabilitative Interdisciplinary Management & Evaluation of Disposition Team QI Initiative; PM&R Physician Advisor, UCH MICU Early Mobility Project; Member, Surgical & Trauma Spinal Cord Injury QI Team; Member, Quality Leadership Tam on the Acute Inpatient Rehabilitation Unit

Other Guidelines Related Professional Activities— Member, AAPMR Clinical Guidance on Assessment and Treatment of Fatigue in Postacute Sequelae of SARS-CoV-2 Infection

Research Grants/Other Support—None

Financial/Non-Financial Conflict of Interest—None

Greg S. Vanichkachorn, MD, MPH, FACOEM (Panel Consultant)

Senior Associate Consultant, Mayo Clinic – Rochester; Medical Director, COVID Activity Rehabilitation Program

National, Regional, Local Committee Affiliations— Co-lead, Mayo Clinic Multidisciplinary Approach Guiding Post COVID Investigation, Education, and Symptom Management (MAGPIES) team

Other Guidelines Related Professional Activities—None

Research Grants/Other Support—Principal Investigator, Mayo Clinic – Rochester: Treatment Outcomes from Early Intervention in Post COVID Syndrome, Post COVID Syndrome: Patient Population and Treatment Outcomes

Financial/Non-Financial Conflict of Interest—Consultant for Brain FX™

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