AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

COVID-19 (Coronavirus)

Effective April 29, 2022

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1. SUMMARY OF UPDATES

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

The total depth and breadth of quality literature for the treatment of COVID-19, although growing, still remains fairly limited, especially on certain important sections of guidance. Further, 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. However, the ongoing severity, urgency, and mortality associated with this pandemic do not allow the luxury of time to await the publication of randomized controlled trial data. 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 this ninth 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 **April 29, 2022** 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
- Emphasis on management of the virus as being 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 fluvoxamine, ivermectin, paxlovid, molnupiravir, bebtelovimab, and sotrovimab

- Recommendations against convalescent antibodies, and casirivimab plus imdevimab (Regeneron)

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.

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[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”) (309).

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 (310) (311). 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 (312) (313) (314) (315) (316). Yet, the source of the virus remains highly disputed (317) (318), with conflicting evidence surrounding gain-of-function experiments and viral alterations(319), and early publications denouncing the laboratory leak theory (318) were subsequently retracted (320). 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 continents and nearly all countries studied.

Quarantines were implemented early in the pandemic. However, they were likely ineffective at slowing or preventing the pandemic (321) 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 emphases 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 a (322)(323); and inadequate detection of the spread of cases in regions prior to the recognition of COVID-19 within that area (324). An added fact later identified that precludes eliminating the virus from the global human population is the susceptibility of animals, although the importance of this potential factor regarding spread to humans is still poorly documented. Evidence of infections in many species of animals, presumably documenting the potential for 'animal reservoirs' (325) (326)(327,328,329), 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 breakthrough 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 relied upon for enactment of these measures. The initial guidance focused on handwashing and restricting travel to 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). Some states began to reopen most, if not all businesses, starting in May-June 2020. Subsequently, restrictions have waxed and waned largely in response to rising and falling COVID-19 incidence rates. Typically, a combination of approaches has been used, including the quarantine of affected individuals, contact tracing, isolation, stay-at-home orders, physical distancing, mask use, and the closure of non-essential businesses (66).

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 where conditions of lower temperatures, lower humidity, less intense ultraviolet (UV) irradiation, and higher indoor population densities combined to likely contribute to record levels of cases in nearly all jurisdictions (330) (331) (332). Additionally, controversy regarding the efficacy and sustainability of various public health measures, especially the (re)closure of businesses and schools, has intensified as the case rates plummeted in 2021. Quality data are weak; some countries (e.g., Japan, South Korea) have instituted less stringent measures with seemingly somewhat comparable or better results (333) (334) (335) (336,337,338) (339) (340) (341) (342) (343). A metanalysis found lack of efficacy of lockdowns (5).

However, beginning in approximately October 2020, the delta variant (B.1.617.2) began to circulate in India (344). This variant was estimated to be approximately twice as contagious as the alpha variant (60), which was twice as contagious as the original virus. The delta variant was found in the United States in spring 2021 and subsequently was found in nearly all countries. While the original delta variant arose in a largely unvaccinated population, it has caused breakthrough infections among the 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 breakthrough fatalities, particularly among the immunocompromised (345) (346), most of the delta variant cases were among the non-vaccinated, as the vaccines still proved to be highly effective in preventing hospitalizations (346) (347) (348)(349,350,351) (352)(353). There were few moves to reinstate restrictions in the United States; however, Australia and some other countries re-instituted severe restrictions with no good evidence of commensurate benefits. Subsequently, there were at least two more 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) (344). However, these variants were eventually displaced by omicron.

In mid-November 2021, the omicron variant (B.1.1.529) was described in Botswana and South Africa (354), with the identification retrospectively from a sample from recently-arrived diplomats November 11, 2021 in Botswana (355). However, 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 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 other source (356)(357). 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. It displaced delta as the predominant variant in the United States in less than one month, by December 25, 2021 (358). 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.

Worldwide, the pandemic continues to provide numerous challenges, especially in regards to the increasingly rapid rates of successive variant transmission, and among countries with lagging immunization rates or that relied on less effective vaccines. Challenges include surges, hotspot outbreaks, attempts at surge prevention, and mitigation; COVID-19 diagnostic testing availability, accuracy, capacities, and limitations; unique treatment challenges and sparse to varying evidence of efficacy; increasingly global public restlessness with restrictions; and increasing business/economic concerns. The economic damages include 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 (359) (360) (361) (362).

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, "termination" of the COVID-19 pandemic is being redefined, as we have come to realize that eradication is impossible. Omicron's substantially lower severity, including an ~91% lower risk of mortality (363), is facilitating the transition from pandemic to endemic management. Attention is now turning to issues such as vaccination breakthrough cases, the frequency of booster immunizations, the duration of vaccine-related immunity, the relative importance of vaccine-related compared with natural immunity, therapeutics, and subsequent viral variants.

3.1. VIRUS CHARACTERISTICS

Contagiousness

COVID-19's SARS-CoV-2 virus appears to be more contagious than the prior coronaviruses, and each successive widespread variant has been ever more successful at spreading (364). 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 (365) (366).

Initially, the virus was thought to be primarily spread through direct contact, resulting in a primary national focus on handwashing (367) (368) (369) . 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) (370) (371) (372,373,374,375,376,377,378,379,380) (381) (382,383,384,385,386,387,388,389,390)(391)(392).

Aerosols can remain suspended in the air potentially for hours (370), 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 (390) (393)[51]. One experimental study estimated aerosolized virions retained infectivity and virion integrity for up to 16 hours (394), 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 beyond 6-foot distances has yet to be clearly demonstrated (395,396,397,398,399,400,387). There is some evidence of a dose-response relationship between dose and clinical severity (401). Regardless, the recognition of aerosol spread has significant impacts on selecting the best preventive measures.

The contagiousness and virulence of the SARS-CoV-2 virus delta variant appear 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., Ro) (402), which is far higher than typical influenza transmission rate of ~1.3 (403). The Ro for delta has been estimated at 5 and the Rho for omicron is estimated at over 7. However, 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 (404). Superspreading has continued to be a purported major mechanism of spread with successive variants (405) (406) (370) (407).

The asymptomatic infection rate of omicron in South African healthcare workers has been reported at 16%, which is approximately 6-fold higher than with the beta or delta variants (408). This striking asymptomatic carriage rate is theorized to help contribute to the rapid dissemination of omicron. Other estimates have ranged as high as 70-90% of cases worldwide being asymptomatic (409) (410). Evidence found prior variants also had evidence of high rates of asymptomatic cases, (411,412) (413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433); however, omicron has exceeded those rates.

The virus's survivability on surfaces varies depending on the material; it has been estimated with experimental methods to survive up to 9 days (434), 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 (390). 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 (434). 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) (435). Survival of the virus in aerosols is thought to be as long as 16 hours (394). 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 (330) (436,437,438,331), and prior data on the SARS coronavirus are corroborative (439). 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 (440). The ecological data indicate that there were slower rates of infection with higher temperatures in Delhi, India, and Pakistan (330) (331), although there was no correlation with humidity (330). 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 (331). Other data suggest lower infections with higher humidity (332) (441). This suggests highly variable disease transmission risks based on seasonality and in indoor compared with outdoor environments.

Incubation and period of infectious viral shedding

The incubation period is the amount of time that occurs between exposure and the onset of symptoms. The incubation period of the SARS-CoV-2 virus was initially estimated to be approximately 5–6 days (323,442,443), while the estimate for delta was 4 days, and the estimates for omicron are 3 days (444). Previously, 97.5% of cases occurred by 11.5 days after exposure and infrequent cases of up to 14 days (445,371,446). There are some recent reports suggesting infectivity is still possible at 10 days(447) (448). Viral shedding may antedate symptoms by 1–2 days, peak viral load occurs 1-3 days before symptoms, (449) 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 (450), although this study measured peak RNA material, which may not correlate directly with maximum viral replication (450).

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) (451,452). Yet, it is less clear whether these particles are infectious, and there are far fewer studies of viral shedding that relied on viral culture suggesting active virus. Even those few studies with viral culture results may not yield enough virus particles that are sufficient to provide an infectious dose (452).

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 (453,454). 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 (455,456,457). 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 (455). No study detected live virus beyond the ninth day (453). 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 (458,459,460,461,462,463), which accelerated markedly with omicron. The risk of re-infection with omicron has been estimated at 5.4 times that of delta (464). Previously, a prior infection was estimated to have provided 85% protection against reinfection, but this estimate has now fallen to 19% (464). Yet, the cases are milder on average.

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

There are at least six distinct types or clinical presentations of COVID-19's SARS-CoV-2 virus infections, the first and third of which incur no healthcare visits; pre-symptomatic individuals may or may not incur healthcare visits (26):

- 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 section for more details).(465,466,467,468,469,470)(471)

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 (472); these symptoms differ compared with prior variants. COVID-19 symptoms may include the following, listed here for prior variants and omicron (407) (371) (473,474,475,476):

- fever, low or high grade (80–88%; omicron: 54%)
- dry cough (63–69%; omicron: 83%) (445,477)

- loss of appetite (39–84%; omicron: 33%) (478)
- 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%) (479)
- hemoptysis (1%)
- rhinorrhea (runny nose; omicron: 78%)
- sneezing (omicron: 43%)
- anosmia and dysgeusia (loss of smell and taste; 85% moderate/severe or anosmic; omicron: 12-23%) (480)

Severity of disease may be related to the inoculation dose (481). The wearing of masks has been theorized to increase the proportion of asymptomatic cases by lowering that inoculation dose (481,482).

Note: The following discussion of symptoms is based on reports of prior variants. It is premature to incorporate findings from omicron reports, although there is a dearth of reports of severe outcomes, unlike with prior variants.

Cardiovascular symptoms and signs were sometimes noted on initial presentation with prior variants (465,466,467,468,469,470). Immunothrombotic dysregulation associated with COVID-19 pneumonia has been described (483). Coagulopathy associated with antiphospholipid antibodies and multiple infarcts have been reported (484,485). Seizures have been reported as a presenting disorder (486). Young and old patients have presented with large-vessel strokes as an initial manifestation of COVID-19 infection (486,487). Pulmonary arterial thromboses have been reported (488). Among ICU patients, 31–59% of patients incurred venous or arterial thromboembolic event(s) (489,490), compared with 10–25% of patients hospitalized for other reasons (490,491). 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 (492). Anti-phospholipid antibodies associated with thrombosis have also been identified in severe COVID-19 pneumonias (492). Recovering competitive athletes also have been found to have cardiac abnormalities on magnetic resonance imaging (MRI) (471).

Dermatological abnormalities such as urticaria, vasculitides, and pityriasis rosea have been described (493,494,495,496). The most common dermatological presentations have been polymorphic and erythematous, chilblain-like, and urticarial lesions (497). Various neurological and psychiatric presentations including stroke-like symptoms, altered mental status, dementia-like syndromes, and new or recurrent affective disorders have been reported (498,499,500,501,502,503,504,505)(506)(299)(298). 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 (507). 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 (508), along with the isolation of viral RNA from urine (509). Most (71%) of those who die from COVID-19 have findings consistent with disseminated intravascular coagulation (510).

Because the symptoms for most patients are typical of nonspecific respiratory tract infections, they can be difficult to distinguish from other diseases (77,78). 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 (511). 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 (512).

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 (513,511,514). The CDC estimates that 40–45% of transmission occurs prior to symptom onset and that the infectiousness is comparable between asymptomatic and symptomatic individuals (513,323). Children tend to be asymptomatic or have milder symptoms, which suggests a mechanism that may accelerate disease transmission throughout the population (511), although this is not proven. It is also possible that the immune system of most children effectively detects the virus with resultant lower average viral loads and thus contagion; however, nasopharyngeal viral loads are not well correlated, whereas saliva viral loads have been correlated with severity (515,516). Regardless, one-third of hospitalized children require ICU stays (517). 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 (518).

Mortality

The mortality rate for COVID-19 has changed considerably over the course of the epidemic, being much lower through successive waves and variants (519) (61). The mortality risk for omicron was 15% of the risk of delta (520); 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) (520).

The mortality of COVID-19 was initially estimated to be approximately 10-fold higher than that of typical seasonal influenza (521). Subsequently, severity estimates have been reported as low enough

to be comparable with prior influenza epidemics (432,522,523,524), with a range of infection fatality rates of 0.03–0.5% and corrected rates of 0.02–0.4% (525). The CDC also estimated the overall *symptomatic* case fatality ratio is 0.004, or 1 in 250 (323). Mortality can be predicted based on risk factors and clinical findings on presentation (526).

Mortality risks prior to omicron increased sharply with age, with a prior symptomatic case fatality ratio of 1 in 2000 among those 0–49 years of age, 1 in 500 among those 50–64 years of age, and 1 in 77 among those 65+ years of age (323). The mortality rate for males is 57–64% higher than that for females. Nursing home residence is a particularly potent fatality risk (527,528,529,530,531). 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 (380,532,533,534,535,536,537)(538); however, approximately 1% of fatalities occur in previously healthy patients (539). 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 (540). The O and Rh- blood group types appear to have slightly lower risk of infection and severe disease(541). 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 (542). Past outbreaks of coronavirus infections had considerably higher mortality rates: 34% for MERS and 10% for SARS. However, the mortality rate is not the only factor in determining the seriousness of a disease; a high rate of infectivity and/or easy transmissibility could result in many more total deaths despite a lower case fatality rate.

3.3. BUSINESS CONSIDERATIONS

The actions an employer can 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 virus's aerosol and rapid spread combined with lowered morbidity in a largely immunized and/or immune population. Industry sectors with higher risks of workplace COVID-19 outbreaks have reportedly included manufacturing, agriculture, forestry, fisheries, transportation, and warehousing (2). Regardless and importantly, there appears to be a strong potential for a patchwork of different health department regulations in different jurisdictions during the 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 is likely to be effective at 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/KN85 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 particularly given that the current vaccination rates vary more than 100-fold across the globe (4), and it can be anticipated that differences by 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 arise than the omicron or delta variants, then consideration of re-institution of some public health measures may be indicated. Otherwise, most public health measures are proving of little if any use for omicron and were also of little if any 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 (543,544). 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.

As the omicron surge has occurred with most of the population protected by vaccines that are partially effective, it is unclear whether the updated vaccine boosters planned for release in Spring 2022 to cover omicron will be necessary. As the projected updated vaccination release will be after the omicron surge has been exhausted, adverse effects on a population basis may be greater due to widespread natural immunity, especially if given too quickly after the surge when the antibody levels are highest. Further, the data for booster benefit are largely in the elderly and those at high risk; there are limited data that boosters make a difference in transmission. Given mild clinical omicron variant presentations in most of the population and unknown long term effects of repeated boosters, further requirements for the young, healthy population currently appear premature

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 extraordinarily 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 with or without temperature measurements. Electronic questionnaires are likely to be more effective than temperature measurements because 69% of seriously ill individuals are afebrile (545). Evidence suggests temperature screening is ineffective and detects only one case for every 40 cases missed (546); temperature measurements are also likely to miss all subclinical and many symptomatic cases (323). 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% (371); thus, cases with high indices of clinical suspicion should typically be treated as presumptive cases (371). 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) (547) (548). Accordingly, the CDC modified the return-to-work provisions to 5 days (549). This phenomenon is typical of an endemic disease where infected and asymptomatic or minimally ill workers are not removed (547) (548). 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.

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 (550). If there is believed to be SARS-CoV-2 virus transmission in the area (currently true of essentially all US urban and many rural areas, although the rates are now decreasing markedly), then anyone with even mild symptoms of a respiratory tract infection (e.g., cough, fever, fatigue) should stay home to be sure they do not progress to a clear, and potentially severe, COVID-19 infection (511), as well as to prevent transmission to others. Sick employees should also be encouraged to undergo testing if available. They should be instructed to call a provider or healthcare organization in advance, discuss the symptoms, seek testing if available (especially at outdoor tents), and wear a mask in public settings.

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

Readers are advised to refer to current CDC guidance, as this changes frequently (551) (549). 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 (552,553). 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. The areas where the sick employee worked, including conference rooms and common areas, should undergo deep cleaning and decontamination to prevent spread to other employees.

Employees in contact with an infected coworker

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

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 (554). Otherwise, employees in contact with an infected coworker should continue to undergo medical screening. Close contacts are defined as any individual who was within 6 feet for 15 cumulative minutes over 24 hours starting from 2 days before symptoms onset (555,556). 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) (557). 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. 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 (558,559). 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 manpower shortage situations, medical centers, and critical services, COVID-19 exposed workers are being allowed to work while asymptomatic with self-surveillance for symptoms, physical distancing, disinfection of workspaces, and consistent mask-wearing instead of being quarantined (560). 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 carefully weighed between the industry sector, criticality of the job, job requirements, and risks of an infectious individual in that particular workplace. This option is likely unduly risky if the workforce or work group is mission critical.

High-risk employee issues

For the purposes of these recommendations, high-risk individuals have any of the following conditions (545,561):

- 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 (532)
- diabetes mellitus
- chronic kidney disease, especially those undergoing dialysis
- liver disease
- hypertension
- current cancer
- neurological diseases, including stroke and dementia

Generally, the risks of severe illness associated with the above conditions are greater as the severity of the conditions increase. The presence of multiple conditions increases the risk of severe disease (79).

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

- emphasize distance-based work methods, including telecommuting where feasible.
- place all, but especially high-risk, individuals behind barriers.
- institute physical distancing (10).
- 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).

3.3.2. TRAVEL ISSUES

Travel bans, restrictions, and broad testing are no longer recommended. They are 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 that moves rapidly and without quick detection to a peak surge in 1-2 months in essentially all countries. Such restrictions may again be needed should a future variant surge have markedly higher mortality rates above that associated with the delta or omicron variants. Still, there are risks, especially for some employees on business trips. Travel risks include those associated with travel to and from a site, as well as business conducted at those sites (6). Risks differ considerably by mode of transportation, geographic locations, current state of the epidemic in any given locale, and vaccination rates. Businesses need to weigh the value of the travel against the risks associated with that travel.

Fully vaccinated employees may reasonably travel. For non-vaccinated employees, especially those not known to have natural or vaccine-related immunity, travel valuations should include costs associated with any potential illness and any post-trip quarantine period. Caution is advised for non-essential travel by non-vaccinated and non-immune employees to locales with outbreaks or community spread in progress (6), which includes the entirety of the United States and most of the world (see map to help with other risk considerations (7).

International trips continue to be significantly affected as many countries are limiting travel from countries with outbreaks, despite the increasingly dubious value of these restrictions as demonstrated by the universal rapid spread of omicron. Air travel may be 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-quarantine while working from home for 5 days.

3.3.3. PHYSICAL DISTANCING METHODS

In the transition to an endemic disease, physical distancing is increasingly of less use, particularly for what has become an easily-transmitted, aerosol-spread disease. The primary exceptions involve ring isolation to protect those who have major immunosuppressed conditions (e.g., leukemia; undergoing chemotherapy treatment). Otherwise, physical distancing methods are no longer recommended.

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 the past 30 minutes, and using an N95/KN95 respirator for 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, even for immunocompromised individuals, is increasingly dubious.

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, because it does not rely on training and compliance, and in the initial stages was thought to involve a 6-foot distance (9). 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 are likely to be either minimally or wholly unsuccessful with aerosol-spread viruses and are no longer recommended:

- **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 aerosol-spread, vaccination of the population, and the impairments of communication 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.

PPE measures (respirators, masks, gloves, and eye protection/face shields (10,11,12,13,14,15) 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 state or country 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 exhaust supplies of N95 respirators. In such a case, extended use and re-use of respirators will be essential.

3.3.5. VENTILATION ISSUES

Ventilation issues (general and local fresh air supply) have been markedly underutilized as potential COVID controls (16,17,18,19,20). 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 the future reduction in 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 (21,22).
- air disinfection, such as ultraviolet germicidal irradiation, can be placed within the central HVAC system (19,22). 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 (23). Disinfection of surfaces may have some limited 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 pandemic, it is anticipated that subsequent variant surges may be relatively mild. Regardless of whether the next variant is mild or severe, now is the time for comprehensive after-action reviews (i.e., 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 why things happened, 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.

The following are potential policies and procedures to consider:

- inform and seek support and authorization for the plan from the organization's leadership.
- develop a plan in conjunction with occupational health and safety professionals, government regulations, and public health authorities (including the CDC).
- ensure affected workers have sufficient paid leave to observe a quarantine period or are able to stay home as indicated.
- continue to monitor sickness absence, but expand sick leave provisions to allow employees to stay at home if ill and to care for sick family members.
- teach workers about the principles of microdroplet/aerosol spread viruses.
- 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. 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 (24,25,26,27).
- 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, have employees who develop symptoms stay away from the workplace until clinically evaluated and/or until the symptoms are resolved and any quarantining period has expired.

- 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 manpower shortage situations, medical centers and critical service workers are being allowed to work while asymptomatic with self-surveillance for symptoms and consistent mask-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).

- 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 can determine infection risk in critical and susceptible populations (under medical direction to ensure proper implementation, interpretation, and management). Examples of these critical populations include employees in health care settings, oil drilling platforms, commercial maritime, food preparation, cruise lines, airlines, and assembly lines with workforces working closely together.

- provide proactive assistance to support mental health for the workforce.

- identify and train workplace coordinators who will be responsible for implementing and monitoring the plan.

3.3.8. INDUSTRY-SPECIFIC RECOMMENDATIONS

Below are select industry guidelines, which are in addition to the general guidance above. These guidelines assume lack of herd immunity and/or ongoing community-based spread. Further guidance is available from the CDC (21).

Restaurants

- Menus should ideally be either disposable or laminated and sanitized after each customer contact. Other options are electronic access and use of QR codes.

- Clean and disinfect chairs and tables between use (see Disinfection Practices).

- Assign high-risk employees with multiple co-morbidities or concerns to low-exposure areas, such as working in non-customer-facing areas as much as possible.

- Encourage drive-through and carryout options

Retail

- Stocking by high-risk individuals should ideally be done when customers are not present.

- Encourage customers with high risk to use N95/KN95 respirators and provide N95/KN95 respirators to such affected customers where feasible.

Gyms

- Gym housekeeping should ideally be performed by low-risk employees.

- Increase local and area ventilation to address increased the increased respiratory rates associated with exercise.

Manufacturing

- Evaluate and improve ventilation.

Food Production Facilities

- Evaluate and improve ventilation.

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 (28,29,30). 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 (31,32). Initial reports that children do not become infected appear increasingly dubious (33); however, that they are resilient to symptomatic and/or severe disease is not in question.

Schools in most countries were at least temporarily closed in spring 2020 in response to the pandemic. However, students' learning by distance-based methods has been reportedly suboptimal and sometimes poor. The burden of the inability to educate students using traditional methods also disproportionately falls on the poor and immigrant populations, which have fewer skills and resources to educate and/or guide their children's learning (34,35,36,37,38). 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 (36). 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 (39). Schools also play important roles in students' social development and mental health (40,41,42).

Restarting of schools was controversial, 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 (43). The main contrary example is Israel, where school-based transmission to teachers was briefly noted (44,45).

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 distance-based teaching methods.

There may be a consideration for institution of distance-based teaching methods with a future surge; however, this would not be recommended due to adverse effects, including marked reductions in learning associated with lockdowns (46), unless a subsequent variant causes markedly higher morbidity and mortality than delta or omicron. If subsequent variants become more transmissible, It is also highly improbable that masks be effective in schools regardless of any potential increases in morbidity. Thus, due to an absence of evidence of efficacy and evidence of harms, including marked reductions in learning associated with lockdowns (46), physical methods such as masking and distancing are not recommended for schools.

3.4. DISABILITY AND RETURN-TO-WORK CONSIDERATIONS

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

Preliminary reports suggest recovery duration is, unsurprisingly, at least partially correlated with measures of case severity. At least one symptom persisting for at least 60 days has been reported among hospitalized survivors, with the most prevalent symptoms being fatigue, dyspnea, joint pain, chest pain, cough, and anosmia (303). 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 (562). However, persistent symptoms are reported in individuals with mild cases, and long-term symptoms have been reported (563). There also are many cases that require home healthcare after discharge (564).

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.

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” (565). 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 can include a lack of full implementation and utilization of evidence-based treatments, and lack of effort and compliance. Other factors may potentially involve advocagenic, psychological, and other influences.

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

Currently, for patients without hospitalization, there are no quality data on returning to work, short-term disability, or long-term disability. One random sample (n=292) of affected individuals diagnosed as outpatients reported 65% had returned to normal health at a median of 16 days; no or few comorbidities and age statistically impacted those rates, with 74% among those 18–34 years of age, 68% among those 35–49 years of age, and 53% among those 50 years and older returning to normal health (566). Regarding short-term disability and return to work, recovery from post-infection fatigue is estimated to take approximately 2–3 weeks and appears to correlate with clinical duration and severity. For patients with mild to moderate pneumonia treated with oxygen supplementation, recovery is estimated to require 4–8 weeks after hospitalization or clinical recovery. Severe pneumonia and ARDS have worse prognoses.

The overall trajectory of recovery from COVID-19 remains unclear. Prior experience with diseases that have similar manifestations, such as ARDS, suggest there is significant risk of delayed return to work and long-term disability, as approximately 50% of individuals surviving ARDS have not returned to work after 1 year (567,568). 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 (569). Lung diffusion abnormalities can take up to 5 years to resolve in ARDS cases (569,570).

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 (568,569,570,571,572,573,574). 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 (568,571,575,576). Cardiac problems are common with COVID-19, with cardiomyopathy, arrhythmia, and direct cardiac muscle injury affecting approximately 30%, 20%, and 10% of patients, respectively (258); they are contributing causes to fatality (258,259,260).

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 (261). 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 (568,569,570,571,572,577). There is also the potential for a minority of patients to be permanently totally impaired (572).

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 (578). 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 (579) and 6th Edition (580).

4. VACCINES

Vaccine development progressed at record speed on more than 270 COVID-19 vaccine candidates (550,581,582,583). These efforts used at least four types of vaccine classes or approaches against this infection (virus, viral vector, nucleic acid, and protein-based) (582). Although vaccine development was estimated to require 12–18+ months if successful, it was achieved in approximately 9–10 months (584). Several more of these COVID-19 vaccines are in advanced stages of development and have potential for approval. Efficacy data have been published. Safety data suggest the vaccines are largely safe. Reported rates of initial vaccine efficacy range from 62% to 95% (585) (586)(587) (588). After initiating vaccination programs, COVID-19 infections declined markedly (589). However, vaccine efficacy fell with subsequent waves of new variants (590). Accordingly, booster shots which have increasingly been suggested to have retained partial efficacy against the delta and omicron variants have been emphasized (590,591,592).

The London School of Hygiene & Tropical Medicine's COVID-19 Vaccine Tracker is updated weekly with multiple COVID-19 vaccine databases, including a vaccine pipeline tracker, clinical trials

database, and living review (581,588). The CDC has also provided guidance regarding what is recommended for those who have been vaccinated (593).

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 (594).

4.1. 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* (47), 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.

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 (49). 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 (50). Of these, 10 were women, 8 had a prior history of allergy or allergic reactions, 9 described itching, 9 described pain, and 7 described fatigue or other systemic symptoms. Most were treated with antihistamines and topical steroids, and two received oral steroids. Reactions resolved by day 14 to 19. All then received the second vaccine dose, with only minor rash or itching reported; none were severe.

In addition, there have been reports of 36 cases of immune thrombocytopenic purpura (ITP) following the vaccination of 31 million people as of February 8, 2021, but no cases were associated with any one vaccine or vaccine lot. The majority of patients received platelet transfusions, IVIG, and/or steroids along with hospital care; there was one reported death. Importantly, ITP has been associated with other vaccines, including the MMR, DTaP, varicella, hepatitis B, and pneumonia vaccines (51), 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 (52).

Thus far, probably the most important adverse effect appears to be myocarditis among young males. The population-based risk has been estimated at 5.3-fold overall, with highest risk of 13.6-fold among those 16-19 years old males (52).

4.2. 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 (53,54).

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 (55). 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 (56).

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 (57).

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 (58).

The most important variants to subsequently arise are the Delta (B.1.617.2) and Omicron (B.1.1.529)(59). Delta became the predominant variant by summer 2021 (REF) (60). 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 (61).

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 (62). 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 (63). 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 (64).

4.3. VACCINE RECOMMENDATIONS

Vaccines for the Prevention of COVID-19

Recommended

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

Strength of evidence Strongly Recommended, Evidence (A)

Level of confidence High

Indications

Indicated for nearly all adults. Particularly indicated for those with increased risk of severe COVID-19 disease (e.g., elderly, obesity, diabetes mellitus, COPD, cardiovascular disease, renal disease, immunosuppressed states).

Common RCT exclusion criteria include pregnancy, immunodeficiency, immunosuppression, use of glucocorticoids 20+ mg/day in the past 6 months, and prior vaccine allergic reactions. However, studies also now 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 evidence supports durability of the antibody responses from natural immunity. Regardless, CDC guidance recommends vaccination irrespective of prior infection(s) (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 mortatlity 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).

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%) [316, 335, 336]. 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 [337](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 all show that booster immunizations raise antibody levels and markedly 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 suggets 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 (65). 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, 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. Masking mandates have been used for control of COVID-19 both in the workplace and in some jurisdictions (e.g., statewide) (66).

Masking for the Prevention of COVID-19 Transmission

Not Recommended

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 and changes in understanding of disease transmission. However, masking appears ineffective. In contrast with masks, N95 respirators may be indicated for select populations, such as high-exposure workers and workers with high personal risks (see Respirator recommendation).

Strength of evidence Not Recommended, Insufficient Evidence (I)

Level of confidence Low

Rationale

Most RCTs of masking to protect from respiratory viruses have been negative (see below). Recently in the COVID-19 pandemic, the omicron variant was found and peaked throughout the world in ~2 months and produced nearly identical epidemic curves irrespective of population-based masking requirements. A prior large, cluster-randomized trial found only an 11% reduction in risk of infection, however the trial was 2 SARS-CoV-2 strains ago when the disease was much less transmissible (Abaluck et al., 2022). Since then, omicron has rapidly moved around the world irrespective of masking and/or physical distancing-business openness in countries and/or states. 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). One trial of mask use for COVID-19 assessing household transmission failed to find at least 50% reduction in risk and reported that most disease acquisition was thought to be community-based (Bundgaard et al., 2020).

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).

Randomized trial data with more remote and less transmissible strains showed only 11% reduction in risk and subsequent data suggest a lack of significant efficacy and inability to either alter the rate of, or shape of epidemic curves. Thus, masking is not recommended. Although there are no

significant quality data for COVID-19, N95 respirator use may be selectively recommended to attempt 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

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 (see Masking recommendation). In contrast with masks, N95 respirators may be indicated for select populations (e.g., high-exposure workers, workers with high personal risks).

Strength of evidence Recommended, Insufficient Evidence (I)

Level of confidence Low

Rationale

Most RCTs of masking to protect from respiratory viruses have been negative (see below). Recently in the COVID-19 pandemic, the omicron variant was found and peaked throughout the world in ~2 months and produced nearly identical epidemic curves irrespective of population-based masking requirements. A prior large, cluster-randomized trial found only an 11% reduction in risk of infection, however the trial was 2 SARS-CoV-2 strains ago when the disease was much less transmissible. Since then, omicron has rapidly moved around the world irrespective of masking in countries and/or

states. 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. One trial of mask use for COVID-19 assessing household transmission failed to find at least 50% reduction in risk and reported that most disease acquisition was thought to be community-based (Bundgaard et al., 2020). A low-quality large cluster randomized trial in Bangladesh found an 11% reduction in risk of infection (Abaluck 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). 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). 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). Randomized trial data with more remote and less transmissible strains showed only 11% reduction in risk and subsequent data suggest a lack of significant efficacy and inability to either alter the rate of or shape of epidemic curves. Thus, masking is not recommended. Although there are no significant quality data for COVID-19, 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 regardless. 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' vapor trails while using inadequate protection for a highly contagious aerosol).

Studies are beginning to be published concerning the efficacy of lockdowns. Most studies have reported some reductions in COVID-19 transmission after the implementation of a lockdown (67,68), although it has been reported that lockdowns were not effective in Europe (67). An ecological study suggested greater spread where restaurant dining was allowed (69). One analysis of multiple countries found non-significant small reductions in COVID-19 case rates in most countries, which was not felt to be outweighed by the costs (67). Reports have questioned the cost-benefit efficacy of lockdowns (70,71)(5). Adverse mental health effects have been reported (72,73,74,75,76). The subject of lockdowns requires considerably greater research, especially as future surges attributed to variants seem likely; the re-implementation of such lockdown policies may necessitate a stronger evidence base.

The overall 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;
- are likely to have contributed to increased problems with anxiety, depression, other mental health disorders and drug overdoses;
- were associated with job loss and unemployment; and
- were generally accompanied by cessation of in-classroom teaching at schools, which were also ineffective and harmful.

Lockdown measures are not recommended (5).

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 (77,78):

- 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 (79). 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 (80).

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) (81).

7.2. DIAGNOSTIC TESTING

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

- polymerase chain reaction (PCR)-based testing (aka, nucleic acid amplification test), typically using swabs (595);
- antigen testing, and

- antibody testing of blood serum.

PCR testing is considered to be diagnostic of the infection because it detects the actual virus or viral particles. Antigen tests have been approved by the U.S. Food and Drug Administration (FDA) and are also considered diagnostic (596). 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 (597). 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 (REF).

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 (598). One study detected higher SARS-CoV-2 titers in saliva compared to nasopharyngeal swabs, with less longitudinal variability (599). A meta-analysis found similar sensitivities and lower costs for saliva sampling compared with nasopharyngeal swabs (600). Thus, saliva testing is increasingly replacing swabs to provide near universal sampling coverage for both symptomatic and asymptomatic patients (601). 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 (602).

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 (603). 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 (604,605):

- 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 (606).

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 is ill-advised given that the risk of false-negative tests are 20–67% (371). Thus, there is a strong indication to presumptively treat cases who test negative, which requires experienced medical judgment. Repeat testing may be indicated for those with a negative test but a high index of suspicion.

PCR testing is also recommended for inpatient and outpatient preoperative assessments. Preoperative tests must be ordered sufficiently ahead of surgery such that the results are received in time to address/respond to the results (generally 72–96 hours before surgery).

Strength of evidence Recommended, Insufficient Evidence (I)

ANTIGEN TESTING

Antigen tests detect viral proteins either on or within the virus. These have been FDA-approved and are considered diagnostic (596). Antigen testing is growing in popularity as its main strength is rapid test results, which are provided in minutes compared with up to several days for PCR tests. 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 (607).

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. 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)

ANTIBODY TESTING

Antibody testing detects the body's humoral response to the virus (608,609,610,611,612,613). Most antibody tests detect IgG, although some tests attempt to also detect IgM or IgA. The median IgM seroconversion is 11–13-days (or 5–7-days after symptoms onset), while the median seroconversion for IgG is 14-days (or 8-days after symptoms onset), although IgM may wane after 2- to 3-weeks, and IgG persists for a far longer period of time (614). A positive antibody test does not exclude the potential for the patient being infectious with COVID-19. Antibody tests are in early stages of deployment and reported reliability varies widely (610,611,612). Because there is no reference standard and widespread testing of large populations have not been reported, the determination of test accuracy, sensitivity, and specificity remain problematic. In addition, the timing of the antibody testing is critical to accurate detection: testing too soon after infection onset, or too late after infection resolution, can further increase risks of negative results.

It has been aspirational that immune status testing (IgG, IgM) would eventually be the most important test for population-based risk assessments, such as herd immunity. This still requires considerable research, including large-scale determinations of sensitivity, specificity, reliability, timing, persistence of the immunoglobulins, and whether the immunoglobulin status identified by testing will be associated with true immunity (615). Preliminary evidence includes a large population-based Spanish study suggesting a 87.6–91.8% seroprevalence rate among those who had PCR confirmation of infection; yet, individuals meeting a case definition of anosmia or at least 3 relevant symptoms had a seroprevalence rate of only 15.3–19.3% (616). 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 (617). Others have correlated titers with disease severity (611). 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 (618).

Evidence also suggests immunoglobulins may not be measurable over time (619). 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 (620,621). Hence, a lack of measurable immunoglobulins may not indicate lack of immunity. If these lines of research remain viable, then it is theoretically possible for immunoglobulin testing, perhaps combined with history, to help designate workers who may more safely interact with the public. If proven, antibody testing may be used to assure a workplace that a previously infected worker is safe to return to work (i.e., that they are not actively infected and unlikely to be shedding virus). Unfortunately, the currently available antibody tests have yet to be sufficiently validated on a widespread basis, and inaccuracies are increasingly reported (622,623). Once these problems are addressed, it is anticipated that antibody testing may become widespread in many workplaces and other populations of concern (e.g., nursing homes, mission-critical workers, irreplaceable workers, dispatch centers, C-suite executives).

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

Antibody Testing for Assessing COVID-19 Immune Status

Sometimes Recommended

Antibody testing is selectively recommended for assessing immune status regarding the potential for COVID-19. These tests should be interpreted by experienced medical and/or public health professional(s) who are thoroughly knowledgeable about numerous factors, including the specific test, its reported performance (e.g., sensitivity, specificity), the prevalence of COVID-19 in the specific community, principles of testing, Bayes' theorem, and assessment of pre-test probability and post-test odds. In general and at this point, antibody testing should be limited to only mission-critical workers and special populations. As the experience with these tests improves, the populations assessed may markedly expand. As a general statement, a person who has recovered from COVID-19, has a duration of at least 10-days since first symptoms, and has demonstrated antibodies would not be infectious or capable of transmitting infection and scientifically would no longer have to wear a mask or participate in mitigation procedures.

Specific examples where serology might be helpful include the following:

- patients with symptoms consistent with COVID-19 of more than 1-week in duration, for whom PCR testing has been negative and no alternative diagnosis has been found. For these cases, a positive IgG serology would be diagnostic. A negative serology could be repeated at >2-weeks from symptom onset and repeat negative testing would then effectively rule out COVID-19.
- patients with initial negative PCR and serology at <2-weeks after symptom onset but who remain symptomatic beyond 2-weeks without an alternative diagnosis. Repeat serology testing documenting seroconversion would be diagnostic, whereas failure to seroconvert would help to rule out COVID-19.
- symptomatic, febrile, PCR-positive patients with an unknown time since infection where presence of antibodies might help in choice of therapeutic modalities (e.g., antivirals and/or convalescent serum before antibodies arise).

Strength of evidence Recommended, Insufficient Evidence (I)

7.3. IMAGING

Radiographs for the Diagnosis of COVID-19

Recommended

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

Computed Tomography for the Diagnosis of COVID-19

Recommended

Computed tomography (CT) scans are recommended for the diagnostic evaluation of COVID-19. CT is commonly performed (Udugama et al., 2020, Sun, 2020) and shows patchy infiltrates and ground-glass opacities (Chan et al., 2020, Li et al., 2020, Li et al., 2020, Iwasawa et al., 2020, Liu et al., 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 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).

Strength of evidence Recommended, Insufficient Evidence (I)

8. TREATMENT RECOMMENDATIONS

8.1. OVERVIEW

Treatment is increasingly guided by randomized controlled trials (RCTs), yet it continues to evolve as data are published. Many additional studies are underway. However, variants are providing a significant challenge as they provide 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 (624,625,626,627,628,629,630,631)(632)(633). The FDA continues to provide unprecedented flexibility to accelerate the development of new drugs and testing. No treatment is yet unequivocally indicated for asymptomatic cases; there is an NIH recommendation for prophylactic treatment with tixagevimab plus cilgavimab, although it is unclear if this is an effective approach for the latest variant(s) (634).

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, azithromycin, baloxavir, baricitinib, chloroquine, colchicine, favipiravir, glucocorticosteroids, hydroxychloroquine, immunoglobulin, interferons, ivermectin, lopinavir/ritinovir, nitric oxide, paxlovid, ribavirin remdesivir, sarilumab, siltuximab, statins, Sotrovimab, thrombolytics, tocilizumab, zinc (635,636,637,638), vitamin C (639), and vitamin D (640,641,642,643). Many of these treatments have no quality evidence of efficacy, and some have evidence of a lack of efficacy. There is no clear evidence of lower risk of mortality with statin use (644). Vitamin D levels have been strongly correlated with COVID-19 disease severity (640,642,643); 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 (640). Still, while some studies are suggestive, strong evidence that vitamin D supplementation affects mortality risk has not been published. In general, considering public health, having a vitamin D level of at least 20-30 ng/mL is reasonable (238) (237)(645))

Glucocorticosteroids have been shown in multiple quality trials to reduce mortality (646,647,648). Data also suggest that low-molecular-weight heparin likely reduces mortality and shortens ICU stays (649).

If individuals develop more severe symptoms or have complications (e.g., ARDS or respiratory failure), they are primarily treated with non-invasive ventilatory support measures, glucocorticosteroids, anti-cytokine storm agents, mechanical ventilation (including prone positioning), other respiratory support measures, and prophylaxis for deep vein thrombosis, including low-molecular-weight heparins (650,651,652). Evaluations should include exclusion of other causes (e.g., influenza). The efficacy of glucocorticoids appears to be related to the stage of the COVID-19 infection. Glucocorticosteroids used early in the time course of infection do not appear to improve outcomes, and in theory could potentially allow viral replication to increase and foster the development of other infections.

Multiple agents have been studied to attempt to suppress the purported cytokine storm; most of the trials are centered around interleukin-6 (IL-6) (653). Yet, most quality data on IL-6 receptor antagonists have been negative. There is ongoing controversy regarding a cytokine storm in relation to ARDS caused by COVID-19 [457]. There are many cytokines believed to be involved in the cytokine release syndrome (IL-2, IL-7, G-CSF, IFN-γ, inducible protein 10, MIP 1-β, TNF-α).

Antiviral medications may have minimal to no role in advanced pneumonia or ARDS (654), particularly as viral replication appears to peak at or about the time of symptoms onset. However, antiviral therapies are showing increasing promise to lessen the severity of the disease among outpatients who are treated early in the disease. Two therapies targeting this window were previously approved by FDA under emergency use authorization: bamlanivimab and casirivimab/imdevimab; however, the omicron variant appears to evade these therapies. Data on hydroxychloroquine (HCQ) suggest efficacy early in the symptomatic phase, while there is also clear evidence of inefficacy for later stage use (655). 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 (656); there appear to be parallels with influenza medications used within 48 hours of symptoms onset.

Projecting this pandemic forward through expected waves of variant surges, it is expected that monoclonal antibodies will potentially become rapidly partially or wholly ineffective, especially those targeting the spike protein when a new variant arises to thwart that antibody. Antiviral medications that target the replication processes of the virus may also become ineffective. However, based on other viruses (e.g., influenza), the rate of such resistance is anticipated to occur at a far slower rate.

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

- **Outpatient**

  Mild: No treatment unless high risk for progression to severe disease

  Moderate/severe:

  1. Sotrovimab
  2. Molnupiravir
  3. Paxlovid (Nirmatrelvir/Ritonovir)

4. Fluvoxamine
5. Ivermectin
6. Hydroxychloroquine for 5 days
7. Vitamin D, Zinc

- **Inpatient moderate**
    1. Glucocorticosteroids
    2. Low-molecular-weight heparin/unfractionated heparin
    3. Remdesivir
    4. Oxygen supplementation
    5. Vitamin D
- **Inpatient severe/critical**
    1. Glucocorticosteroids
    2. Low-molecular-weight heparin/unfractionated heparin
    3. Remdesivir
    4. Oxygen supplementation
    5. Prone positioning (due to shunting) and/or non-invasive ventilation (NIV)
    6. Mechanical ventilation, prone
    7. Extracorporeal membrane oxygenation (ECMO)
    8. Vitamin D

Additional treatments are being studied, including antiviral mouthwashes and nasal sprays (657,658)(659,660),(661,662)(663) melatonin (664,665,666,667,668,669,670), 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 (77,671,672,673,674,675,676,677,678). An association between adverse mental health and financial concerns has been noted (679). Recent data from a small autopsy study suggest findings similar to Alzheimer disease in the brains of those deceased from COVID (680).

8.2. HYDROXYCHLOROQUINE OR CHLOROQUINE

Hydroxychloroquine has been used for the treatment of COVID-19 (635,638,654,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,97). There also are many in vitro studies suggesting antiviral activity (720,721,722,723,724,725,726,727,728). Chloroquine has been used for the treatment of COVID-19 (729). Hydroxychloroquine has been used for prophylaxis for COVID-19, most typically among healthcare workers (717,730).

Hydroxychloroquine for Treatment of COVID-19 - Use in First 3 Days of Symptoms

Recommended

Hydroxychloroquine (HCQ) is recommended for use in the first 3 days of symptom onset.

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

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). 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).

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). Because there is quality evidence of efficacy for the early use of HCQ, it is recommended for these select patients.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 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

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

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:

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- Hydroxychloroquine 400mg BID x 1 day, then 400mg QD for 4 days.
- 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 (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) 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). 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, by analogy to hydroxychloroquine, chloroquine is not recommended for treatment of hospitalized COVID-19 patients. See the Hydroxychloroquine Rationale for Recommendation for details.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to 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. 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 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). 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.

8.3. 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 (82,83,84,85). Azithromycin has been used for treatment of COVID-19, as both stand-alone and combined therapy (86,87,88).

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). 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, AZQ 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, Lagier et al., 2020, Arshad et al., 2020, Guérin et al., 2020, Gautret 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 adjunctive treatment of selected patients with more severe COVID-19.

Strength of evidence Not Recommended, Evidence (C)

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, 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, AZQ 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 (Lagier et al., 2020, Gautret et al., 2020, Arshad et al., 2020, Guérin et al., 2020, Gautret 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.

8.4. 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 (89,90,91,92,93,94,95,96).

Favipiravir for the Treatment of COVID-19

No Recommendation

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

Strength of evidence No Recommendation, Insufficient Evidence (I)

Level of confidence Low

Rationale

RCTs among those who were treated late and/or who initiated treatment while hospitalized are 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).

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).

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). There is one non-randomized controlled trial suggesting acceleration of viral clearance compared with lopinavir-ritonavir (Cai et al., 2020).

There is a dearth of evidence of early treatment and conflicting evidence for the late use of favipiravir. Thus, there is no recommendation for either early or late use.

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.

8.5. LOPINAVIR/RITONAVIR

Lopinavir-ritonavir has been used for the treatment of COVID-19 (97,98,99,100,101,102,103,104,105,106).

Lopinavir/Ritonavir for the Treatment of COVID-19 - Combination Therapy

Recommended

Lopinavir-ritonavir is recommended in combination therapy (Hung et al., 2020), but is not recommended as a stand-alone treatment for COVID-19.

Strength of evidence Recommended, Evidence (C)

Level of confidence Low

Indications

Most evidence has suggested a lack of efficacy of Lopinavir-Ritonavir and adjunctive use with ribavirin and interferon beta-1b in moderately and severely affected patients with COVID-19 (Hung et al., 2020). Some evidence has suggested 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). 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).

Most studies suggest lopinavir 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.

Lopinavir/Ritonavir for the Treatment of COVID-19 - Stand-alone Treatment

Not Recommended

Lopinavir-ritonavir is not recommended as a stand-alone treatment for COVID-19.

Strength of evidence Not Recommended, Evidence (C)

Level of confidence Low

Indications

Most evidence has suggested a lack of efficacy. Adjunctive use with ribavirin and interferon beta-1b in moderately and severely affected patients with COVID-19 (Hung et al., 2020). Some evidence has suggested 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). 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 (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). Most studies suggest lopinavir 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.

8.6. REMDESIVIR

Remdesivir has been used to treat COVID-19 (107,108,109,110,111,112,113,114) and is recommended by other systematic reviews (115).

Remdesivir for the Treatment of COVID-19 - Use in First 3 Days of Symptoms

No Recommendation

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

Strength of evidence No Recommendation, Insufficient Evidence (I)

Level of confidence Low

Indications

Severe COVID-19 patients, with <94% O2 saturation or need for O2 supplementation, mechanical ventilation, or extracorporeal membrane oxygenation (Hinton, 2020). Patients included in trials had creatinine clearance >30 mL/min; ALT and AST <5 times upper limit of normal.

Benefits

Shortened ICU stay, but minimal to no impact on survival

Harms

Increased hepatic enzymes, diarrhea, rash, renal 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 for 9 additional days (Beigel et al., 2020, Grein et al., 2020).

Indications for discontinuation

Completion of a course, intolerance, adverse effect.

Rationale

There is one high-quality RCT of remdesivir suggesting a lack of clinical efficacy, although it also suggests non-significant trends toward earlier clinical improvements (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). 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). 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).

Remdesivir is invasive (IV), has minimal adverse effects, is high cost, has conflicting evidence of modest efficacy (particularly for the treatment of hospitalized patients requiring oxygen), and thus is selectively recommended. There are other treatments with stronger efficacy at reducing mortality (e.g., glucocorticosteroids, low-molecular-weight heparin).

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.

Remdesivir for the Treatment of COVID-19 - Use Beyond First 3 Days of Symptoms

Sometimes Recommended

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

Strength of evidence Recommended, Insufficient Evidence (I)

Level of confidence Low

Indications

Severe COVID-19 patients, with <94% O2 saturation or need for O2 supplementation, mechanical ventilation, or extracorporeal membrane oxygenation (Hinton, 2020). Patients included in trials had creatinine clearance >30 mL/min; ALT and AST <5 times upper limit of normal.

Benefits

Shortened ICU stay, but minimal to no impact on survival

Harms

Increased hepatic enzymes, diarrhea, rash, renal 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 for 9 additional days (Grein et al., 2020, Beigel et al., 2020).

Indications for discontinuation

Completion of a course, intolerance, adverse effect.

Rationale

There is one high-quality RCT of remdesivir suggesting a lack of clinical efficacy, although it also suggests non-significant trends toward earlier clinical improvements (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 (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). 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). 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). Remdesivir is invasive (IV), has minimal adverse effects, is high cost, has conflicting evidence of modest efficacy (particularly for the treatment of hospitalized patients requiring oxygen), and thus is selectively recommended. There are other treatments with stronger efficacy at reducing mortality (e.g., glucocorticosteroids, low-molecular-weight heparin).

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.

8.7. LOW-MOLECULAR-WEIGHT HEPARIN

Low-molecular-weight heparin has been used for the treatment of hospitalized, severely affected patients with COVID-19; the degree of coagulopathy has been associated with worsened survival (116) (117) (118) (119) (120) (121) (122) (123) (124) (125) (126) (127)(128). Fondaparinux and unfractionated heparin have also been recommended in the *Chest* guidelines (129). Thrombectomies and other procedures have been performed in COVID-19 patients with known venous thromboembolism (129,130).

Low-Molecular-Weight Heparin for the Treatment of COVID-19

Recommended

Low-molecular-weight heparin is recommended for the treatment of select patients with COVID-19 (Di Perri, 2020, van Haren et al., 2020, Ayerbe et al., 2020, Hippensteel et al., 2020, Moores et al., 2020, Canoglu et al., 2020, DArdes et al., 2020, Falcone et al., 2020, Jose Ramon Gonzalez-Porras, 2020, Ma et al., 2020, Mattioli et al., 2020, Paolisso et al., 2020, Pavoni et al., 2020, Shi et al., 2020, Stattin et al., 2020, Vergori et al., 2020, White et al., 2020, Zhang et al., 2020, Gonzalez-Ochoa et al., 2020, Nadeem et al., 2021).

Strength of evidence Recommended, Evidence (C)

Level of confidence Moderate

Indications

Severely affected COVID-19 patients, especially those with known evidence or suspicion of having coagulopathy (e.g., small-vessel thromboses, large-vessel arterial and/or venous thromboses [e.g., infarcts, DVTs, pulmonary emboli], thrombocytopenia, increased D-dimer, increased fibrin degradation products, prolonged coagulation times). May also be indicated for those who are hospitalized and either (i) sedentary, as there is some evidence of post-mortem coagulopathy in

those without pre-morbid suspicions of coagulopathy and/or (ii) on a worsening clinical trajectory that suggests trending towards critical status and/or cytokine storm (Nadkarni et al., 2020).

Benefits

Possible improved survival, improved oxygenation, reduced time on ventilator (Lemos et al., 2020), reduced risks of DVT, pulmonary emboli, myocardial infarction, cerebrovascular thromboembolic disease.

Harms

Usual risks of heparin, particularly bleeding complications. In rare cases, acute COVID-19 infection is associated with the development of anti-heparin- platelet factor 4 autoantibodies that bind heparin and platelets, and may be associated with thrombocytopenia and increased risk of thrombosis (Cai et al., 2020, Dragonetti et al., 2020). In that case, alternate methods of anticoagulation, such as with apiaxban or others, should be instituted.

Frequency/Dose/Duration

Per manufacturer's recommendations. A stepped approach with more intensive prophylaxis for more severely affected patients has been reportedly successful (Atallah et al., 2020). Unfractionated heparin is another therapeutic option.

Indications for discontinuation

Recovery from COVID-19 and resolution of findings of coagulopathy with regaining of normal ambulation. Also discontinue for significant adverse effects. May be continued after hospital discharge for a period of time during recovery and while still not as active and ambulatory as pre-morbid.

Rationale

One RCT reported efficacy of enoxaparin over standard anticoagulation (unfractionated heparin, generally 5,000U TID) to significantly increase gas exchange and reduce need for ventilatory support (Lemos et al., 2020). A trial of sulodexide found reduced need for hospitalization and oxygen therapy (Gonzalez-Ochoa et al., 2020). Reductions in mortality have been reported in non-randomized studies (Ayerbe et al., 2020, Albani et al., 2020, Hsu et al., 2020, Paranjpe et al., 2020, Ionescu et al., 2020, Hanif et al., 2020), including an estimated 47–50% reduced risk of mortality among those on therapeutic anticoagulation among 4,389 in a hospital system (Nadkarni et al., 2020). Another cohort of patients on mechanical ventilation was found to have a 54% reduction in mortality (Paranjpe et al., 2020, Dobesh et al., 2020).

An early escalating thromboprophylactic approach has been suggested as preventive among hospitalized patients with less severe disease (Daughety et al., 2020).

Low-molecular-weight heparins are minimally invasive, have potentially significant adverse effects, are moderately costly, and have evidence suggesting associations with lower mortality rates and fewer complications among severely affected COVID-19 patients; thus, they are selectively recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to December 2020 using the following terms: Low Molecular Weight Heparin; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 60 articles in PubMed, 837 in Scopus, 11 in CINAHL, 22 in Cochrane Library, 4,410 in Google Scholar, and 0 from other sources†. We considered for inclusion 16 from PubMed, 21 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 13 from Google Scholar, and 0 from other sources. Of the 51 articles considered for inclusion, 2 randomized trials and 13 systematic reviews met the inclusion criteria. There were no exclusion criteria.

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

8.8. FLUVOXAMINE

Fluvoxamine has been used for the treatment of COVID-19 patients (131)(132)(133). Observational evidence suggests that two SSRI antidepressants, fluvoxamine and fluoxetine (but not other SSRIs), reduce mortality by 10% (134).

Fluvoxamine for the Treatment of COVID-19

Recommended

Fluvoxamine is recommended for the treatment of patients with COVID-19, particularly within 7 days of symptoms onset.

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.

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

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. Fluvoxamine is non-invasive, has low adverse effects, is low cost, and is 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: 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.

8.9. PAXLOVID

Paxlovid (nirmatrelvir/ritonovir) has been approved by the U.S. FDA through an emergency use authorization for the treatment of COVID-19 patients (135).

Paxlovid (Nirmatrelvir/Ritonovir) for Treatment of COVID-19

Recommended

Paxlovid (nirmatrelvir/ritonovir) 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

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/Ritonovir) 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

Interim analyses from one moderate-quality RCT suggests 89% reduction in risk of hospitalization and/or death associated with Paxlovid (Nirmatrelvir/Ritonovir), especially when used within 3 days of symptoms onset (Mahase, 2021). There were 10 deaths in the placebo group vs. 0 in the Paxlovid group over 28 days (Mahase, 2021). As interim analyses from one RCT suggest major efficacy to prevent hospitalization and/or death, Paxlovid (Nirmatrelvir/Ritonovir) is non-invasive, has considerable adverse effects, is high cost, and is 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: 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 inCINAHL, 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 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.

8.10. MOLNUPIRAVIR

Molnupiravir has been approved by the U.S. FDA through an emergency use authorization for the treatment of COVID-19 patients (136,137,138,139)(140).

Molnupiravir for the Treatment of COVID-19

Recommended

Molnupiravir is recommended for the treatment of patients with COVID-19, particularly within 3 days of symptoms 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 (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

48% reduction in the probability of hospitalization and/or death (Jayk Bernal et al., 2022).

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). 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). 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). The 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.

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.

8.11. IL-6 RECEPTOR ANTAGONISTS

Various interleukin-6 receptor antagonists have been used for the treatment of hospitalized patients with COVID-19 (141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175).

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

Not Recommended

Interleukin-6 inhibitors (sarilumab, siltuximab, and tocilizumab) are not recommended for the treatment of selected patients with COVID-19.

Strength of evidence Not Recommended, Evidence (C)

Level of confidence Low

Rationale

One moderate-quality trial suggested a reduced need for mechanical ventilation but no improved survival (Salama et al., 2020). One trial found improved organ-support free days and survival with both tocilizumab and sarilumab (Gordon et al., 2021), and another suggested modest efficacy (Horby et al., 2021). However, six other moderate-quality RCTs found a lack of efficacy of tocilizumab (Stone et al., 2020, Salvarani et al., 2020, Rosas et al., 2021) and sarilumab (Lescure et al., 2021, Veiga et al., 2021, Wang et al., 2020, Soin et al., 2021). Two suggested a trend towards efficacy (Sivapalasingam et al., 2021, Lescure et al., 2021). One moderate-quality RCT found trends towards reduced mortality by 2 weeks but not 4 weeks associated with tocilizumab (Hermine et al., 2020). One controlled study suggested increased adjusted survival rates among the group of patients treated with tocilizumab, although there were baseline differences likely favoring survival among the treated (Somers et al., 2020). Another controlled but non-randomized study of tocilizumab added to a standard-care regimen of HCQ, lopinavir, plus ritonavir suggested efficacy if administered earlier in the hospital course (Capra et al., 2020). One retrospective study found no benefit of tocilizumab (Campochiaro et al., 2020). One case series suggested significant survival and oxygenation benefits (Xu et al., 2020).

As there is now evidence that mostly suggests of a lack of efficacy of the IL-6 receptor antagonists, they are not recommended. There also are currently other treatments with demonstrated 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: interleukin-6, tocilizumab, sarilumab, siltuximab; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 11,008 articles in

PubMed, 28,542 in Scopus, 142 in CINAHL, 68 in Cochrane Library, 30,600 in Google Scholar, and 10 from other sources†. We considered for inclusion 25 from PubMed, 0 from Scopus, 0 from CINAHL, 1 from Cochrane Library, 2 from Google Scholar, and 10 from other sources. Of the 38 articles considered for inclusion, 12 randomized trials and 24 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. 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.

8.13. 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 has been used for the treatment of patients with COVID-19 (176) (177) (178) (179) (180).

Baricitinib for the Treatment of COVID-19

No Recommendation

There is no recommendation regarding baricitinib for the treatment of COVID-19 (Kalil et al., 2020).

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). Severely affected patients with COVID-19 with cytokine storm manifestations, including ARDS. Also indicated for those requiring supplemental oxygen and/or mechanical ventilation. Other treatments may be combined (e.g., glucocorticosteroids). The U.S. FDA issued an Emergency Use Authorization for use in combination with remdesivir (Administration, 2020, Administration, 2020).

Benefits

Data conflict regarding efficacy for prior variants.

Harms

Fever, chills, tiredness, muscle pain, increased urination, stomach pain, diarrhea, weight loss, cough, dyspnea.

Frequency/Dose/Duration

Doses used have included 4mg loading and 2mg/day for or 4mg/day (Rodriguez-Garcia et al., 2020).

Indications for discontinuation

Completion of a course, intolerance, adverse effects.

Rationale

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, has conflicting evidence of modest efficacy, and has some evidence suggesting efficacy, although that evidence was developed prior to the omicron variant; thus, there is no recommendation.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to November 2020 using the following terms: 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.

8.14. 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 have been approved for use by FDA under the emergency use authorization provision (181).

Casirivimab plus Imdevimab (Regeneron) for the Treatment of COVID-19

No Recommendation

There is no recommendation regarding the combination of casirivimab plus imdevimab (Regeneron) for the treatment of patients with mild to moderate COVID-19 at risk of severe disease. The National Institutes of Health has cautioned that the combination of casirivimab plus imdevimab is not likely to have significant efficacy against the omicron variant ((NIH), 2022).

Strength of evidence No Recommendation, Insufficient Evidence (I)

Level of confidence Low

Indications

Generally only for outpatient treatment of mild to moderate COVID-19 cases and at high risk of disease progression. Criteria for adults included BMI 35+, chronic renal disease, diabetes mellitus, immunocompromising condition, current receipt of immunosuppressive treatment, age 65+, age 55+ with comorbidity (cardiovascular disease, hypertension, COPD). Oxygen therapy is an exclusion.

Prophylactic use is for those not fully vaccinated or not expected to mount an adequate immune response and either exposed to an infected close contact or who are at high risk from an individual in the same institutional setting (e.g., nursing home, prison). However, as the combination of Casirivimab plus Imdevimab targets the receptor binding site, it is believed to have lower efficacy against the omicron variant, NIH has cautioned that efficacy is not anticipated ((NIH), 2022); thus, sotrovimab is preferably recommended if available.

Benefits

Data conflict regarding efficacy for prior variants.

Harms

Allergic reactions which may be severe; other than localized complications from parenteral administration.

Frequency/Dose/Duration

N/A

Indications for discontinuation

Completion of a course, intolerance, adverse effect.

Rationale

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, is not anticipated to have significant efficacy against omicron ((NIH), 2022), and thus there is no recommendation. Sotrovimab is preferably recommended if available. Casirivimab/imdevimab may be a reasonable choice when other options are exhausted.

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, 1,682in 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.

8.15. 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 has been used to treat COVID-19, often with etesevimab. These have been approved for use by FDA under the emergency use authorization provision (182) (183). The National Institutes of Health has cautioned that the combination of bamlanivimab with etesevimab is not likely to have significant efficacy against the omicron variant (184).

Bamlanivimab plus Etesevimab for the Treatment of COVID-19 - Within 5 Days of Symptom Onset

No Recommendation

There is no recommendation for or against bamlanivimab plus etesevimab are not recommended for the treatment of patients within 5 days of mild to moderate COVID-19 (IDSA, 2021). Sotrovimab is predicted to have preserved efficacy against the omicron variant and thus is recommended as preferable when available ((NIH), 2022).

Strength of evidence No Recommendation, Insufficient Evidence (I)

Level of confidence Low

Indications

Generally only for outpatient treatment of patients with mild to moderate COVID-19 cases and those at high risk of disease progression and when sotrovimab is unavailable. Ideally within 3-5 days of symptoms onset. FDA criteria for adults include BMI 35+, chronic renal disease, diabetes mellitus, immunocompromising condition, current receipt of immunosuppressive treatment, age 65+, age 55+ with comorbidity (cardiovascular disease, hypertension, COPD). Oxygen therapy is an exclusion.

As the receptor binding site is targeted by these antibodies, and while not proven, this is believed to result in less efficacy than with e.g., Sotrovimab when used to treat subsequent variants including omicron ((NIH), 2022).

Benefits

Reduced risk of hospitalization and death.

Harms

Unclear. Reported reactions include anaphylaxis and a serious infusion-related reaction.

Frequency/Dose/Duration

One IV infusion of 2,800mg bamlanivimab. May also be given in combination with 2,800mg IV etesevimab.

Indications for discontinuation

Completion of a course, intolerance, adverse effect.

Rationale

RCTs involve variants prior to 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 there is no recommendation. Sotrovimab is preferably recommended if available ((NIH), 2022). Bamlanivimab/etesevimab may be a reasonable choice when other options are exhausted.

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.

Bamlanivimab plus Etesevimab for the Treatment of COVID-19 - Hospitalized or Late Cases

Not Recommended

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

Strength of evidence Not Recommended, Evidence (C)

Level of confidence Low

Indications

Generally only for outpatient treatment of patients with mild to moderate COVID-19 cases and those at high risk of disease progression and when sotrovimab is unavailable. Ideally within 3-5 days of symptoms onset. FDA criteria for adults include BMI 35+, chronic renal disease, diabetes mellitus, immunocompromising condition, current receipt of immunosuppressive treatment, age 65+, age 55+ with comorbidity (cardiovascular disease, hypertension, COPD). Oxygen therapy is an exclusion.

As the receptor binding site is targeted by these antibodies, and while not proven, this is believed to result in less efficacy than with e.g., Sotrovimab when used to treat subsequent variants including omicron ((NIH), 2022).

Benefits

Reduced risk of hospitalization and death.

Harms

Unclear. Reported reactions include anaphylaxis and a serious infusion-related reaction.

Frequency/Dose/Duration

One IV infusion of 2,800mg bamlanivimab. May also be given in combination with 2,800mg IV etesevimab.

Indications for discontinuation

Completion of a course, intolerance, adverse effect.

Rationale

RCTs involve variants prior to 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. Another study suggested a 72% reduction in the risk of hospitalization among those at high risk. 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 there is no recommendation. Sotrovimab is preferably recommended if available ((NIH), 2022). Bamlanivimab/etesevimab may be a reasonable choice when other options are exhausted.

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.

8.16. 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 has been approved for use by the U.S. FDA under the emergency use authorization provision (185)(186)(187).

Sotrovimab for the Treatment of COVID-19 - Within 5 Days of Symptom Onset

Recommended

Sotrovimab is moderately recommended for the treatment of patients with mild to moderate COVID-19 (Administration, 2021, Administration et al., 2022).

Strength of evidence Moderately Recommended, Evidence (B)

Level of confidence Low

Indications

Generally only for outpatient treatment of patients with mild to moderate COVID-19 cases and those at high risk of disease progression. Ideally within 3-5 days of symptoms onset. FDA criteria for adults include age 65+, BMI 25+, pregnancy, chronic renal disease, diabetes mellitus, immunocompromising condition, current receipt of immunosuppressive treatment, cardiovascular disease, hypertension, chronic lung disease, sickle cell disease, neurodevelopmental disorders, and having medical appliance dependence (e.g., tracheostomy, gastrostomy, positive pressure ventilation). Oxygen therapy, increased oxygenation requirements compared with baseline, and hospitalization status are exclusions.

Benefits

Reduced risk of hospitalization and death.

Harms

Hypotension, dizziness, arrhythmias, chest pain, dyspnea, fever, chills, nausea, headache, confusion, sweating, muscle pain.

Frequency/Dose/Duration

One IV infusion of 500mg sotrovimab.

Indications for discontinuation

N/A

Rationale

The RCTs preceded the omicron variant. However, sotrovimab is projected by NIH to have retained efficacy against this variant unlike most other monoclonal antibodies ((NIH), 2022). In one high-quality RCT of early use of sotrovimab , disease progression with hospitalization or death occurred among 7% on placebo vs. 1% on sotrovimab (Gupta et al., 2021). One RCT of use among hospitalized patients found a lack of efficacy (Self et al., 2021).

Sotrovimab is invasive, has some adverse effects, is high cost, has evidence of efficacy for early use but not late use, and is anticipated to have significant efficacy against omicron ((NIH), 2022). Thus, it is recommended for early, but not late, use.

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, 1from Google Scholar, and 0from other sources. Of the 4articles considered for inclusion, 2randomized trials and 1systematic reviewmet 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.

Sotrovimab for the Treatment of COVID-19 - Hospitalized or Late Cases

Not Recommended

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

Strength of evidence Not Recommended, Evidence (C)

Level of confidence Low

Indications

Generally only for outpatient treatment of patients with mild to moderate COVID-19 cases and those at high risk of disease progression. Ideally within 3-5 days of symptoms onset. FDA criteria for adults include age 65+, BMI 25+, pregnancy, chronic renal disease, diabetes mellitus, immunocompromising condition, current receipt of immunosuppressive treatment, cardiovascular disease, hypertension, chronic lung disease, sickle cell disease, neurodevelopmental disorders, and having medical appliance dependence (e.g., tracheostomy, gastrostomy, positive pressure ventilation). Oxygen therapy, increased oxygenation requirements compared with baseline, and hospitalization status are exclusions.

Benefits

Reduced risk of hospitalization and death.

Harms

Hypotension, dizziness, arrhythmias, chest pain, dyspnea, fever, chills, nausea, headache, confusion, sweating, muscle pain.

Frequency/Dose/Duration

One IV infusion of 500mg sotrovimab.

Indications for discontinuation

N/A

Rationale

The RCTs preceded the omicron variant. However, sotrovimab is projected by NIH to have retained efficacy against this variant unlike most other monoclonal antibodies ((NIH), 2022). In one high-quality RCT of early use of sotrovimab, disease progression with hospitalization or death occurred among 7% on placebo vs. 1% on sotrovimab (Gupta et al., 2021). One RCT of use among hospitalized patients found a lack of efficacy (Self et al., 2021). Sotrovimab is invasive, has some adverse effects, is high cost, has evidence of efficacy for early use but not late use, and is anticipated to have significant efficacy against omicron ((NIH), 2022). Thus, it is recommended for early, but not late, use.

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 0 from 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.

8.17. BEBTELOVIMAB

Bebtelovimab for the Treatment of COVID-19

Recommended

Bebtelovimab is recommended for treatment of COVID-19 under the FDA Emergency Use Authorization process (February 11, 2022).

Strength of evidence Recommended, Insufficient Evidence (I)

Level of confidence Low

Indications

Adults and teenagers 12 years of age and older with an early case of confirmed COVID-19 within 7 days of symptoms onset, who are at high risk of progression to severe disease. Not indicated for those hospitalized and/or on oxygen therapy. FDA EUA does not authorize use for severe disease (Administration, 2022).

Benefits

Purported improvement in the clinical case and reduction in risk of progression.

Harms

Infusion-related symptoms/signs, pruritis, and rash. Limited data are not yet available (Administration, 2022).

Frequency/Dose/Duration

Bebtelovimab 175mg IV, one administration

Indications for discontinuation

N/A

Rationale

Bebtelovimab has no phase 3 trials published in the peer-reviewed literature. There are preliminary data published (Administration, 2022)(Administration, 2022) on which the FDA issued its Emergency Use Authorization. Bebtelovimab is minimally invasive, has low adverse effects, is high cost, has preliminary evidence of efficacy, and is thus recommended.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to 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 article 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.

8.18. IVERMECTIN

Ivermectin has been used for the treatment of COVID-19 (188)[(189) (190) (191) (192) (193) (194) (195). There is experimental evidence of its ability to inhibit viral replication (197).

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., 2020, 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

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 many RCTs assessing ivermectin. 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 several trials assessing use of ivermectin for early treatment (e.g., within 3-5 days). 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). 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)(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 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). As data somewhat conflict, there is no recommendation regarding Ivermectin for treatment of late COVID-19 disease.

One low-quality study with patients of unclear symptoms duration found ivermectin to be comparable to HCQ/AZT/Ivermectin combination therapy, although there appear to have been baseline differences in oxygen saturation (Babalola et al., 2021).

There are a 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.

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 differences (Galan et al., 2021). One trial suggested no differences in duration of hospitalization (Abd-Elsalam et al., 2021). One trial suggested accelerated viral clearance (Babalola et al., 2021). A trial among patients of unclear severity (severely affected per abstract, mildly affected per Table) found lack of efficacy (Saxena et al., 2021).

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

Recommended

Ivermectin is recommended for early treatment of COVID-19, within 3 days of symptom onset. However, it is not recommended for late treatment of COVID-19 (Podder et al., 2020, Chaccour et al., 2020, Krolewiecki et al., 2020, Niaee et al., 2020, 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 Recommended, Evidence (C)

Level of confidence Low

Indications

Outpatients with COVID-19 and less than 3 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 many RCTs assessing ivermectin. 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 several trials assessing use of ivermectin for early treatment (e.g., within 3-5 days). 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). 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)(Administration, 2022), 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 (>3 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 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). As data somewhat conflict, there is no recommendation regarding Ivermectin for treatment of late COVID-19 disease. One low-quality study with patients of unclear symptoms duration found ivermectin to be comparable to HCQ/AZT/Ivermectin combination therapy, although there appear to have been baseline differences in oxygen saturation . There are a 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. 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 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).

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 many RCTs assessing ivermectin. 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 several trials assessing use of ivermectin for early treatment (e.g., within 3-5 days). 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). 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)(Administration, 2022), 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 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). As data somewhat conflict, there is no recommendation regarding Ivermectin for treatment of late COVID-19 disease.

One low-quality study with patients of unclear symptoms duration found ivermectin to be comparable to HCQ/AZT/Ivermectin combination therapy, although there appear to have been baseline differences in oxygen saturation .

There are a 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.

There are some RCTs treating patients of unclear symptom duration. A comparative trial of HCQ, CQ and Ivermectin among hospitalized, severely-affected patients of unclear symptoms duration found lack of 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).

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.

8.19. CONVALESCENT COVID-19 ANTIBODIES

Convalescent COVID-19 antibodies have been used to treat COVID-19 (175) (198) (199) (200) (201) (202) (203) (204) (205) (206) (207) (208) (209) (210) (211) (212) (213) (214) (215) (216).

Convalescent COVID-19 Antibodies for Treatment of COVID-19

Not Recommended

The use of convalescent antibodies is not recommended for the treatment of patients with COVID-19.

Strength of evidence Moderately Not Recommended, Evidence (B)

Level of confidence Moderate

Rationale

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).

Convalescent antibodies are invasive, have adverse effects, and are costly. Nearly all quality data suggest they are ineffective for treatment of COVID-19 and thus they are 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: 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.

8.20. 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 recommended for treatment 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: 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.

8.21. INTERFERON BETA-1B

Interferon beta-1b has been used both as sole therapy and combination therapy for the treatment of patients with COVID-19 (217) (118).

Interferon Beta-1b for the Treatment of COVID-19 - Combination Therapy

Recommended

Adjunctive use of interferon beta-1b is recommended for the treatment of selected patients with COVID-19.

Strength of evidence Recommended, Evidence (C)

Level of confidence Low

Indications

Adjunctive use with lopinavir-ritonavir and ribavirin 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

Two successful trials utilized sole therapy with interferon beta-1b 250ug SQ QOD for 2 weeks (Rahmani et al., 2020). The combination regimen used successfully for the treatment of COVID-19 is lopinavir 400mg, ritonavir 100mg every 12hrs, ribavirin 400mg every 12hrs, plus 3 doses of 8M IU interferon beta-1b on alternate days (Hung et al., 2020).

Indications for discontinuation

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

Rationale

Two successful moderate-quality trials utilized sole therapy with interferon beta-1b and one study found accelerated clinical improvement and a non-statistically significant reduction in death by 67% at 1-month (Rahmani et al., 2020). The second trial found comparable results to the other RCT with faster clinical improvement (9 vs 11 days), fewer adverse events, and ~67% reduction in mortality (6.1 vs. 18.2%) when compared with treatment with the control group (lopinavir-ritonavir/HCQ or atazanavir/ritonavir/HCQ) (Rahmani et al., 2020). 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). Another three-arm trial found faster clinical recovery and non-significant trends in mortality compared to

control (mortality 20% for beta1a vs. 30% for beta1b vs. 45% controls) (Darazam, 2021). However, one RCT found a lack of efficacy (WHO, 2020). Based on the two moderate-quality RCTs showing considerable evidence of efficacy, stand-alone treatment with interferon beta-1b is moderately recommended.

A moderate-quality RCT found a lack of efficacy for combined favipavir with interferon beta-1b compared with HCQ for moderate to severe COVID-19 pneumonia patients (Khamis et al., 2021).

Based on one trial with demonstrated efficacy, the regimen of triple-combination therapy using lopinavir, ritonavir, ribavirin, and interferon beta-1b is recommended (Hung et al., 2020), although it should be noted that it is possible that the only medication effective in the combination therapy is interferon beta-1b.

Other interferons are being investigated. One successful trial used a different interferon in a Phase 2 trial that was nebulized interferon-1a (SNG001) (Monk et al., 2021). A trial with interferon beta-1a when added to (lopinavir-ritonavir/HCQ or atazanavir/ritonavir/HCQ) found earlier 14-day hospital discharge rates (67% vs. 44%) (Davoudi-Monfared et al., 2020). A trial on interferon-kappa plus TFF2 and including many potentially active cointerventions found reduced viral RNA (Fu et al., 2020).

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: Interferon beta-1b; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 44 articles in PubMed, 2,504 in Scopus, 8 in CINAHL, 5 in Cochrane Library, 3,280 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 13 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0from other sources. Of the 16 articles considered for inclusion, 1 randomized trial and 15 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.

Interferon Beta-1b for the Treatment of COVID-19 - Stand-alone Treatment

Recommended

Adjunctive use of interferon beta-1b is recommended for the treatment of selected patients with COVID-19.

Strength of evidence Moderately Recommended, Evidence (B)

Level of confidence Low

Indications

Adjunctive use with lopinavir-ritonavir and ribavirin 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

Two successful trials utilized sole therapy with interferon beta-1b 250ug SQ QOD for 2 weeks (Rahmani et al., 2020). The combination regimen used successfully for the treatment of COVID-19 is lopinavir 400mg, ritonavir 100mg every 12hrs, ribavirin 400mg every 12hrs, plus 3 doses of 8M IU interferon beta-1b on alternate days (Hung et al., 2020).

Indications for discontinuation

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

Rationale

Two successful moderate-quality trials utilized sole therapy with interferon beta-1b and one study found accelerated clinical improvement and a non-statistically significant reduction in death by 67% at 1-month (Rahmani et al., 2020). The second trial found comparable results to the other RCT with faster clinical improvement (9 vs 11 days), fewer adverse events, and ~67% reduction in mortality (6.1 vs. 18.2%) when compared with treatment with the control group (lopinavir-ritonavir/HCQ or atazanavir/ritonavir/HCQ) (Rahmani et al., 2020). 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). Another three-arm trial found faster clinical recovery and non-significant trends in mortality compared to control (mortality 20% for beta1a vs. 30% for beta1b vs. 45% controls) (Darazam, 2021). However, one RCT found a lack of efficacy (WHO, 2020). Based on the two moderate-quality RCTs showing considerable evidence of efficacy, stand-alone treatment with interferon beta-1b is moderately recommended.

A moderate-quality RCT found a lack of efficacy for combined favipavir with interferon beta-1b compared with HCQ for moderate to severe COVID-19 pneumonia patients (Khamis et al., 2021).

Based on one trial with demonstrated efficacy, the regimen of triple-combination therapy using lopinavir, ritonavir, ribavirin, and interferon beta-1b is recommended (Hung et al., 2020), although it should be noted that it is possible that the only medication effective in the combination therapy is interferon beta-1b.

Other interferons are being investigated. One successful trial used a different interferon in a Phase 2 trial that was nebulized interferon-1a (SNG001) (Monk et al., 2021). A trial with interferon beta-1a when added to (lopinavir-ritonavir/HCQ or atazanavir/ritonavir/HCQ) found earlier 14-day hospital

discharge rates (67% vs. 44%) (Davoudi-Monfared et al., 2020). A trial on interferon-kappa plus TFF2 and including many potentially active cointerventions found reduced viral RNA (Fu et al., 2020).

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: Interferon beta-1b; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 44 articles in PubMed, 2,504 in Scopus, 8 in CINAHL, 5 in Cochrane Library, 3,280 in Google Scholar, and 0 from other sources†. We considered for inclusion 1 from PubMed, 13 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 16 articles considered for inclusion, 1 randomized trial and 15 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.

8.22. RIBAVIRIN

Ribavirin has been used to treat patients with COVID-19 (218) (219) (220) (221).

Ribavirin for the Treatment of COVID-19 - Combination Therapy

Recommended

Adjunctive use of ribavirin is recommended for the treatment of selected patients with COVID-19.

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 recommended (Hung et al., 2020). However, there is no quality evidence demonstrating efficacy and thus no recommendation for stand-alone treatment with ribavirin.

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.

Ribavirin for the Treatment of COVID-19 - Stand-alone Treatment

No Recommendation

Adjunctive use of ribavirin is recommended for the treatment of selected patients with COVID-19.

Strength of evidence No Recommendation, Insufficient Evidence (I)

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 recommended (Hung et al., 2020). However, there is no quality evidence demonstrating efficacy and thus no recommendation for stand-alone treatment with ribavirin.

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.

8.23. ZINC

Zinc serum levels have been found to be low in those with more severe COVID-19 disease (222) (223) (224). Zinc supplementation has been used typically as adjunctive treatment to reduce severity of COVID-19 (225) (226).

Zinc for the Treatment of COVID-19

Recommended

Zinc is recommended for potential prevention of more severe disease as well as for the treatment of patients with COVID-19.

Strength of evidence Recommended, Insufficient Evidence (I)

Level of confidence Low

Indications

Ongoing use during the epidemic, as well as for mild, moderate, and severe COVID-19 disease. Also especially recommended for those with zinc deficiency.

Benefits

Potential to reduce disease severity.

Harms

Negligible.

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).

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.

8.24. 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 (227) (228) (229) (230) (231) (232) (233) (235) (236) (237) (238) (239) (240) (241) (242) (243) (244). 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 for potential prevention of more severe disease as well as for the treatment of patients with COVID-19.

Strength of evidence Recommended, Evidence (C)

Level of confidence Low

Indications

Ongoing use during the epidemic, as well as for mild, moderate, and severe COVID-19 disease. High-dose use may be considered for those with onset of COVID-19 disease. Also recommended for those with vitamin D deficiency and/or risks for deficiency.

Benefits

Potential to reduce disease severity

Harms

Negligible

Frequency/Dose/Duration

A moderate-quality trial utilized calcifediol 0.532mg on day 1, 0.266mg days 3 and 7 and weekly in addition to HCQ+AZT until hospital discharge (Entrenas Castillo et al., 2020). Other daily dosing used among healthy individuals at risk include 600 IU/day for up to 70 years of age and 800 IU/day for those over 70 years of age (>100% Recommended Daily Allowance).

Indications for discontinuation

After cessation of the epidemic.

Rationale

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). Another RCT for treatment of asymptomatic of mildly symptomatic but vitamin D deficient individuals treated with vitamin D supplementation cleared virus sooner and with reduced

fibrinogen levels (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). 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). Vitamin D levels have been strongly correlated with COVID-19 disease severity (Lau et al., 2020, D'Avolio et al., 2020).

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 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: 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.

9. REHABILITATION

9.1. OVERVIEW

Although most patients with COVID-19 completely recover, some cases may experience a multitude of disorders (731). It is beyond the scope of this guideline to address every possible presentation, combination, and permutation (190). Indeed, it is arguably impossible to do so. Instead, this guideline addresses what currently appear to be the most common conditions needing rehabilitative services after COVID-19. This also may suggest a framework for approaching treatment of less common presentations.

For simplicity, clarity, and consistency with other diagnoses and the general medical literature, this review defines symptoms lasting less than 1 month as *acute*, from 1–3 months as *subacute*, and more than 3 months as *chronic*. Some of the alternate terms for these conditions include "ongoing symptomatic," "post-COVID syndrome" (565), "post-acute sequalae of COVID," and "long COVID."

The severity of the COVID-19 infection has been associated with the risk of long-term symptoms and impairments (247). For example, approximately two-thirds of outpatients diagnosed with COVID-19 return to normal health by the fourth week (732). In contrast, of those who were evaluated in an

emergency department (66% hospitalized), 50.9% developed chronic COVID-19 symptoms (733). Yet, a mild case does not preclude development of chronic COVID-19 symptoms. The comparatively large numbers of mildly affected patients likely mean that most patients with chronic symptoms will be found in this group, despite the higher risk among those who are more severely affected.

Evidence also suggests that symptoms improve over time. Overall, 5–51% of patients have symptoms persisting up to 12 weeks (566,734,735,736), whereas 2–15% have symptoms beyond 12 weeks after onset (733,734,736,737,738). Long-term symptoms have wide-ranging estimates of prevalence and include fatigue (17–98%) (566,733,734,735,736,739,740,741), dyspnea (17–93%) (566,733,734,735,736,739,740,741), cough (29–43%), chest pain (44–88%) (566,733,734,735,740), back pain, muscle pain, and headache (38–91%) (733). Cognitive changes, such as impaired memory, concentration, and multitasking ability, are also reportedly common. Risk factors for chronic COVID-19 beyond severity of the initial disease appear to include increased age, having more comorbidities, and psychological disorders (736,742).

Acute mental health disorders are common and reportedly affect 55% of those having visited an emergency department (75% were hospitalized) in the first month (743). New-onset psychiatric illness was reported in 5.8% [801]. Of these, 4.7% were anxiety disorders and 2% were depression (744). One report noted persistence of post-traumatic stress among survivors (745). 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 (247).

Some rehabilitation protocols are heavily multidisciplinary, reportedly including pulmonologists, physiatrists, neurologists, cardiologists, physical therapists, occupational therapists, psychologists, neuropsychologists, psychiatrists, speech therapists, and nutritionists (746,747)(748). Telemedicine has been used for rehabilitation of COVID-19 patients (747,749). There are no quality trials to assess the various disciplines on rehabilitation teams, comparative trials of different treatment regimens, and/or efficacy of telemedicine approaches.

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 (245,246) (247)(248). The most common spirometric abnormalities after initial recovery are reduced diffusion capacity and restrictive ventilatory defects (249,250). Risk and severity of spirometric abnormalities are correlated with COVID-19 severity (250).

Pulmonary rehabilitation is used for COVID-19 (251) and has been shown to be successful for functional improvements in individuals with non-COVID-related pulmonary deficits (252,253), including those from pneumonia (254), interstitial lung disease (255), and SARS (256). It commonly includes behavioral components (257). Consensus guidelines have also been produced (248).

Pulmonary Rehabilitation for Treatment of Pulmonary Problems Related to COVID-19

Recommended

Pulmonary rehabilitation is recommended for the treatment of pulmonary problems related to COVID-19.

Strength of evidence Recommended, Insufficient Evidence (I)

Level of confidence Moderate

Indications

Indicated for COVID-19 affected patients with pulmonary dysfunction and/or dyspnea, especially when combined with activity reductions or exercise intolerances attributed to the infection's pulmonary complications. 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 (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

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

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 pulmonary conditions (McCarthy et al., 2015, Hill, 2006, Cheng et al., 2018, Dowman et al., 2021, Lau et al., 2005). Pulmonary rehabilitation has negligible adverse effects, is moderate to high cost depending on number of treatments and durations required, and is recommended for patients meeting indications.

Evidence

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar from January 2019 to February 2021 using the following terms: rehabilitation; coronavirus infections, coronavirus, COVID-19, novel coronavirus, SARS-CoV-2, 2019-nCoV; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, prospective studies; clinical study; observational study clinical trial; non-randomized controlled trials as topics. We found and reviewed 112 articles in PubMed, 4,699 in Scopus, 3 in CINAHL, 13 in Cochrane Library, 34,300 in Google Scholar, and 0 from other sources†. We considered for inclusion 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 (258), and cardiac problems contribute to COVID-19 fatalities (258,259,260,261). Vascular inflammation, hypotension, and direct muscle damage are all potential mechanisms (262,263). 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 (262,263), although ongoing, subclinical cardiac problems have been detected among recovered patients (261,264).

Cardiac rehabilitation is used for COVID-19 (265) and has been shown to be successful for functional improvements in individuals with non-COVID-related cardiac deficits (266,267,268,269,270), including those from myocardial infarction (262), 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

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 pulmonary conditions. Cardiac rehabilitation has negligible adverse effects, is moderate to high cost depending on numbers of treatments and durations required, and is recommended for patients meeting indications.

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.

9.4. EXERCISE THERAPY

Research has supported rehabilitation for hospital-associated deconditioning prior to the COVID pandemic (271,272,273). 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 (274)(275). Early therapy has also been used in the ICU and pre-discharge for COVID patients (276,277,278). A review of physical therapy suggests that there will eventually be efficacy, but currently the available literature is sparse and mostly low quality (279)(280).

For those with fibromyalgia, please refer to the ACOEM Chronic Pain Guideline. Also consider chronic fatigue syndrome and myalgic encephalomyelitis (281).

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, Insufficient Evidence (I)

Level of confidence Moderate

Indications

Indicated for COVID-19 affected patients with debility and/or chronic fatigue attributed to the COVID-19. 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. 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 no quality trials of outpatient-based exercise therapy for the treatment of physical debility and/or chronic fatigue attributed to COVID. 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.

† 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.

9.5. MEMORY AND COGNITION

Memory issues are also potentially problematic for some workers who have had COVID (282,283,284,285,286,287,288,289,290,291,292,293,294). 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 (247), 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 (295,296,297)(298,299). Cognitive rehabilitation has been successfully used for various infectious disease complications, especially for HIV (300) and severe malaria (301). One guideline recommended cognitive screening, assessment of contributing other conditions, imaging, testing, and consensus statements on treatment options (302).

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 (esp. 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 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.

† 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.

9.6. JOINT PAIN

Joint pain is common in subacute and chronic COVID (303,304,305), with 27.3% reporting joint pain at 2 months after COVID onset (303). 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 not undergone rigorous trials for efficacy. Only low-quality trials have thus far been reported. One combined anxiety, depression, and stress, reporting that cognitive behavioral therapy (CBT) was effective (306). Another trial found progressive muscle relaxation helpful for anxiety and sleep quality (307). Another trial found an internet-based intervention on depression and anxiety to be effective (308).

In the absence of quality evidence specific to COVID-19, analogy to existing quality evidence and evidence-based guidance is recommended for screening, diagnosis, and treatments. These are addressed in detail in guidelines on Anxiety Disorders, Depressive Disorders, and Posttraumatic Stress Disorder.

Utilizing evidence for generalized anxiety disorder, anxiety related to COVID-19 is recommended to be best initially treated with education (I), CBT (B,C), aerobic exercise (C), and strengthening exercise (I). Due to strong addictive potential, benzodiazepines are not recommended for routine use (C). Other potential early treatments include insight-oriented therapies (I), distractive methods (C), exposure therapy/prolonged exposure therapy (I), virtual reality exposure therapy (I) and mindfulness therapy (I). Other medications with evidence of efficacy include buspirone (C), quetiapine (B), beta-blockers (B), pregabalin (B), and hydroxyzine (C). Details are in the Anxiety Disorders Guideline.

Utilizing evidence for major depressive disorder, depression related to COVID is best treated initially by reducing or eliminating sedating medication (I), education (I), antidepressant medication (SSRI, SNRI, TCA, MAOI) (B), cognitive behavioral therapy (B), aerobic exercise (C), and strengthening exercise (I). Benzodiazepine medication is not recommended. Other recommended medications include antipsychotics, olanzapine/fluoxetine, agomelatine, eszopiclone, nefazodone, zolpidem for sleep disorders (C). Weight loss may be selectively indicated in patients with obesity (B). Transcranial magnetic stimulation (C), repetitive transcranial magnetic stimulation (C), low-field magnetic stimulation (B), and light therapy (C) are also potential treatments. Severe cases may be treated with electroconvulsive therapy (B). See Depressive Disorders Guideline.

Utilizing evidence for posttraumatic stress disorder, PTSD related to COVID is best treated initially with aerobic exercise (B), strengthening exercise (B), cognitive behavioral therapy (B), exposure therapy (B), prolonged exposure therapy (B), virtual reality (B), imagery rehearsal training (B), and narrative exposure therapy (C). Medications with evidence of efficacy include sertraline (B), paroxetine (B), fluoxetine (I), escitalopram (I), citalopram (C), venlafaxine (B), mirtazpine (B), phenelzine (C), nefazodone (C), quetiapine (I), olanzapine (C), and prazosin (I). Other treatments potentially indicated include guided imagery (I), deep breathing exercises (I), meditation (I), and mindfulness (I). See the Posttraumatic Stress Disorder Guideline.

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ACOEM acknowledges the following organizations and their representatives who served as reviewers of the Coronavirus (COVID-19) Guideline. Their contributions are greatly appreciated. By listing the following individuals or organizations, it does not infer that these individuals or organizations support or endorse the Coronavirus (COVID-19) Guideline developed by ACOEM. Reviewers from three additional societies wished to remain anonymous.

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