**Name of Journal:** *World Journal of Pharmacology*

**Manuscript NO:** 69374

**Manuscript Type:** REVIEW

**Treatment of SARS-CoV-2 (COVID-19): A safety perspective**

Davis J *et al*. Safety of COVID-19 therapeutics

Joshua Davis, Ugochukwu Umeh, Rand Saba

**Joshua Davis,** Department of Emergency Medicine, Vituity, Wichita, KS 67214, United States

**Ugochukwu Umeh,** College of Medicine, Medical University of Lublin, Lublin 20-093, Poland

**Rand Saba,** Department of Surgery, Ascension Providence Hospital, Southfield, MI 48075, United States

**Author contributions:** Davis J devised the concept and drafted the manuscript; All authors contributed to data collection, editing for critical content, and approved and take final responsibility for the final manuscript.

**Corresponding author: Joshua Davis, MD, Attending Doctor,** Department of Emergency Medicine, Vituity, 929 N. St. Francis Avenue, Wichita, KS 67214, United States. jjvwd@udel.edu

**Received:** June 28, 2021

**Revised:** August 22, 2021

**Accepted:** September 16, 2021

**Published online:** November 20, 2021

**Abstract**

The goal of this review is to report a balanced perspective of current evidence for efficacy of treatments for coronavirus disease 2019 (COVID-19) against the historical safety of these treatments as of May 2021. We preselected therapies of interest for COVID-19 based on national guidelines and modified over time. We searched PubMed and Medline for these specific COVID-19 treatments and data related to their efficacy. We also searched for prior randomized controlled trials of each therapy to assess adverse effects, and we obtained the Food and Drug Administration Approval label for this information. Several drugs have been approved for the treatment of COVID-19, and many more are under study. This includes dexamethasone, remdesivir, hydroxychloroquine/chloroquine, lopinvir/ritonavir, interferon or interleukin inhibitors, convalescent plasma and several vitamins and minerals. The strongest evidence for benefit is mortality benefit with dexamethasone in patients with COVID-19 and hypoxemia, although there is a signal of harm if this is started too early. There are several other promising therapies, like interleukin inhibitors and ivermectin. Hydroxychloroquine/chloroquine, lopinvir/ritonavir, and convalescent plasma do not have enough evidence of benefit to outweigh the known risks of these drugs.

**Key Words:** COVID-19; Coronavirus; SARS-CoV-2; SARS; Drug safety; Pharma-cotherapy

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:**Davis J, Umeh U, Saba R. Treatment of SARS-CoV2 (COVID-19): A safety perspective. *World J Pharmacol* 2021; 10(1): 1-32

**URL:** <https://www.wjgnet.com/2220-3192/full/v10/i1/1.htm>

**DOI:** https://dx.doi.org/10.5497/wjp.v10.i1.1

**Core tip:** Coronavirus disease 2019 (COVID-19) has radically changed the approach to healthcare and public health in the last year. Over 100 million people worldwide have been affected. Dexamethasone appears to be the most efficacious drug for appropriately selected patients with COVID-19 (*i.e.*, those requiring supplemental oxygen). Remdesivir may reduce length of hospitalization with mild side effects. While they do not have enough evidence to be recommended at this time, ivermectin and zinc should be studied further for early illness and interferon and interleukin blockade should be studied for critical illness. Hydroxychloroquine/chloroquine, azithromycin, and vitamins C and D have no evidence of benefit at this time.

**INTRODUCTION**

Coronavirus disease 2019 (COVID-19) is caused by a novel, highly infectious strain of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Seven coronavirus strains have been shown to infect humans. The first strains of coronaviruses to infect humans were identified in 1960s and were reported to cause common cold like symptoms. Since then, two highly pathogenic strains have been associated with prior pandemics. The first, termed SARS-CoV, was identified in 2003, and reported to cause severe pneumonia and acute respiratory distress syndrome (ARDS)[1]. The other, Middle Eastern Respiratory Syndrome (MERS) Coronavirus was identified in 2012 and is highly virulent and is also known to cause pneumonia, respiratory distress, and renal failure in some cases[2]. SARS-CoV-2, the cause of COVID-19, is the newest of these highly pathogenic coronaviruses.

Due to the worldwide impact and high mortality of this virus, therapeutics for COVID-19 are under ongoing intense investigation. There are currently four drug therapies with approval or emergency use authorization (EUA) under the US Food and Drug Administration (FDA): The antiviral remdesivir with or without barcitinib, convalescent plasma, and the immunotherapies bamlanivimab/etesevimab and casirivimab/imdevimab. The steroid dexamethasone is also a widely used therapy for hospitalized patients. Several other therapies have been studied; some have shown consistent lack of evidence [hydroxychloroquine (HCQ)/chloroquine (CQ) and lopinavir/ritonavir (LPV/RTV)], and some have ongoing research and early promise (serotonin reuptake inhibitors, angiotensin modulators, interleukin inhibitors, interferon treatments, histamine blockers, and vitamin and mineral supplements). There is rapidly evolving evidence on therapeutics for COVID-19, but haste in the research has also led to some disappointments.

Every drug has a potential for adverse effects, which must be weighed against its efficacy. Therefore, the goal of this review is to present a balanced review of efficacy and safety data for the most highly promising COVID-19 therapeutics.

**Dexamethasone**

Corticosteroids, such as dexamethasone, have been the only drugs to consistently show mortality benefit in COVID-19[3].Early observational data suggested that steroids were associated with increased mortality and disease severity[4,5], and many guidelines initially discouraged their use[6]. However, the large randomized controlled RECOVERY trial in the UK then showed significant mortality benefit at a 6-mg daily dose in patients requiring supplemental oxygen[7]. Patients with more severe illness benefitted the most, and patients not requiring supplemental oxygen actually showed a signal of harm. Several other studies have confirmed these findings[3]. Therefore, steroids should be reserved for patients requiring supplemental oxygen and not generic outpatients with COVID-19.

In other causes of severe pneumonia, corticosteroids have also shown benefit[8]. Steroids are nonselective immunosuppressants, and their benefit in severe COVID-19 suggests that an inflammatory cascade contributes to severe illness. Hydrocortisone, but not methylprednisolone, is associated with similar benefit but with less robust data[3,9].More recent guidelines almost universally endorse the use of dexamethasone in moderate to severe COVID-19 (Table 1)[10].

Corticosteroids have been well studied for many indications, and their side effect profile is well understood. Hyperglycemia and hypernatremia are the most commonly observed side effects, with highly variable rates reported[8,11]. Up to 40% increased odds of stress ulcers and gastrointestinal bleeding can be seen in hospitalized patients using steroids[12,13]. In intensive care patients, steroid-induced myopathy is a well-recognized complication[11,14]; however, there are no great data on the incidence of steroid-induced myopathy. Steroid-induced neuropsychiatric complications are also rare but well recognized[15].These include psychosis, agitation, mania, and insomnia. Other commonly recognized side effects of corticosteroid use have not been shown to be statistically increased when used for short courses in the hospital. However, large studies, even some using short courses of steroids, have shown an association with these risks. These include decreased bone density and pathological fractures[16], increased risk of infections and sepsis[17,18], glaucoma[19,20], venous thromboembolism[17], hypertension[21], and weight gain[22,23].

A rare, but recognized complication of immunosuppression, particularly with corticosteroids, is *Stronglyoides* hyperinfection/dissemination[24]. This typically occurs in patients with chronic unrecognized asymptomatic infection when given an immunosuppressant, like dexamethasone or other corticosteroids, and it appears to be unrelated to dose or duration of steroid administration[25,26]. Chronic *Strongyloides* infection is more common in patients from tropical regions[27].

Given the mortality benefit demonstrated in several studies, the use of dexamethasone in COVID-19 patients requiring supplemental oxygen is prudent, despite the known side effects. Preventive strategies for these side effects should be observed. This includes appropriate patient selection (*i.e.*, only patients requiring supplemental oxygen), appropriate dosing of steroids (6 mg daily dexamethasone for non-critically ill patients), close monitoring of electrolytes and blood sugar, low threshold for stress ulcer prophylaxis, early mobilization and physical therapy, appropriate deep venous thrombosis prophylaxis, and delirium precautions.

**Remdesivir**

Remdesivir is a broad-spectrum antiviral drug proposed for the treatment of coronavirus and Ebola virus infections. This nucleotide analog is metabolized into an ATP analog in the cells and inhibits viral RNA-dependent RNA polymerase[28-30]. Case reports for remdesivir in Ebola virus infection showed promise[31,32]; however, clinical trial data did not support its efficacy[33] and it was never approved. *In vitro* data showed efficacy for SARS-CoV[34], MERS-CoV[35] and SARS-CoV-2[36].

Of course, these preclinical data fostered interest in the use of remdesivir for patients with COVID-19. Early observational data without a comparison group showed that, among patients who received remdesivir under compassionate use agreement, 68% improved[29]. A small randomized trial showed no benefit[37]. Further randomized trials, though, showed a decrease in hospital length of stay and clinical improvement among hospitalized patients, but no statistical difference in mortality[38,39]. And, later analyses demonstrated that a 5-day course dose was equally as effective as a 10-day course[40]. The FDA approved remdesivir under EUA on May 1, 2020[41], and full approval on October 22, 2020[42].

Interestingly, in the final report of the largest randomized controlled trial, there were more adverse events in the placebo group than the remdesivir group[38]. An elevation in liver enzymes is known to occur in some people[43] and is an indication to cease treatment (when levels reach 10 times the upper limit of normal)[44]. In fact, this was the most common adverse event in the observational compassionate use data, with a rate of 23%[29]. However, only international normal ratio elevation, and not aspartate transaminase, alanine transaminase (ALT) or bilirubin, was increased compared to placebo in the randomized controlled trial[38]. As remdesivir contains sulfobutylether-beta-cyclodextrin sodium, a renally cleared solubilizing preservative, its use in patients with a glomerular filtration rate < 30 mL/min is not recommended, although the clinical significance of its use in patients with renal disease is not known[44]. A single patient receiving loading-dose remdesivir in the Ebola trial had profound hypotension during the infusion ultimately leading to cardiac arrest[33]. This was adjudicated as possibly related to the remdesivir, but it is not clear if it was part of the underlying Ebola virus infection either. Again, hypotension was not shown to be increased in the randomized controlled trial[38].

While further research is needed, there do appear to be some clinically important outcomes when remdesivir is used in hospitalized patients with COVID-19, namely clinical improvement, but there is no certain mortality benefit. However, its safety profile seems beneficial, especially when patients are selected appropriately. Of course, all drugs carry some risk of allergic or infusion reactions, but these seem exceedingly rare. Therefore, in appropriate hospitalized patients with COVID-19, remdesivir should be considered.

**LPV/RTV**

LPV/RTV are protease inhibitors that were once drugs of choice in multidrug regimens for treating HIV infection. Several studies have reported efficacy of LPV and RTV along with other compounds for treatment of HIV infection[45-47]. After initial preclinical trials showed *in vitro* efficacy against SARS-CoV[48,49], LPV/RTV treatment along with ribavirin was trialed in patients with SARS-CoV[50] and MERS-CoV[51], but there was no proven evidence in randomized trials. Combination of LPV/RTV was administered to 43 health care workers (HCWs) in South Korea exposed to MERS-CoV. The study reported no incidence of MERS in HCWs receiving the drug as postexposure prophylaxis (PEP); whereas, six HCWs in the non-PEP group showed symptoms of MERS[52].

LPV/RTV was, understandably, of interest for use against SARS-CoV-2. However, an early randomized controlled trial in hospitalized patients showed no difference in either time to clinical improvement or mortality. Therefore, interest in its use in COVID-19 rapidly waned. Several trials since then have confirmed no clinically or statistically significant improvement in patients with COVID-19 receiving LPV/RTV[53-55].

In one randomized trial of LPV/RTV in COVID-19, total adverse events were similar between groups and serious adverse events were more common in the control group[55]. Gastrointestinal side effects (nausea, vomiting, diarrhea and abdominal pain) and leukopenia were more common in the group receiving LPV/RTV. Four serious gastrointestinal events (gastritis and bleeding) were attributed to LPV/RTV. In a retrospective study of LPV/RTV in SARS-CoV infection, mild adverse reactions were experienced by 11 of 41 patients (27%) in the treatment group: gastrointestinal upset (27%), liver dysfunction (22%), headache (15%) and blurred vision (7%). Only one patient required early discontinuation because of a significant rise in ALT to more than twice the normal level. Anemia occurred in 71% of patients in the treatment group; two of whom required a transfusion[50]. In a small PEP study, nearly all (96%) patients who received LPV/RTV reported at least one symptom, with the most common being diarrhea (41%), nausea (41%), stomatitis (18%) and fever (14%). All patients who received LPV/RTV had hyperbilirubinemia, 45% had anemia, and 40% had leukopenia. Other liver enzymes were normal, and all laboratory values normalized after therapy[52].There has been a suggestion of bradycardia as related to LPV/RTV[50-56]. In HIV studies, gastrointestinal side effects are most common. Asthenia/malaise, headache, and rash are also reported[57]. With long-term use, metabolic syndrome, high cholesterol and weight gain have been reported[57];however, in a short-term randomized controlled trial, 55 patients (52%) in the standard-care group and 65 (68%) in the LPV/RTV group had elevated lipids. Lipid elevations in patients receiving LPV/RTV have led to reports of pancreatitis, rarely fatal, although it is unclear if this is related to LPV/RTV[58.59]. The US FDA also notes the possibility of hepatotoxicity, immune reconstitution syndrome, dysrhythmia, and hyperglycemia, although a causal relationship has not been established for any of these[59].

Given the lack of efficacy in randomized trials COVID-19, and the consistent signal of adverse effects, LPV/RTV cannot be recommended at this time.

**HCQ/CQ**

HCQ and CQ are drugs primarily used for prevention and treatment of malaria and treatment of other inflammatory conditions, such as rheumatoid arthritis and lupus[30]. The exact mechanism of action of these drugs is poorly understood. Their antimalarial properties are thought to be related to inhibition of blood product degradation, leading to a toxic buildup of heme, which kills the parasites[60]. In rheumatic disease, several immunomodulatory mechanisms have been proposed, but none is definitively accepted[61]. In practice, HCQ is used more commonly than CQ due to its better tolerability, but they are presumed to have a similar efficacy and mechanism of action.

*In vitro* studies identified antiviral properties of CQ[62], namely inhibition of viral entry into the cell[63,64]. This was confirmed to also be effective *in vitro* against SARS-CoV-2[37,62]. Several early observational studiessuggested some clinical benefit of HCQ in COVID-19 and garnered much media and political attention[65-67]. The US FDA initially authorized HCQ under EUA on March 28, 2020[68], but subsequently withdrew it on June 15, 2020 due to lack of efficacy in several controlled trials[69]. To date, there are several large randomized trials (including unpublished data from trials stopped early for futility) that showed no benefit of HCQ in COVID-19: mild illness[70] and PEP[71].Therefore, it is not recommended for use by most guidelines (Table 1).

HCQ has been associated with several adverse effects such as gastrointestinal distress, headache, allergic reactions, nausea, anxiety, skin rash, fatigue, dizziness, dry mouth, hyperglycemia, loss of appetite, cramps, depression, palpitations, tachycardia, vomiting, chest, and back and joint pain[72]. QT prolongation, hypoglycemia, myopathy, and retinal damage are well known adverse effects documented by the US FDA[73]. Interestingly, QT prolongation, which has previously been thought to be the most common adverse effect, has not been shown to be clinically relevant in all of the large randomized studies in COVID-19. That is, there has been no significant increase in cardiac dysrhythmias, so any QT prolongation is likely insignificant[74,75]. Most of the side effects were gastrointestinal in nature (*e.g.*, nausea, vomiting and diarrhea), followed by neurological (*e.g.*, dizziness, irritability and tinnitus). In randomized studies of HCQ on patients with COVID-19, side effects were nearly always higher in HCQ compared to placebo groups (Supplementary Table 1).

There are also case reports of serious adverse effects of HCQ treatment such as renal phospholipidosis in patient with undifferentiated connective tissue disease[76], cardiomyopathy in rheumatoid arthritis patients[77,78], and psychosis in a patient with Q fever[79] and one with lupus[80]. Psychiatric side effects have been reported and are well accepted, but have not borne out, *per se*, to be significant in large studies[81,82]. This, however, is confounded by the fact that side effects are often bundled and reported as “neuropsychiatric”, where neurological symptoms like headache are paired with psychiatric symptoms like anxiety, depression, and psychosis[82].

CQ is almost universally associated with more intolerance and severe complications than HCQ is[83,84]. Therefore, HCQ should almost universally be chosen over CQ when indicated. However, the randomized clinical evidence for HCQ overwhelmingly shows that it is not effective monotherapy against COVID-19, and the US FDA revoked emergency use authorization of HCQ[69]. Given its proven lack of efficacy on clinically significant outcomes and high rates of intolerance and risk of severe side effects, neither HCQ or CQ should be used in the treatment of patients with COVID-19.

**Vitamin C**

Ascorbic acid or vitamin C is a water-soluble vitamin that is known for its anti-inflammatory, antioxidant and immunomodulatory properties[85]. High-dose intravenous vitamin C (often with thiamine) has been purported to improve outcomes in sepsis[86], but several large randomized trials have largely disproven this[87-89]. However, it is still a subject of ongoing research and debate[90], as some randomized trials have shown benefit in secondary outcomes like organ dysfunction or a nonsignificant trend toward reduction in mortality[87,88].

Studies have shown that severe COVID-19 infection is associated with a cytokine storm that in turn triggers immune reaction involving Th1 cells, severe inflammation, and elevated proinflammatory cytokines such as granulocyte–macrophage colony-stimulating factor and interleukin (IL)-6[91]. Vitamin C has known immunomodulatory properties, and is suspected to therefore suppress the cytokine storm[91-93]. It also is a strong antioxidant[92].

In a retrospective controlled study, oral administration of 500–1500 mg ascorbic acid had no effect on mortality and extubation rates in COVID-19 patients[94].A case study on a COVID-19-positive 74-year-old patient with acute respiratory syndrome and sepsis reported intravenous administration of vitamin C (high dose) led to clinical improvement and rapid recovery of the patient within 5 d[95]. In another case study, a 35-year-old COVID-19 patient with mild symptoms was recommended to take 200 mL herbal tea (ginger and garlic with lemon fruit) over 12 h with daily supplementation of 2000 mg/d vitamin C. Other members of the family were recommended to take vitamin C (adults 1000 mg/d and children 500 mg/d) as prophylaxis. The patient recovered and none of the family members were infected[96]. Despite the initial reports on the beneficial effects of vitamin C for COVID-19 patients, no controlled studies have shown benefit, although no large, well-conducted studies have been completed. There are several ongoing studies of intravenous vitamin C with or without other medications in patients with COVID-19[97-99].

Vitamin C is largely thought to be safe since it is an essential nutrient; however, the doses used in critically ill patients are well above physiological needs. The typical recommended daily allowance in healthy men and women is 75 and 90 mg/d, respectively, with a tolerable upper intake level of 2 g/d[100]. The initial studies utilized 1.5 g intravenously every 6 h[86],but subsequent studies have gone as high as 50 mg/kg (*e.g.*, 3.5 g for a 70-kg patient) every 6 h[101]. The large CITRIS-ALI study found no study-related adverse events at the higher dose. In the VITAMINS trial, which used vitamin C with thiamine and hydrocortisone, two patients in the intervention group had adverse events. One had hyperglycemia, which was likely from the steroids, and one had fluid overload, which was unlikely related to the study interventions[87]. Studies in other populations have confirmed very low risk of side effects[102-104]. One patient had hypokalemia and one had kidney stones in a systematic review of cancer patients receiving vitamin C[103].

There is no great clinical evidence for the use of vitamin C in patients with COVID-19, although it is likely very safe. Further research is needed on its efficacy before it can be routinely recommended, but it might be considered in select cases.

**Vitamin D**

Vitamin D is a fat-soluble steroid hormone involved in calcium homeostasis. It also has recognized immunomodulatory effects, with vitamin D deficiency associated with autoimmunity and an increased risk of infections[105]. Deficiency in vitamin D is ubiquitous, with nearly half of Americans having vitamin D deficiency[106]. Deficiency in vitamin D is associated with an increased risk of respiratory infections[107,108], but, more importantly, supplementation of vitamin D has shown to ameliorate this risk[109]. It is understandable, therefore, that vitamin D has been proposed as a treatment for COVID-19.

In *in vitro* studies, vitamin D has been shown to be a potential mitigating agent for SARS-CoV-2 infection[110]. A case series of four patients also suggested a benefit[111]. Critically ill patients are known to have vitamin D deficiency[112-114]. However, several randomized trials of vitamin D supplementation in critically ill patients with vitamin D deficiency have shown no benefit[115]. In several studies in COVID-19, vitamin D deficiency was associated with critical illness[116-119]. One small study on supplementation in vitamin-D-deficient outpatients with COVID-19 showed that vitamin D reduced viral loads and fibrinogen levels[120]. Another open label, randomized study (*n* = 63) showed that vitamin D supplementation (calcifediol 0.532 mg on day 1 and 0.266 mg on subsequent days) in hospitalized patients reduced the risk of intensive care upgrade compared to standard care[121]. In a larger preprint randomized study (*n* = 240), vitamin D (single dose 200 000 IU cholecalciferol) supplementation did restore vitamin D levels but had no effect on clinical outcomes: hospital length of stay, intensive care unit (ICU) admission, mechanical ventilation, or mortality[122].

The most recognized side effect of vitamin D supplementation is hypercalcemia at very high doses. Associated nausea, pain, neuropsychiatric effects, constipation and fatigue can occur. The recommended daily allowance of vitamin D is 600–800 IU for adults, and the upper tolerable limit is 4000 IU daily in adults. Some patients experience gastrointestinal upset with vitamin D supplementation. There is also an association with an increased risk of urinary tract infections[123]. In the large prior randomized studies on critically ill patients, serious adverse events were rare and similar between vitamin D and placebo groups[115]. In one of these studies (with a single 540 000 IU dose), levels of calcium were shown to be slightly elevated in some patients, but with no difference in clinical outcomes. There were no differences in incidence of renal stones, and a slight nonsignificant increase in falls (7.1% *vs* 5.3%) and fall-related fractures (0.8% *vs* 0.4%) in the vitamin D group. In the other study (with a single 540 000 IU dose followed by 5 monthly 90 000 IU doses), one patient was found to be moderately hypercalcemic and have undiagnosed hyperparathyroidism, and another patient accidentally took all subsequent doses (540 000 IU) in the 1 mo following the study with no adverse event other than elevated vitamin D levels. Study drug discontinuation, fractures and falls were similar between the two groups[115]. Neither of the randomized studies in COVID-19 reported any adverse effects[121,123].

Vitamin D is likely to be safe in reasonable doses. Prior data have shown that a large number of Americans are deficient in vitamin D and critically ill patients are also deficient in vitamin D, but prior data on supplementation in critically ill patients with sepsis have not shown any benefit. The data on vitamin D in COVID-19 are largely confounded by observational bias, and whether vitamin D supplementation improves outcomes in COVID-19 remains unclear. Vitamin D should not routinely be recommended for the treatment or prevention of COVID-19 at this time, but it likely has low risk of harm.

**Zinc**

Zinc is a trace mineral that is essential for several body functions. It plays vital role in signaling pathways and is essential for normal immune, cardiovascular, nervous and reproductive systems[85,124]. Zinc deficiency results in immune dysfunction and supplementation of zinc improves T-cell function[125]. A randomized control study involving 231 HIV-infected patients reported zinc supplementation delayed failure of immune system and improved clinical symptoms in patients[126]. Moreover, supplementation of zinc has been reported effective as prophylaxis for respiratory tract infections, pneumonia and diarrhea in children[127,128].

Adjunctive therapy with zinc has shown improved dermatitis and mucositis in cancer patients treated by radiotherapy[129], reduced cardiovascular risk in patients with acute renal failure[130], improved clinical symptoms in asthmatic children[131], improved sleep quality[132], and reduced insulin resistance and blood glucose, and improved pancreatic beta cell function along with improved lipid profile in prediabetic patients[133]. It also has been shown in some studies to reduce symptoms of viral respiratory infections in adults[134].

Zinc has been shown, *in vitro*, to have a potent antiviral effect[135], specifically against coronaviruses. For example, SARS-CoV-infected Vero-E6 cells treated with a combination of zinc and pyrithione showed inhibition of RNA-dependent RNA polymerase elongation and reduced template binding[136]. Another study showed that zinc reduces angiotensin converting enzyme (ACE)-2, the primary entry site of SARS-CoV-2 into cells, in rats[137].Interesting is the notion that another proposed treatment, HCQ, serves as a zinc ionophore, aiding its entry into cells where zinc can then exert its antiviral effects. One limitation to many of these animal model coadministration studies is the use of ultra-supra-physiological concentrations of zinc[138].

Zinc deficiency in COVID-19 patients has been associated with severe infection, increased complications and mortality[139,140]. In a case report series of four patients with COVID-19, high dose oral zinc (up to 200 mg) was associated with improved respiratory symptoms after 1 d[141]. A prospective study with 242 patients did not find a significant correlation between zinc supplementation and mortality[142]. There are no standalone randomized trials of zinc in patients with COVID-19, although there is one randomized study where it was coadministered with HCQ, and zinc was not shown to increase the effects of HCQ[143]. There are also several observational studies of zinc with other therapies, like HCQ, with mixed results[144-146].There is one ongoing randomized study of high-dose intravenous zinc as adjunctive therapy in COVID-19 critically ill patients, a pilot randomized controlled trial, and several other ongoing studies with coadministration of zinc with other therapies[147-150].

The recommended daily allowance of zinc is 11 mg/d for men and 8 mg/d for women[151]. Zinc supplementation can inhibit copper absorption and lead to copper deficiency[152,153]. Paradoxically, one study showed that 150 mg zinc supplementation caused immune dysfunction and dyslipidemia in healthy volunteers[154,155]. Zinc is found in high concentrations in the prostate, and zinc supplementation has been associated with hospitalizations for genitourinary issues[156], and even prostate cancer at doses > 100 mg/d[157]. High doses of zinc are also associated with gastrointestinal side effects, like nausea, vomiting, diarrhea and cramping.

There are several known adverse effects of zinc, some of which can be serious. Therefore, despite the possible role of zinc in prophylaxis/treatment of COVID-19, well conducted, randomized studies need to be conducted before it should be used in clinical practice.

**Azithromycin**

The macrolide antibiotic azithromycin is used in bacterial respiratory infections. In addition to antibacterial effects, it has immunomodulatory properties within the respiratory tract[158-160]. It also has antiviral activities[161]. *In vitro* studies have shown antiviral activity of azithromycin against Ebola, Zika, dengue and rhinoviruses[162-169]. In mice infected with H1N1 influenza virus, azithromycin pretreatment led to reduced fever and viral load[169]. Studies on mice have also shown azithromycin to be effective against enterovirus and coxsackievirus[170].

Azithromycin accumulates in high concentrations in epithelial cells, like those found in the lungs. *In vitro* studies with SARS-CoV-2-infected cells have shown antiviral activity of azithromycin[171]. There are several proposed mechanisms, but one is that macrolides like azithromycin interfere with binding of SARS-CoV-2 spike proteins to ACE2 receptor on host cells[172,173]. Macrolides also may alter the pH of the lysosomes, and therefore inhibit viral replication[174].In other studies, lower concentrations of azithromycin were shown to have antiviral activity only when combined with HCQ[171].

Clinical studies using azithromycin in combination with other drugs have reported its potential antiviral activity, although results are mixed and inconclusive. In studies on infants with respiratory syncytial virus, azithromycin showed mixed results and no clear benefit on symptoms or inflammatory markers[175-177]. In a retrospective study of 329 patients infected with H1N1 influenza virus, combination treatment with oseltamivir and azithromycin was associated with decreased symptom severity compared to oseltamivir alone[178]. Another small randomized trial, however, showed that the combination of oseltamivir and azithromycin had a small effect on maximum fever (likely not clinically relevant) but had no effect on inflammatory cytokines compared to placebo. In observational data of 349 MERS patients, azithromycin treatment was not associated with clinical improvement, reduction in viral load, or mortality[179]. However, in a retrospective study on critically ill patients with SARS-CoV, azithromycin use was associated with decreased mortality and decreased ventilator-days[180].

Most studies with azithromycin in COVID-19 have been used with combination therapy, often with HCQ. In an uncontrolled evaluation of COVID-19 infected patients treated with azithromycin and HCQ, 97.5% of patients had no detectable virus by day 5[66]. These authors also showed an association with combination therapy increasing viral clearance over HCQ alone[66]. Other observational studies have shown no significant difference for azithromycin and HCQ in reducing viral load or clinical improvement[181].In Iran, 56 COVID-19 patients were administered with combination of HCQ, LPV/RTV with or without azithromycin. The patients who received azithromycin had overall better condition at discharge, with shorter duration of hospital stay; however, mortality rate was the same as the control group that did not receive azithromycin[182]. A randomized trial showed no clinically significant difference among patients receiving azithromycin with HCQ compared to HCQ alone[183].

The use of azithromycin has been associated with a wide range of mild to moderate adverse effects. Most antibiotics are known to cause gastrointestinal side effects like nausea, vomiting, diarrhea and cramping, and azithromycin is no exception. *Clostridium difficile* infections are also side effects of many antibiotics, with macrolides having a moderate risk[184,185]. The inappropriate use of antibiotics can also increase resistance patterns, rendering them useless for bacterial infections in the future. Azithromycin is known to prolong QTc, with some case reports of fatal Torsades de pointes[186], and association with cardiac death in large analyses[187]. All drugs carry the risk of anaphylaxis, but this has been rarely documented with azithromycin[188]. The concerning feature is the delayed biphasic reaction, despite cessation, of which the US FDA warns[189]. Cholestatic hepatitis and transaminitis have also been reported in several patients taking azithromycin[190-193]. As noted above, azithromycin is often coadministered with other drugs, like HCQ, that may also prolong the QTc and increase the risk for cardiac adverse events and fatal dysrhythmias[194,195].

Azithromycin has known deleterious side effects and no clinical evidence for benefit of monotherapy in COVID-19. Therefore, it should not be used for treatment of COVID-19 unless sufficient evidence of clinically significant efficacy is clearly demonstrated.

**Interferon**

Interferons (IFNs) are immune system mediators with varying biological functions such as antiviral activity, pathogenic antiproliferative activity and immunomodulatory functions. Clinical studies have reported efficacy of IFN treatment for chronic viral cardiomyopathy[196] and multiple sclerosis[197], and it was previously the treatment of choice for viral hepatitis[198,199]. There are several subtypes of IFNs, the most common being alpha and beta. While there are some differences, the alpha and beta subtypes share a common multicomponent, cell surface receptor and elicit a similar range of biological responses, including antiviral, antiproliferative and immunomodulatory activities[200]. In an *in vitro* study on SARS-CoV- and MERS-CoV-infected cells, IFN-β treatment showed significant antiviral activity[201-203].

A clinical human study using combination of IFN-β1b (0.025 mg intravenously on alternate days) and LPN/RTV (400/100 mg over 12 h) for treatment of MERS patients (*n* = 95) reported lower mortality in treated patients, with greater effect in patients receiving treatment within 7 d of infection[204]. In another observational study, IFN-β along with mycophenolic acid treatment reduced mortality of MERS; however, the treatment was effective in patients with less severe disease compared to patients with severe symptoms[205].

In a clinical trial involving 80 COVID-19 patients treated with 250 μg IFN-β1b on alternate days for 2 wk, the patients showed earlier clinical improvement with reduced rate of mechanical ventilation and reduced mortality with no adverse effects[206]. IFN-β1b (8 million IU on alternate days) in combination with LPN/RTN (400/100 mg BID) and ribavirin (400 mg BID) administered to 144 COVID-19 patients showed clinical improvement in symptoms, reduced viral load, and shorter recovery time of mild to moderately ill patients[207]. A randomized trial on 81 COVID-19 patients conducted in Iran reported administration of IFN-β1a (12 million IU three times/wk), HCQ (d 1: 400 mg BID; d 2–14: 200 mg BID), and LPN/RTV (400/100 mg BID) (or atazanavir/ritonavir) for 14 d showed no change in clinical recovery time, mildly shortened discharge time of patients, and significantly reduced 90-d mortality compared to the control group[208]. Another randomized trial of 60 severely ill patients randomized to IFNβ1a (subcutaneous injections of 12 000 IU on d 1, 3 and 6), IFNβ1b (subcutaneous injections of 8 000 000 IU on d 1, 3 and 6), or placebo showed a mild difference in time to clinical improvement in the IFN groups, driven mostly by the IFNβ1a, but there was no significant difference in mortality[209].

The most common acute adverse events with IFN administration are flu-like: nausea/vomiting, fever/chills, myalgias and headache[205,206]. Adverse effects appear to be dose related, with 66% of patients treated with high-dose IFN having at least one Grade 3 adverse event and 14% a Grade 4 event. The rates of adverse events were lower in lower-dose groups, with only one patient (0.05%) having a Grade 4 adverse event in one study[210] and Grade 3 events in about 10%–15% of patients[211-213]. In the randomized study by Hung *et al*[207] on COVID-19 patients treated with IFN-β1b, ribavirin and LPV/RTV, adverse events such as nausea, diarrhea, increase in liver enzymes, and fever were observed in patients, but no significant difference was seen between the treatment and control groups. Similar findings, with the addition of some electrolyte and hematological laboratory changes, were found in a randomized trial of IFN-β1b, HCQ, and LPV/RTV or atazanvir/ritonavir[208]. Again, there were no significant differences between the groups, with more of the adverse events occurring with a higher frequency in the control group. In another study with similar therapy, there were eight (19%) infusion-related reactions, one (2%) hypersensitivity reaction, and a clinically significant increase in neuropsychiatric events (*n* = 4, 10% *vs* 0%). There are well-recognized longer-term side effects of IFN therapy, although these are mostly with longer therapy for cancer or viral hepatitis. The most common is chronic fatigue[214]. There have also been a wide range of other reported effects: gastrointestinal, hepatic, psychiatric, endocrine and rarer neurological, autoimmune, pulmonary, and cardiac complications[214].

The evidence gathered by clinical studies so far suggests the potential of IFN-based therapies, particularly IFN-β1b and IFN-β1a, as a therapeutic option for COVID-19; however, more clinical trials with larger populations should be conducted to confirm this. Furthermore, there is a significant potential of adverse effects with this therapy.

**Interleukin antagonist therapies (tocilizumab, sarilumab and anakinra)**

SARS-CoV-2 is associated with elevated levels of IL-6 and cytokine storm in patients with severe infection[215,216]. Tocilizumab (TCZ), and sarilumab are monoclonal antibody blocking agents for IL-6 receptor, and siltuximab is a monoclonal antibody directed at IL-6. Historically, the FDA approved TCZ (intravenous) for rheumatoid and juvenile arthritis[217], sarilumab (subcutaneous) for rheumatoid arthritis[218],and siltixumab (intravenous) for Castleman’s disease[219]; however, the US FDA more recently added an indication to TCZ for patients with cytokine storm receiving CAR-T (chimeric antigen receptor T) immunotherapy in 2017[220]. They have been used successfully in other inflammatory conditions. Some examples include Takayasu arteritis[221] and systemic sclerosis[222].

IL-1, particularly IL-1α and IL-1β, is also elevated in patients with severe COVID-19[223], and the inflammatory overactivation (cytokine storm) in these patients has been compared to that found in hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS). Therefore, the IL-1 receptor antagonist anakinra (subcutaneous) has also been proposed to be helpful in critically ill patients with COVID-19[224,225]. Anakinra was initially approved by the US FDA for the treatment of rheumatoid arthritis and then the rare congenital deficiency of IL-1 receptor antagonist and neonatal onset multisystem inflammatory disease[226]. It has also been used successfully in several other inflammatory conditions; most notably HLH/MAS[227-229].

Canakinumab is a monoclonal antibody against IL-1β, specifically. It also, has been suggested for use in COVID-19, but is only currently approved for use in periodic fever syndromes (*e.g.*, familial Mediterranean fever) and juvenile idiopathic arthritis[230].

Preclinical evidence of effectiveness of TCZ was suggested by an *in vitro* study with lipopolysaccharide-induced THP-1 cell line as a sepsis model. In this study, TCZ treatment for 24 h reduced phagocytosis, cytokine production and immune activation, implying potential of TCZ as a therapeutic option for cytokine storm[231]. In a study in mice with severe H1N1 influenza virus infection, IL-6 was associated with activation of the immune system that in turn induced muscular dysfunction during respiratory distress and TCZ treatment attenuated severe muscular dysfunction[232]. In another rat sepsis model, TCZ treatment reduced mortality in rats with sepsis and inhibited the inflammatory process inducing renal and lung injury[233]. Analysis of single cells of critically ill COVID-19 patients receiving TCZ showed inhibition of inflammation and associated cytokines. The immune cells (CD8+ T cells and B cells) were stable, thereby suggesting cytokines and their receptors as potential targets for future therapies[234].

The first case report on effectiveness of TCZ administration (a single IV dose at 8 mg/kg) to a 60-year-old patient with multiple myeloma and severe COVID-19 showed that he recovered from infection within 10 d of drug administration[235]. An uncontrolled case series of critically ill COVID-19 patients suggested TCZ was associated with rapid clinical improvement[236,237]. In an observational study on 1351 patients (40% critically ill), TCZ treatment was associated with reduced mortality and mechanical ventilation[238]. Another observational study on COVID-19 patients (*n* = 196) suggested effectiveness of TCZ + steroid treatment in clinical improvement of intubated patients[239]. Given that steroids have known benefit and the observational nature of the data, it is unclear how much of this benefit can be attributed to TCZ *per se*.

There have been several equivocal randomized trials on the use of TCZ in patients with COVID-19. In one study, TCZ within 24 h of admission did not improve outcomes in 123 patients with PaO2/FiO2 between 200 and 300 and inflammatory phenotype (*i.e.*, fever or elevated C-reactive protein)[240]. Another randomized trial of 377 patients with COVID-19 who were hospitalized but not intubated showed that TCZ reduced the composite mortality of mechanical ventilation or mortality, but not mortality alone[241]. The other randomized trial on the topic showed no difference between TCZ and placebo in terms of death or need for mechanical ventilation[242]. Preliminary results from the industry-sponsored study COVACTA also showed disappointing results in composite outcome or mortality for patients with severe COVID-19[243]. The other industry-sponsored study on TCZ in patients hospitalized with COVID-19 (EMPACTA) showed preliminary results with a relative 44% reduction (19% *vs* 12%) in the composite outcome of mechanical ventilation or death, but, again, no difference in 28-d mortality[244]. The preprint of a large (*n* = 755), randomized trial of patients (the REMAP-CAP study) showed critically ill COVID-19 patients receiving 8 mg/kg of TCZ within 24 h of ICU admission had a 7.8% absolute reduction in mortality[245]. This study also had a smaller group who received 400 mg sarilumab, which had a 13.6% reduction in mortality, but a much wider confidence interval, although still statistically significant. TCZ and sarilumab were effective across all secondary outcomes, including 90-d survival, time to ICU and hospital discharge, and improvement in the World Health Organization ordinal scale at day 14. Secondary analyses in this study suggested that steroids in combination with IL-6 antagonism had an additive protective effect[245]. The industry-sponsored study on sarilumab (and the only other large, *n* = 420, randomized trial to date in COVID-19) showed no difference in clinical improvement[246].

Anakinra was shown to be associated with improved clinical outcomes in two small retrospective case–control studies[247,248], and two small prospective observational studies[249,250]. No randomized study have been performed to date, but several are ongoing[251,252].

Of course, interleukin inhibitors raise concern for serious infections. Indeed, in the long-term randomized trials of these agents, there is an increase in risk of infections, mostly pneumonia, sinusitis, pharyngitis, and urinary infections[217-219,226,230]. There were reports of serious infections requiring hospitalization and opportunistic infections, but they were less common. This will be important to consider when selecting patients who are critically ill with COVID-19 for these medications, and may have concomitant bacterial infections. The three subcutaneous formulations (sarilumab, canakinumab and anakinra) are associated with local injection site reactions, at rates of 5%–10% for sarilumab[218], 7%–9% for canakinumab[226], and about 15% for anakinra[230].Laboratory abnormalities appear to be associated with this class of medications and include neutropenia, thrombocytopenia, liver function abnormalities, and elevated triglycerides (Table 2).Reports of mild symptoms like nausea, headache, nausea, and abdominal pain exist, but appear no higher than for placebo. There have been rare reports of gastrointestinal perforation, mostly associated with coadministration of steroids and nonsteroidal anti-inflammatory drugs. Anaphylaxis is a known rare complication (< 1%).

In the five of six randomized trials of TCZ for COVID-19, concomitant infections were shown to be higher in the placebo/standard care groups. Mild reactions were more common than serious ones.Laboratory abnormalities seem to contribute the most to any increased signal of adverse effects, mostly neutropenia and sometimes elevated liver function tests. Differences in triglyceride levels were not reported. Gastrointestinal perforation did not appear to be increased, even when steroids were coadministered.

Therefore, there appears to be some emerging evidence of the benefit of interleukin blockade in critically ill patients with COVID-19, with the most promising agent being TCZ. There are theoretical risks of serious adverse events, most notably serious infections, but they do not appear to be increased in randomized trials. There are some mild events, with neutropenia being the most common. In carefully selected critically ill patients, early administration of TCZ (within the first 24 h) may be considered. Other agents require further study, which is ongoing.

**Ivermectin**

Recently, the antiparasitic agent ivermectin has gained interest as an outpatient treatment for COVID-19, mostly by the I-MASK group[253]. Despite that it is primarily known as an antiparasitic agent, ivermectin is known to have *in vitro* activity against many viruses, including West Nile encephalitis virus[254], HIV[255,256], and dengue[255-257],Chikungunya[258], adenovirus[259] and influenza[256,260] viruses. Ivermectin also has several anti-inflammatory properties *in vitro* and in animal models[261-263]. Most notably, ivermectin has been shown to have antiviral properties against SARS-CoV-2 *in vitro* and in animal models[264-266].

Ivermectin has been proposed not only for treatment, but also prophylaxis of patients at high risk for COVID-19[267]. Preliminary data from a large randomized trial show that ivermectin (2 doses, 72 h apart) may reduce development of symptoms of close household contacts of patients with COVID-19 (7.4% *vs* 58.4%). Another preprint study randomized 200 household contacts to ivermectin and personal protective equipment (PPE) or PPE alone and showed progression to symptomatic disease improved with ivermectin (10% *vs* 2%)[268].

In one observational study, ivermectin with doxycycline was associated with improved viral clearance[269]. There are several retrospective/observational trials that suggest an association between ivermectin and improved clinical outcomes[270,271], including mild to moderate COVID-19[272], and patients hospitalized with COVID-19[273]. One randomizedstudy on 70 patients hospitalized with COVID-19 in Iraq randomized them to receive both ivermectin (2–3 d) and doxycycline *versus* standard therapy. They showed a reduction in progression, and an improvement in mortality in severe patients, but worsened mortality in critically ill patients; all limited by the small sample size[274]. A small, three-arm study in Bangladesh randomized 72 patients hospitalized with COVID-19 to either ivermectin (5-d course), ivermectin and doxycycline, or placebo. They showed that clinical symptoms of fever, cough and sore throat were comparable among the three groups. Virological clearance was earlier in the ivermectin treatment arm when compared to the placebo group (9.7 *vs* 12.7 d), but this was not the case for the ivermectin and doxycycline arm (11.5 d)[275]. One large study randomized 100 patients each to HCQ plus standard care or ivermectin plus standard care in severe and mild/moderate groups (4 relevant groups), and showed that ivermectin improved progression of disease and mortality compared to HCQ and improved multiple laboratory parameters (this study has subsequently been retracted due to concerns of plagiarism and falsified data)[268]. Larger randomized trials are ongoing, with one study of 400 patients with mild disease and less than 7 d of symptoms recently published showing no benefit of 300 μg/kg ivermectin daily for 5 d[276].

For parasitic infections, symptoms associated with Mazotti reactions (life-threatening allergic response to proteins released by dying parasites) are noted, but they would be unlikely to occur in viral infections like COVID-19. Based on US FDA data, less than 2% of patients had each of the following minor symptomatic adverse effects: rash, fatigue, gastrointestinal symptoms, somnolence, headache, myalgia and tremor. Slightly more patients reported dizziness/vertigo[277]. There were minor laboratory abnormalities in a small proportion of patients (1%–3%): leukopenia, eosinophilia and elevated liver functions[277]. Rare neurological manifestations, as severe as coma, have been noted and are thought to be due to congenital absence of ATP-binding cassette subfamily B member 1 transporter[278]. Two randomized trials of treatment of patients with COVID-19 with ivermectin reported no adverse events in either group, but these studies were small (142 patients combined) [274,275]. In a larger, more recent study, 154 patients (77%) in the ivermectin group and 161 (81.3%) in the placebo group reported adverse events.[276] Fifteen patients (7.5%) in the ivermectin group *versus* five (2.5%) in the placebo group discontinued treatment due to an adverse event. Headache was the most common, occurring in 52% of patients in the ivermectin group and 56% on patients in the placebo group[276].

Ivermectin has promise and a relatively reassuring safety profile in other indications, but there is not enough clinical evidence at this time to support its use for treatment of COVID-19. Further research should be directed at this intervention.

**Convalescent Plasma Therapy**

Passive immunization or plasma transfusion has been used for treatment and prevention of infectious diseases since the 19th century. Pathogen-specific immunoglobulins isolated from plasma or whole blood of surviving patients can serve as a lifesaving therapy for those suffering from an infectious disease. This technique was used to treat diphtheria and bacterial infections in the 19th century[279] and the Spanish influenza outbreak[279,280]. Moreover, plasma transfusion therapy has been used in H5N1 (Asian avian) influenza virus infection[280,281], H1N1 (swine flu) influenza virus infection[282,283], and Ebola virus infection[284-287]. Passive immunotherapy has also been favorable for treatment of SARS[288,289] and MERS[290,291]. It is not considered first line for any of these indications.

The US FDA offered convalescent plasma therapy for clinically serious patients on EUA based on reported efficacy of the treatment during historic outbreaks[292]. Several small uncontrolled case series involving COVID-19 patients reported complete recovery with no adverse effects after patients received plasma transfusion[293-296]. In another observational study with 5000 critically ill participants, plasma transfusion was associated with decreased mortality when received earlier or if the transfused plasma had higher IgG levels. A large observational Mayo Clinic study on 20 000 patients showed similar results to earlier transfusion[297].

On top of the aforementioned case series, observational studies of plasma transfusion for treatment of COVID-19 infection suggested beneficial effects[298,299]. However, subsequently, three randomized trials (2 of which were stopped early) showed no benefit[300-302].

The risks of convalescent plasma mostly mirror those of any transfusion: infections (*e.g*., HIV, hepatitis, *etc.*), immune reactions, anaphylaxis, hemolysis, and transfusion- associated circulatory overload, and transfusion-associated lung injury. These risks are generally thought to be less in plasma than red blood cell transfusions, but cases of the development of ARDS after convalescent plasma transfusion have been reported[285,290]. In the large Mayo Clinic study with 20 000 patients, the incidence of serious adverse events was low; these included transfusion reactions (< 1%), thromboembolic or thrombotic events (< 1%), and cardiac events (3%). Most thromboembolic or thrombotic events (*n* = 55) and cardiac events (*n* = 562) were judged to be unrelated to the transfusion[297]. In one randomized trial, minor adverse events of pain at the local infusion site, chills, nausea, bradycardia, and dizziness were reported in one patient (0.4%) each. Fever and tachycardia were reported in three patients (1.3%) each. Dyspnea and intravenous catheter blockage were noted in two participants each (0.8%). Mortality was assessed as possibly related to convalescent plasma transfusion in three patients (1.3%)[300].In another study in Wuhan on 86 patients (43 assigned to receive convalescent plasma), no serious adverse events were reported[301]. Another large randomized trial on 101 patients (51 randomized to receive convalescent plasma) reported two serious adverse events related to convalescent plasma administration: one patient with chills and rash 2 h after administration, deemed a nonsevere allergic reaction and a probable non-severe febrile hemolytic transfusion reaction; and another patient with life-threatening COVID-19 who developed severe dyspnea and cyanosis within 6 h of administration, which was deemed possibly transfusion-related dyspnea[302].

Given there was no proven efficacy in several randomized trials and a risk of serious reactions and adverse events, convalescent plasma should not be used for the treatment of COVID-19 at this time.

**Discussion**

The on-going COVID-19 pandemic highlights the limitation and the need for exploring therapeutic options for coronavirus infections. Though previous SARS (2003) and MERS (2012) outbreaks initiated *in vitro*, *in vivo*, and clinical research, so far there is no specific drug to treat coronavirus infections. These outbreaks and the current coronavirus pandemic indicate the possibility of future coronavirus outbreaks and the threat these viruses pose to public health globally. Even mutations of the current SARS-CoV-2 have already been reported[303,304]. Since drug development is a time-consuming process, repurposing the existing drugs offer the fastest option for treatment of infectious diseases. However, this does not negate the need for well-done randomized trials to evaluate efficacy. Safety can be extrapolated from prior randomized studies, but also needs to be examined in studies in patients with this novel disease process. Recently published *in vitro* and *in vivo* studies on the efficacy of different therapeutic options for prophylaxis and treatment of SARS-CoV-2 infection were analyzed for this review.

Dexamethasone and other steroids are a widely accepted intervention for COVID-19 patients requiring oxygen, which have shown in several studies to reduce mortality and disease progression. They do have well-known side effects, many of which can be monitored (hyperglycemia) or reduced (gastrointestinal bleeding, myopathy). They have the strongest evidence for efficacy, but must be used in appropriate patients (*i.e.*, those requiring supplemental oxygen).

An analysis of the data presented in this review suggests remdesivir and TCZ (an IL-6 receptor antibody) are promising therapeutic options for select patients with COVID-19, but they, too, have risks of adverse events. Remdesivir should be considered for patients hospitalized with COVID-19 and TCZ considered for early administration in a select group of critically ill patients with COVID-19. In large trials, the rates of serious adverse events using these drugs seem to be low. Nevertheless, randomized, placebo and controlled clinical trials with larger and geographically diverse population size must be conducted to test the efficacy of these treatment options.

Although available data on different treatments such as azithromycin, IFNs, anakinra, and ivermectin have provided some evidence on their efficacy against COVID-19, this review demonstrates clearly that additional data are needed to establish the efficacy of these treatments at a clinical level. Available data are only preliminary and lack larger population and comparative data; moreover, incidences of adverse events should be analyzed to establish the safety of these drugs for clinical administration.

Vitamin C has not shown to be reliably effective in septic shock, but there are no major studies in COVID-19. Zinc also has plausible mechanistic antiviral properties and a signal of benefit in prior studies on respiratory infection but no large studies as monotherapy in COVID-19. Vitamin D also has no benefit in randomized studies in general critically ill patients, but it has shown some mixed evidence in the few randomized trials in COVID-19. These supplements are all likely safe interventions that need further research.

The previously widely used therapies HCQ, LPV/RTV, and convalescent plasma have robust randomized evidence of no beneficial effect. They, like all therapies, have the potential for adverse effects. They should be abandoned for COVID-19 therapy unless convincing new evidence emerges. These therapies highlight the problems with basing treatment decisions on mechanistic studies, case reports, or observational data. Clinicians would be wise to bear this recent history in mind when evaluating potential new therapies.

Additionally, more therapeutic options including use of alternative medicine, supplements, drug combinations, and nonpharmacological therapies must be considered and tested for effective management of COVID-19 infection.

**Limitations**

This review is limited by the limitations of the studies included: limited available data, lack of comparative data, lack of randomization, and number of participants. While we did search several databases and use several methods, this review is not a systematic review and is therefore subject to bias and missing potentially germane articles. Research is rapidly ongoing on the topic of COVID-19 diagnosis and treatment, so the conclusions in this article are based on available evidence. Also, this review was done on drugs used in isolation. It is possible that combination therapy may yield different results or safety risks.

**CONCLUSION**

Dexamethasone appears to be the most efficacious drug for patients with COVID-19, but it should only be used in patients requiring supplemental oxygenation. Remdesivir may reduce length of hospitalization with mild side effects. While they do not have enough evidence to be recommended at this time, ivermectin, and zinc should be studied further for early illness and IFN and interleukin blockade should be studied for critical illness. HCQ/CQ, vitamins C/D, and azithromycin have no convincing evidence of benefit at this time.

**REFERENCES**

1 **van der Hoek L**, Pyrc K, Jebbink MF, Vermeulen-Oost W, Berkhout RJ, Wolthers KC, Wertheim-van Dillen PM, Kaandorp J, Spaargaren J, Berkhout B. Identification of a new human coronavirus. *Nat Med* 2004; **10**: 368-373 [PMID: 15034574 DOI: 10.1038/nm1024]

2 **Lu G**, Hu Y, Wang Q, Qi J, Gao F, Li Y, Zhang Y, Zhang W, Yuan Y, Bao J, Zhang B, Shi Y, Yan J, Gao GF. Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26. *Nature* 2013; **500**: 227-231 [PMID: 23831647 DOI: 10.1038/nature12328]

3 **Sterne JAC**, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, Annane D, Azevedo LCP, Berwanger O, Cavalcanti AB, Dequin PF, Du B, Emberson J, Fisher D, Giraudeau B, Gordon AC, Granholm A, Green C, Haynes R, Heming N, Higgins JPT, Horby P, Jüni P, Landray MJ, Le Gouge A, Leclerc M, Lim WS, Machado FR, McArthur C, Meziani F, Møller MH, Perner A, Petersen MW, Savovic J, Tomazini B, Veiga VC, Webb S, Marshall JC; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020; **324**: 1330-1341 [PMID: 32876694 DOI: 10.1001/jama.2020.17023]

4 **Xiong S**, Liu L, Lin F, Shi J, Han L, Liu H, He L, Jiang Q, Wang Z, Fu W, Li Z, Lu Q, Chen Z, Ding S. Clinical characteristics of 116 hospitalized patients with COVID-19 in Wuhan, China: a single-centered, retrospective, observational study. *BMC Infect Dis* 2020; **20**: 787 [PMID: 33092539 DOI: 10.1186/s12879-020-05452-2]

5 **Wendel Garcia PD**, Fumeaux T, Guerci P, Heuberger DM, Montomoli J, Roche-Campo F, Schuepbach RA, Hilty MP; RISC-19-ICU Investigators. Prognostic factors associated with mortality risk and disease progression in 639 critically ill patients with COVID-19 in Europe: Initial report of the international RISC-19-ICU prospective observational cohort. *EClinicalMedicine* 2020; **25**: 100449 [PMID: 32838231 DOI: 10.1016/j.eclinm.2020.100449]

6 **Chatterjee K**, Wu CP, Bhardwaj A, Siuba M. Steroids in COVID-19: An overview. *Cleve Clin J Med* 2020 epub ahead of print [PMID: 32819962 DOI: 10.3949/ccjm.87a.ccc059]

7 **RECOVERY Collaborative Group**, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 693-704 [PMID: 32678530 DOI: 10.1056/NEJMoa2021436]

8 **Stern A**, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. *Cochrane Database Syst Rev* 2017; **12**: CD007720 [PMID: 29236286 DOI: 10.1002/14651858.CD007720.pub3]

9 **Jeronimo CMP**, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Safe IP, Borba MGS, Netto RLA, Maciel ABS, Neto JRS, Oliveira LB, Figueiredo EFG, Oliveira Dinelly KM, de Almeida Rodrigues MG, Brito M, Mourão MPG, Pivoto João GA, Hajjar LA, Bassat Q, Romero GAS, Naveca FG, Vasconcelos HL, de Araújo Tavares M, Brito-Sousa JD, Costa FTM, Nogueira ML, Baía-da-Silva DC, Xavier MS, Monteiro WM, Lacerda MVG; Metcovid Team. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With Coronavirus Disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial. *Clin Infect Dis* 2021; **72**: e373-e381 [PMID: 32785710 DOI: 10.1093/cid/ciaa1177]

10 **National Institutes of Health**. Therapeutic Management of Adults With COVID-19. National Institutes of Health (NIH). [cited 1 May 2021]. Available from: https://www.covid19treatmentguidelines.nih.gov/therapeutic-management

11 **Rochwerg B**, Oczkowski SJ, Siemieniuk RAC, Agoritsas T, Belley-Cote E, D'Aragon F, Duan E, English S, Gossack-Keenan K, Alghuroba M, Szczeklik W, Menon K, Alhazzani W, Sevransky J, Vandvik PO, Annane D, Guyatt G. Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis. *Crit Care Med* 2018; **46**: 1411-1420 [PMID: 29979221 DOI: 10.1097/CCM.0000000000003262]

12 **Butler E**, Møller MH, Cook O, Granholm A, Penketh J, Rygård SL, Aneman A, Perner A. The effect of systemic corticosteroids on the incidence of gastrointestinal bleeding in critically ill adults: a systematic review with meta-analysis. *Intensive Care Med* 2019; **45**: 1540-1549 [PMID: 31501997 DOI: 10.1007/s00134-019-05754-3]

13 **Narum S**, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. *BMJ Open* 2014; **4**: e004587 [PMID: 24833682 DOI: 10.1136/bmjopen-2013-004587]

14 **Amaya-Villar R**, Garnacho-Montero J, García-Garmendía JL, Madrazo-Osuna J, Garnacho-Montero MC, Luque R, Ortiz-Leyba C. Steroid-induced myopathy in patients intubated due to exacerbation of chronic obstructive pulmonary disease. *Intensive Care Med* 2005; **31**: 157-161 [PMID: 15580474 DOI: 10.1007/s00134-004-2509-9]

15 **Gable M**, Depry D. Sustained corticosteroid- induced mania and psychosis despite cessation: A case study and brief literature review. *Int J Psychiatry Med* 2015; **50**: 398-404 [PMID: 26644319 DOI: 10.1177/0091217415612735]

16 **Buckley L**, Guyatt G, Fink HA, Cannon M, Grossman J, Hansen KE, Humphrey MB, Lane NE, Magrey M, Miller M, Morrison L, Rao M, Byun Robinson A, Saha S, Wolver S, Bannuru RR, Vaysbrot E, Osani M, Turgunbaev M, Miller AS, McAlindon T. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Care Res (Hoboken)* 2017; **69**: 1095-1110 [PMID: 28585410 DOI: 10.1002/acr.23279]

17 **Waljee AK**, Rogers MA, Lin P, Singal AG, Stein JD, Marks RM, Ayanian JZ, Nallamothu BK. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ* 2017; **357**: j1415 [PMID: 28404617 DOI: 10.1136/bmj.j1415]

18 **Yao TC**, Huang YW, Chang SM, Tsai SY, Wu AC, Tsai HJ. Association Between Oral Corticosteroid Bursts and Severe Adverse Events: A Nationwide Population-Based Cohort Study. *Ann Intern Med* 2020; **173**: 325-330 [PMID: 32628532 DOI: 10.7326/M20-0432]

19 **Mandapati JS**, Metta AK. Intraocular pressure variation in patients on long-term corticosteroids. *Indian Dermatol Online J* 2011; **2**: 67-69 [PMID: 23130227 DOI: 10.4103/2229-5178.85993]

20 **Sihota R**, Konkal VL, Dada T, Agarwal HC, Singh R. Prospective, long-term evaluation of steroid-induced glaucoma. *Eye (Lond)* 2008; **22**: 26-30 [PMID: 16823461 DOI: 10.1038/sj.eye.6702474]

21 **Mebrahtu TF**, Morgan AW, West RM, Stewart PM, Pujades-Rodriguez M. Oral glucocorticoids and incidence of hypertension in people with chronic inflammatory diseases: a population-based cohort study. *CMAJ* 2020; **192**: E295-E301 [PMID: 32392512 DOI: 10.1503/cmaj.191012]

22 **Da Silva JA**, Jacobs JW, Kirwan JR, Boers M, Saag KG, Inês LB, de Koning EJ, Buttgereit F, Cutolo M, Capell H, Rau R, Bijlsma JW. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. *Ann Rheum Dis* 2006; **65**: 285-293 [PMID: 16107513 DOI: 10.1136/ard.2005.038638]

23 **Rogers CC**, Alloway RR, Buell JF, Boardman R, Alexander JW, Cardi M, Roy-Chaudhury P, First MR, Succop P, Munda R, Woodle ES. Body weight alterations under early corticosteroid withdrawal and chronic corticosteroid therapy with modern immunosuppression. *Transplantation* 2005; **80**: 26-33 [PMID: 16003229 DOI: 10.1097/01.tp.0000164290.17030.bc]

24 **Stauffer WM**, Alpern JD, Walker PF. COVID-19 and Dexamethasone: A Potential Strategy to Avoid Steroid-Related Strongyloides Hyperinfection. *JAMA* 2020; **324**: 623-624 [PMID: 32761166 DOI: 10.1001/jama.2020.13170]

25 **Ghosh K**, Ghosh K. Strongyloides stercoralis septicaemia following steroid therapy for eosinophilia: report of three cases. *Trans R Soc Trop Med Hyg* 2007; **101**: 1163-1165 [PMID: 17662320 DOI: 10.1016/j.trstmh.2007.05.021]

26 **Krolewiecki A**, Nutman TB. Strongyloidiasis: A Neglected Tropical Disease. *Infect Dis Clin North Am* 2019; **33**: 135-151 [PMID: 30712758 DOI: 10.1016/j.idc.2018.10.006]

27 **Asundi A**, Beliavsky A, Liu XJ, Akaberi A, Schwarzer G, Bisoffi Z, Requena-Méndez A, Shrier I, Greenaway C. Prevalence of strongyloidiasis and schistosomiasis among migrants: a systematic review and meta-analysis. *Lancet Glob Health* 2019; **7**: e236-e248 [PMID: 30683241 DOI: 10.1016/S2214-109X(18)30490-X]

28 **Dong L**, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther* 2020; **14**: 58-60 [PMID: 32147628 DOI: 10.5582/ddt.2020.01012]

29 **Grein J**, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, Nicastri E, Oda R, Yo K, Quiros-Roldan E, Studemeister A, Redinski J, Ahmed S, Bernett J, Chelliah D, Chen D, Chihara S, Cohen SH, Cunningham J, D'Arminio Monforte A, Ismail S, Kato H, Lapadula G, L'Her E, Maeno T, Majumder S, Massari M, Mora-Rillo M, Mutoh Y, Nguyen D, Verweij E, Zoufaly A, Osinusi AO, DeZure A, Zhao Y, Zhong L, Chokkalingam A, Elboudwarej E, Telep L, Timbs L, Henne I, Sellers S, Cao H, Tan SK, Winterbourne L, Desai P, Mera R, Gaggar A, Myers RP, Brainard DM, Childs R, Flanigan T. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N Engl J Med* 2020; **382**: 2327-2336 [PMID: 32275812 DOI: 10.1056/NEJMoa2007016]

30 **Venkatasubbaiah M**, Dwarakanadha Reddy P, Satyanarayana SV. Literature-based review of the drugs used for the treatment of COVID-19. *Curr Med Res Pract* 2020; **10**: 100-109 [PMID: 32572376 DOI: 10.1016/j.cmrp.2020.05.013]

31 **Jacobs M**, Rodger A, Bell DJ, Bhagani S, Cropley I, Filipe A, Gifford RJ, Hopkins S, Hughes J, Jabeen F, Johannessen I, Karageorgopoulos D, Lackenby A, Lester R, Liu RS, MacConnachie A, Mahungu T, Martin D, Marshall N, Mepham S, Orton R, Palmarini M, Patel M, Perry C, Peters SE, Porter D, Ritchie D, Ritchie ND, Seaton RA, Sreenu VB, Templeton K, Warren S, Wilkie GS, Zambon M, Gopal R, Thomson EC. Late Ebola virus relapse causing meningoencephalitis: a case report. *Lancet* 2016; **388**: 498-503 [PMID: 27209148 DOI: 10.1016/S0140-6736(16)30386-5]

32 **Dörnemann J**, Burzio C, Ronsse A, Sprecher A, De Clerck H, Van Herp M, Kolié MC, Yosifiva V, Caluwaerts S, McElroy AK, Antierens A. First Newborn Baby to Receive Experimental Therapies Survives Ebola Virus Disease. *J Infect Dis* 2017; **215**: 171-174 [PMID: 28073857 DOI: 10.1093/infdis/jiw493]

33 **Mulangu S**, Dodd LE, Davey RT Jr, Tshiani Mbaya O, Proschan M, Mukadi D, Lusakibanza Manzo M, Nzolo D, Tshomba Oloma A, Ibanda A, Ali R, Coulibaly S, Levine AC, Grais R, Diaz J, Lane HC, Muyembe-Tamfum JJ; PALM Writing Group, Sivahera B, Camara M, Kojan R, Walker R, Dighero-Kemp B, Cao H, Mukumbayi P, Mbala-Kingebeni P, Ahuka S, Albert S, Bonnett T, Crozier I, Duvenhage M, Proffitt C, Teitelbaum M, Moench T, Aboulhab J, Barrett K, Cahill K, Cone K, Eckes R, Hensley L, Herpin B, Higgs E, Ledgerwood J, Pierson J, Smolskis M, Sow Y, Tierney J, Sivapalasingam S, Holman W, Gettinger N, Vallée D, Nordwall J; PALM Consortium Study Team. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N Engl J Med* 2019; **381**: 2293-2303 [PMID: 31774950 DOI: 10.1056/NEJMoa1910993]

34 **Sheahan TP**, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, Leist SR, Pyrc K, Feng JY, Trantcheva I, Bannister R, Park Y, Babusis D, Clarke MO, Mackman RL, Spahn JE, Palmiotti CA, Siegel D, Ray AS, Cihlar T, Jordan R, Denison MR, Baric RS. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med* 2017; **9** [PMID: 28659436 DOI: 10.1126/scitranslmed.aal3653]

35 **Sheahan TP**, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, Montgomery SA, Hogg A, Babusis D, Clarke MO, Spahn JE, Bauer L, Sellers S, Porter D, Feng JY, Cihlar T, Jordan R, Denison MR, Baric RS. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020; **11**: 222 [PMID: 31924756 DOI: 10.1038/s41467-019-13940-6]

36 **Wang Y**, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang Y, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; **395**: 1569-1578 [PMID: 32423584 DOI: 10.1016/S0140-6736(20)31022-9]

37 **Wang M**, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020; **30**: 269-271 [PMID: 32020029 DOI: 10.1038/s41422-020-0282-0]

38 **Beigel JH**, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020; **383**: 1813-1826 [PMID: 32445440 DOI: 10.1056/NEJMoa2007764]

39 **Wilt TJ**, Kaka AS, MacDonald R, Greer N, Obley A, Duan-Porter W. Remdesivir for Adults With COVID-19 : A Living Systematic Review for American College of Physicians Practice Points. *Ann Intern Med* 2021; **174**: 209-220 [PMID: 33017170 DOI: 10.7326/M20-5752]

40 **Goldman JD**, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn MY, Nahass RG, Chen YS, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wei X, Gaggar A, Brainard DM, Towner WJ, Muñoz J, Mullane KM, Marty FM, Tashima KT, Diaz G, Subramanian A; GS-US-540-5773 Investigators. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med* 2020; **383**: 1827-1837 [PMID: 32459919 DOI: 10.1056/NEJMoa2015301]

41 **United States Food and Drug Administration**. Emergency Use Authorization (EUA) for remdesivir, an unapproved product. U.S. Food and Drug Administration Center for Drug Evaluation and Review. [cited 1 May 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda\_docs/nda/2020/EUA%20Review%20Remdesivir\_050120.pdf

42 **United States Food and Drug Administration**. FDA Approves First Treatment for COVID-19. [cited 1 May 2021]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19

43 **Zampino R**, Mele F, Florio LL, Bertolino L, Andini R, Galdo M, De Rosa R, Corcione A, Durante-Mangoni E. Liver injury in remdesivir-treated COVID-19 patients. *Hepatol Int* 2020; **14**: 881-883 [PMID: 32725454 DOI: 10.1007/s12072-020-10077-3]

44 **National Institutes of Health (NIH)**. Remdesivir. National Institute of Health. [cited 1 May 2021]. Available from: https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/

45 **Dubé MP**, Shen C, Greenwald M, Mather KJ. No impairment of endothelial function or insulin sensitivity with 4 wk of the HIV protease inhibitors atazanavir or lopinavir-ritonavir in healthy subjects without HIV infection: a placebo-controlled trial. *Clin Infect Dis* 2008; **47**: 567-574 [PMID: 18636958 DOI: 10.1086/590154]

46 **Tebas P**, Zhang J, Yarasheski K, Evans S, Fischl MA, Shevitz A, Feinberg J, Collier AC, Shikuma C, Brizz B, Sattler F; AIDS Clinical Trials Group (ACTG). Switching to a protease inhibitor-containing, nucleoside-sparing regimen (lopinavir/ritonavir plus efavirenz) increases limb fat but raises serum lipid levels: results of a prospective randomized trial (AIDS clinical trial group 5125s). *J Acquir Immune Defic Syndr* 2007; **45**: 193-200 [PMID: 17527093 DOI: 10.1097/QAI.0b013e318042e204]

47 **Wangpatharawanit P**, Sungkanuparph S. Switching Lopinavir/Ritonavir to Atazanavir/Ritonavir *vs* Adding Atorvastatin in HIV-Infected Patients Receiving Second-Line Antiretroviral Therapy With Hypercholesterolemia: A Randomized Controlled Trial. *Clin Infect Dis* 2016; **63**: 818-820 [PMID: 27402817 DOI: 10.1093/cid/ciw395]

48 **Chen F**, Chan KH, Jiang Y, Kao RY, Lu HT, Fan KW, Cheng VC, Tsui WH, Hung IF, Lee TS, Guan Y, Peiris JS, Yuen KY. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol* 2004; **31**: 69-75 [PMID: 15288617 DOI: 10.1016/j.jcv.2004.03.003]

49 **Wu CY**, Jan JT, Ma SH, Kuo CJ, Juan HF, Cheng YS, Hsu HH, Huang HC, Wu D, Brik A, Liang FS, Liu RS, Fang JM, Chen ST, Liang PH, Wong CH. Small molecules targeting severe acute respiratory syndrome human coronavirus. *Proc Natl Acad Sci U S A* 2004; **101**: 10012-10017 [PMID: 15226499 DOI: 10.1073/pnas.0403596101]

50 **Chu CM**, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, Kao RY, Poon LL, Wong CL, Guan Y, Peiris JS, Yuen KY; HKU/UCH SARS Study Group. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; **59**: 252-256 [PMID: 14985565 DOI: 10.1136/thorax.2003.012658]

51 **Kim UJ**, Won EJ, Kee SJ, Jung SI, Jang HC. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-α for Middle East respiratory syndrome. *Antivir Ther* 2016; **21**: 455-459 [PMID: 26492219 DOI: 10.3851/IMP3002]

52 **Park SY**, Lee JS, Son JS, Ko JH, Peck KR, Jung Y, Woo HJ, Joo YS, Eom JS, Shi H. Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers. *J Hosp Infect* 2019; **101**: 42-46 [PMID: 30240813 DOI: 10.1016/j.jhin.2018.09.005]

53 **RECOVERY Collaborative Group**. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2020; **396**: 1345-1352 [PMID: 33031764 DOI: 10.1016/S0140-6736(20)32013-4]

54 **Li Y**, Xie Z, Lin W, Cai W, Wen C, Guan Y, Mo X, Wang J, Wang Y, Peng P, Chen X, Hong W, Xiao G, Liu J, Zhang L, Hu F, Li F, Zhang F, Deng X, Li L. Efficacy and Safety of Lopinavir/Ritonavir or Arbidol in Adult Patients with Mild/Moderate COVID-19: An Exploratory Randomized Controlled Trial. *Med (N Y)* 2020; **1**: 105-113.e4 [PMID: 32838353 DOI: 10.1016/j.medj.2020.04.001]

55 **Cao B**, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med* 2020; **382**: 1787-1799 [PMID: 32187464 DOI: 10.1056/NEJMoa2001282]

56 **Beyls C**, Martin N, Hermida A, Abou-Arab O, Mahjoub Y. Lopinavir-Ritonavir Treatment for COVID-19 Infection in Intensive Care Unit: Risk of Bradycardia. *Circ Arrhythm Electrophysiol* 2020; **13**: e008798 [PMID: 32809882 DOI: 10.1161/CIRCEP.120.008798]

57 **Cvetkovic RS**, Goa KL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. *Drugs* 2003; **63**: 769-802 [PMID: 12662125 DOI: 10.2165/00003495-200363080-00004]

58 **Calza L**, Manfredi R, Farneti B, Chiodo F. Incidence of hyperlipidaemia in a cohort of 212 HIV-infected patients receiving a protease inhibitor-based antiretroviral therapy. *Int J Antimicrob Agents* 2003; **22**: 54-59 [PMID: 12842328 DOI: 10.1016/s0924-8579(03)00100-6]

59 **United States Food and Drug Administration**. Kaletra: Full prescribing information. [cited 1 May 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda\_docs/Label/2016/021251s052\_021906s046Lbl.pdf

60 **Sullivan DJ**. Theories on malarial pigment formation and quinoline action. *Int J Parasitol* 2002; **32**: 1645-1653 [PMID: 12435449 DOI: 10.1016/S0020-7519(02)00193-5]

61 **Ben-Zvi I**, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. *Clin Rev Allergy Immunol* 2012; **42**: 145-153 [PMID: 21221847 DOI: 10.1007/s12016-010-8243-x]

62 **Yao X**, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020; **71**: 732-739 [PMID: 32150618 DOI: 10.1093/cid/ciaa237]

63 **Keyaerts E**, Vijgen L, Maes P, Neyts J, Van Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. *Biochem Biophys Res Commun* 2004; **323**: 264-268 [PMID: 15351731 DOI: 10.1016/j.bbrc.2004.08.085]

64 **Savarino A**, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis* 2003; **3**: 722-727 [PMID: 14592603 DOI: 10.1016/s1473-3099(03)00806-5]

65 **Gautret P**, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Tissot Dupont H, Honoré S, Colson P, Chabrière E, La Scola B, Rolain JM, Brouqui P, Raoult D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020; **56**: 105949 [PMID: 32205204 DOI: 10.1016/j.ijantimicag.2020.105949]

66 **Gautret P**, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, Mailhe M, Doudier B, Aubry C, Amrane S, Seng P, Hocquart M, Eldin C, Finance J, Vieira VE, Tissot-Dupont HT, Honoré S, Stein A, Million M, Colson P, La Scola B, Veit V, Jacquier A, Deharo JC, Drancourt M, Fournier PE, Rolain JM, Brouqui P, Raoult D. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis* 2020; **34**: 101663 [PMID: 32289548 DOI: 10.1016/j.tmaid.2020.101663]

67 **Million M**, Lagier JC, Gautret P, Colson P, Fournier PE, Amrane S, Hocquart M, Mailhe M, Esteves-Vieira V, Doudier B, Aubry C, Correard F, Giraud-Gatineau A, Roussel Y, Berenger C, Cassir N, Seng P, Zandotti C, Dhiver C, Ravaux I, Tomei C, Eldin C, Tissot-Dupont H, Honoré S, Stein A, Jacquier A, Deharo JC, Chabrière E, Levasseur A, Fenollar F, Rolain JM, Obadia Y, Brouqui P, Drancourt M, La Scola B, Parola P, Raoult D. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. *Travel Med Infect Dis* 2020; **35**: 101738 [PMID: 32387409 DOI: 10.1016/j.tmaid.2020.101738]

68 **United States Food and Drug Administration**. Memorandum Explaining Basis for Revocation of Emergency Use Authorization for Emergency Use of Chloroquine Phosphate and Hydroxychloroquine Sulfate. [cited 1 May 2021]. Available from: https://www.fda.gov/media/138945/download

69 **United States Food and Drug Administration**. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine. [cited 1 May 2021]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and

70 **Mitjà O**, Corbacho-Monné M, Ubals M, Tebe C, Peñafiel J, Tobias A, Ballana E, Alemany A, Riera-Martí N, Pérez CA, Suñer C, Laporte P, Admella P, Mitjà J, Clua M, Bertran L, Sarquella M, Gavilán S, Ara J, Argimon JM, Casabona J, Cuatrecasas G, Cañadas P, Elizalde-Torrent A, Fabregat R, Farré M, Forcada A, Flores-Mateo G, Muntada E, Nadal N, Narejos S, Gil-Ortega AN, Prat N, Puig J, Quiñones C, Reyes-Ureña J, Ramírez-Viaplana F, Ruiz L, Riveira-Muñoz E, Sierra A, Velasco C, Vivanco-Hidalgo RM, Sentís A, G-Beiras C, Clotet B, Vall-Mayans M; BCN PEP-CoV-2 RESEARCH GROUP. Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial. *Clin Infect Dis* 2020 epub ahead of print [PMID: 32674126 DOI: 10.1093/cid/ciaa1009]

71 **Boulware DR**, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, Skipper CP, Nascene AA, Nicol MR, Abassi M, Engen NW, Cheng MP, LaBar D, Lother SA, MacKenzie LJ, Drobot G, Marten N, Zarychanski R, Kelly LE, Schwartz IS, McDonald EG, Rajasingham R, Lee TC, Hullsiek KH. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N Engl J Med* 2020; **383**: 517-525 [PMID: 32492293 DOI: 10.1056/NEJMoa2016638]

72 **Lee W**, Ruijgrok L, Boxma-de Klerk B, Kok MR, Kloppenburg M, Gerards A, Huisman M, Hazes M, de Sonnaville P, Grillet B, Weel A, Basoski N. Efficacy of Hydroxychloroquine in Hand Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Care Res (Hoboken)* 2018; **70**: 1320-1325 [PMID: 29125901 DOI: 10.1002/acr.23471]

73 **United States Food and Drug Administration**. Hydroxychloroquine sulphate tablets, USP. [cited 1 May 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda\_docs/Label/2017/009768s037s045s047Lbl.pdf

74 **Jankelson L**, Karam G, Becker ML, Chinitz LA, Tsai MC. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: A systematic review. *Heart Rhythm* 2020; **17**: 1472-1479 [PMID: 32438018 DOI: 10.1016/j.hrthm.2020.05.008]

75 **Takla M**, Jeevaratnam K. Chloroquine, hydroxychloroquine, and COVID-19: Systematic review and narrative synthesis of efficacy and safety. *Saudi Pharm J* 2020; **28**: 1760-1776 [PMID: 33204210 DOI: 10.1016/j.jsps.2020.11.003]

76 **Wu SZ**, Liang X, Geng J, Zhang MB, Xie N, Su XY. Hydroxychloroquine-induced renal phospholipidosis resembling Fabry disease in undifferentiated connective tissue disease: A case report. *World J Clin Cases* 2019; **7**: 4377-4383 [PMID: 31911921 DOI: 10.12998/wjcc.v7.i24.4377]

77 **Dogar MU**, Shah NN, Ishtiaq S, Shah PN, Shah P, Mathew S, Vittorio TJ. Hydroxychloroquine-induced restrictive cardiomyopathy: a case report. *Postgrad Med J* 2018; **94**: 185-186 [PMID: 29353247 DOI: 10.1136/postgradmedj-2017-135236]

78 **Yogasundaram H**, Putko BN, Tien J, Paterson DI, Cujec B, Ringrose J, Oudit GY. Hydroxychloroquine-induced cardiomyopathy: case report, pathophysiology, diagnosis, and treatment. *Can J Cardiol* 2014; **30**: 1706-1715 [PMID: 25475472 DOI: 10.1016/j.cjca.2014.08.016]

79 **Das SK**, Pareek A, Mathur DS, Wanchu A, Srivastava R, Agarwal GG, Chauhan RS. Efficacy and safety of hydroxychloroquine sulphate in rheumatoid arthritis: a randomized, double-blind, placebo controlled clinical trial--an Indian experience. *Curr Med Res Opin* 2007; **23**: 2227-2234 [PMID: 17692155 DOI: 10.1185/030079907X219634]

80 **Hsu W**, Chiu N, Huang S. Hydroxychloroquine-induced acute psychosis in a systemic lupus erythematosus female. *Acta Neuropsychiatr* 2011; **23**: 318-319 [PMID: 25380045 DOI: 10.1111/j.1601-5215.2011.00575.x]

81 **Lane JCE**, Weaver J, Kostka K, Duarte-Salles T, Abrahao MTF, Alghoul H, Alser O, Alshammari TM, Areia C, Biedermann P, Banda JM, Burn E, Casajust P, Fister K, Hardin J, Hester L, Hripcsak G, Kaas-Hansen BS, Khosla S, Kolovos S, Lynch KE, Makadia R, Mehta PP, Morales DR, Morgan-Stewart H, Mosseveld M, Newby D, Nyberg F, Ostropolets A, Woong Park R, Prats-Uribe A, Rao GA, Reich C, Rijnbeek P, Sena AG, Shoaibi A, Spotnitz M, Subbian V, Suchard MA, Vizcaya D, Wen H, Wilde M, Xie J, You SC, Zhang L, Lovestone S, Ryan P, Prieto-Alhambra D; OHDSI-COVID-19 consortium. Risk of depression, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multinational network cohort study. *Rheumatology (Oxford)* 2021; **60**: 3222-3234 [PMID: 33367863 DOI: 10.1093/rheumatology/keaa771]

82 **Talaricov F,** Chakravarty S, Liu Y, Greenshaw A, Passos IG, Cao B. Psychiatric side effects induced by chloroquine and hydroxychloroquine: A systematic review of case reports and population studies. 2020 Preprint. Available from: medRxiv [DOI: 10.1101/2020.10.05.20207423]

83 **Finbloom DS**, Silver K, Newsome DA, Gunkel R. Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. *J Rheumatol* 1985; **12**: 692-694 [PMID: 4057189]

84 **Ren L**, Xu W, Overton JL, Yu S, Chiamvimonvat N, Thai PN. Assessment of Hydroxychloroquine and Chloroquine Safety Profiles: A Systematic Review and Meta-Analysis. 2020 Preprint. Available from: medRxiv [PMID: 32511539 DOI: 10.3389/fphar.2020.562777]

85 **Zhang L**, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. *J Med Virol* 2020; **92**: 479-490 [PMID: 32052466 DOI: 10.1002/jmv.25707]

86 **Marik PE**, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. *Chest* 2017; **151**: 1229-1238 [PMID: 27940189 DOI: 10.1016/j.chest.2016.11.036]

87 **Fujii T**, Luethi N, Young PJ, Frei DR, Eastwood GM, French CJ, Deane AM, Shehabi Y, Hajjar LA, Oliveira G, Udy AA, Orford N, Edney SJ, Hunt AL, Judd HL, Bitker L, Cioccari L, Naorungroj T, Yanase F, Bates S, McGain F, Hudson EP, Al-Bassam W, Dwivedi DB, Peppin C, McCracken P, Orosz J, Bailey M, Bellomo R; VITAMINS Trial Investigators. Effect of Vitamin C, Hydrocortisone, and Thiamine *vs* Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. *JAMA* 2020; **323**: 423-431 [PMID: 31950979 DOI: 10.1001/jama.2019.22176]

88 **Hwang SY**, Ryoo SM, Park JE, Jo YH, Jang DH, Suh GJ, Kim T, Kim YJ, Kim S, Cho H, Jo IJ, Chung SP, Choi SH, Shin TG, Kim WY; Korean Shock Society (KoSS). Combination therapy of vitamin C and thiamine for septic shock: a multi-centre, double-blinded randomized, controlled study. *Intensive Care Med* 2020; **46**: 2015-2025 [PMID: 32780166 DOI: 10.1007/s00134-020-06191-3]

89 **Mohamed ZU**, Prasannan P, Moni M, Edathadathil F, Prasanna P, Menon A, Nair S, Greeshma CR, Sathyapalan DT, Menon V, Menon V. Vitamin C Therapy for Routine Care in Septic Shock (ViCTOR) Trial: Effect of Intravenous Vitamin C, Thiamine, and Hydrocortisone Administration on Inpatient Mortality among Patients with Septic Shock. *Indian J Crit Care Med* 2020; **24**: 653-661 [PMID: 33024370 DOI: 10.5005/jp-journals-10071-23517]

90 **Lindsell CJ**, McGlothlin A, Nwosu S, Rice TW, Hall A, Bernard GR, Busse LW, Ely EW, Fowler AA, Gaieski DF, Hinson JS, Hooper MH, Jackson JC, Kelen GD, Levine M, Martin GS, Rothman RE, Sevransky JE, Viele K, Wright DW, Hager DN. Update to the Vitamin C, Thiamine and Steroids in Sepsis (VICTAS) protocol: statistical analysis plan for a prospective, multicenter, double-blind, adaptive sample size, randomized, placebo-controlled, clinical trial. *Trials* 2019; **20**: 670 [PMID: 31801567 DOI: 10.1186/s13063-019-3775-8]

91 **Tang Y**, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Front Immunol* 2020; **11**: 1708 [PMID: 32754163 DOI: 10.3389/fimmu.2020.01708]

92 **Carr AC**, Maggini S. Vitamin C and Immune Function. *Nutrients* 2017; **9**: 1211 [PMID: 29099763 DOI: 10.3390/nu9111211]

93 **Keel M**, Ungethüm U, Steckholzer U, Niederer E, Hartung T, Trentz O, Ertel W. Interleukin-10 counterregulates proinflammatory cytokine-induced inhibition of neutrophil apoptosis during severe sepsis. *Blood* 1997; **90**: 3356-3363 [PMID: 9345017 DOI: 10.1182/blood.V90.9.3356]

94 **Patel M,** Hong G, Schmidt B, Al-janabi L, Adusumilli RK, Tusha J, Giri P, Kumar S. The significance of oral ascorbic acid in patients with COVID-19. *Chest* 2020; **158**: A325. [DOI: 10.1016/j.chest.2020.08.322]

95 **Waqas Khan HM**, Parikh N, Megala SM, Predeteanu GS. Unusual Early Recovery of a Critical COVID-19 Patient After Administration of Intravenous Vitamin C. *Am J Case Rep* 2020; **21**: e925521 [PMID: 32709838 DOI: 10.12659/AJCR.925521]

96 **Ohanube G,** Obeta M, Ikeagwulonu R, Jwanse I. COVID-19: A case study of using vitamin C enriched plants and ascorbic acid as cure. *Am J Case Rep* 2020; **8**: 435-437 [DOI: 10.12691/AJMCR-8-11-16]

97 **Beigmohammadi MT**, Bitarafan S, Hoseindokht A, Abdollahi A, Amoozadeh L, Mahmoodi Ali Abadi M, Foroumandi M. Impact of vitamins A, B, C, D, and E supplementation on improvement and mortality rate in ICU patients with coronavirus-19: a structured summary of a study protocol for a randomized controlled trial. *Trials* 2020; **21**: 614 [PMID: 32631405 DOI: 10.1186/s13063-020-04547-0]

98 **Liu F**, Zhu Y, Zhang J, Li Y, Peng Z. Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial. *BMJ Open* 2020; **10**: e039519 [PMID: 32641343 DOI: 10.1136/bmjopen-2020-039519]

99 **Natarajan S**, Anbarasi C, Sathiyarajeswaran P, Manickam P, Geetha S, Kathiravan R, Prathiba P, Pitchiahkumar M, Parthiban P, Kanakavalli K, Balaji P. The efficacy of Siddha Medicine, Kabasura Kudineer (KSK) compared to Vitamin C & Zinc (CZ) supplementation in the management of asymptomatic COVID-19 cases: A structured summary of a study protocol for a randomised controlled trial. *Trials* 2020; **21**: 892 [PMID: 33109252 DOI: 10.1186/s13063-020-04823-z]

100 **Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds**. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington (DC): National Academies Press (US), 2000 [DOI: 10.17226/9810]

101 **Fowler AA 3rd**, Truwit JD, Hite RD, Morris PE, DeWilde C, Priday A, Fisher B, Thacker LR 2nd, Natarajan R, Brophy DF, Sculthorpe R, Nanchal R, Syed A, Sturgill J, Martin GS, Sevransky J, Kashiouris M, Hamman S, Egan KF, Hastings A, Spencer W, Tench S, Mehkri O, Bindas J, Duggal A, Graf J, Zellner S, Yanny L, McPolin C, Hollrith T, Kramer D, Ojielo C, Damm T, Cassity E, Wieliczko A, Halquist M. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. *JAMA* 2019; **322**: 1261-1270 [PMID: 31573637 DOI: 10.1001/jama.2019.11825]

102 **Trankle CR**, Puckett L, Swift-Scanlan T, DeWilde C, Priday A, Sculthorpe R, Ellenbogen KA, Fowler A, Koneru JN. Vitamin C Intravenous Treatment In the Setting of Atrial Fibrillation Ablation: Results From the Randomized, Double-Blinded, Placebo-Controlled CITRIS-AF Pilot Study. *J Am Heart Assoc* 2020; **9**: e014213 [PMID: 32013700 DOI: 10.1161/JAHA.119.014213]

103 **van Gorkom GNY**, Lookermans EL, Van Elssen CHMJ, Bos GMJ. The Effect of Vitamin C (Ascorbic Acid) in the Treatment of Patients with Cancer: A Systematic Review. *Nutrients* 2019; **11**: 977 [PMID: 31035414 DOI: 10.3390/nu11050977]

104 **Wang D**, Wang M, Zhang H, Zhu H, Zhang N, Liu J. Effect of Intravenous Injection of Vitamin C on Postoperative Pulmonary Complications in Patients Undergoing Cardiac Surgery: A Double-Blind, Randomized Trial. *Drug Des Devel Ther* 2020; **14**: 3263-3270 [PMID: 32848365 DOI: 10.2147/DDDT.S254150]

105 **Aranow C**. Vitamin D and the immune system. *J Investig Med* 2011; **59**: 881-886 [PMID: 21527855 DOI: 10.2310/JIM.0b013e31821b8755]

106 **Forrest KY**, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res* 2011; **31**: 48-54 [PMID: 21310306 DOI: 10.1016/j.nutres.2010.12.001]

107 **Lu D**, Zhang J, Ma C, Yue Y, Zou Z, Yu C, Yin F. Link between community-acquired pneumonia and vitamin D levels in older patients. *Z Gerontol Geriatr* 2018; **51**: 435-439 [PMID: 28477055 DOI: 10.1007/s00391-017-1237-z]

108 **Science M**, Maguire JL, Russell ML, Smieja M, Walter SD, Loeb M. Low serum 25-hydroxyvitamin D level and risk of upper respiratory tract infection in children and adolescents. *Clin Infect Dis* 2013; **57**: 392-397 [PMID: 23677871 DOI: 10.1093/cid/cit289]

109 **Martineau AR**, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant CC, Griffiths CJ, Janssens W, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S Jr, Stelmach I, Kumar GT, Urashima M, Camargo CA Jr. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* 2017; **356**: i6583 [PMID: 28202713 DOI: 10.1136/bmj.i6583]

110 **Glinsky GV**. Tripartite Combination of Candidate Pandemic Mitigation Agents: Vitamin D, Quercetin, and Estradiol Manifest Properties of Medicinal Agents for Targeted Mitigation of the COVID-19 Pandemic Defined by Genomics-Guided Tracing of SARS-CoV-2 Targets in Human Cells. *Biomedicines* 2020; **8**: 129 [PMID: 32455629 DOI: 10.3390/biomedicines8050129]

111 **Ohaegbulam KC**, Swalih M, Patel P, Smith MA, Perrin R. Vitamin D Supplementation in COVID-19 Patients: A Clinical Case Series. *Am J Ther* 2020; **27**: e485-e490 [PMID: 32804682 DOI: 10.1097/MJT.0000000000001222]

112 **Ginde AA**, Camargo CA Jr, Shapiro NI. Vitamin D insufficiency and sepsis severity in emergency department patients with suspected infection. *Acad Emerg Med* 2011; **18**: 551-554 [PMID: 21518095 DOI: 10.1111/j.1553-2712.2011.01047.x]

113 **Moromizato T**, Litonjua AA, Braun AB, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and sepsis in the critically ill. *Crit Care Med* 2014; **42**: 97-107 [PMID: 23982028 DOI: 10.1097/CCM.0b013e31829eb7af]

114 **Quraishi SA**, Bittner EA, Blum L, McCarthy CM, Bhan I, Camargo CA Jr. Prospective study of vitamin D status at initiation of care in critically ill surgical patients and risk of 90-day mortality. *Crit Care Med* 2014; **42**: 1365-1371 [PMID: 24557421 DOI: 10.1097/CCM.0000000000000210]

115 **Amrein K**, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, Urbanic Purkart T, Waltensdorfer A, Münch A, Warnkross H, Stojakovic T, Bisping E, Toller W, Smolle KH, Berghold A, Pieber TR, Dobnig H. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. *JAMA* 2014; **312**: 1520-1530 [PMID: 25268295 DOI: 10.1001/jama.2014.13204]

116 **De Smet D,** De Smet K, Herroelen P, Gryspeerdt S, Martens GA. Vitamin D deficiency as risk factor for severe COVID-19: a convergence of two pandemics. 2020 Preprint. Available from: medRxiv [DOI: 10.1101/2020.05.01.20079376]

117 **Lau FH,** Majumder R, Torabi R, Saeg F, Hoffman R, Cirillo JD, Greiffenstein P. Vitamin D insufficiency is prevalent in severe COVID-19. 2020 Preprint. Available from: medRxiv [DOI: 10.1101/2020.04.24.20075838]

118 **Pereira M**, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. *Crit Rev Food Sci Nutr* 2020: 1-9 [PMID: 33146028 DOI: 10.1080/10408398.2020.1841090]

119 **Ye K**, Tang F, Liao X, Shaw BA, Deng M, Huang G, Qin Z, Peng X, Xiao H, Chen C, Liu X, Ning L, Wang B, Tang N, Li M, Xu F, Lin S, Yang J. Does Serum Vitamin D Level Affect COVID-19 Infection and Its Severity?-A Case-Control Study. *J Am Coll Nutr* 2020: 1-8 [PMID: 33048028 DOI: 10.1080/07315724.2020.1826005]

120 **Rastogi A**, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, Puri GD, Malhotra P. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). *Postgrad Med J* 2020 epub ahead of print [PMID: 33184146 DOI: 10.1136/Postgradmedj-2020-139065]

121 **Entrenas Castillo M**, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, Bouillon R, Quesada Gomez JM. "Effect of calcifediol treatment and best available therapy *vs* best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". *J Steroid Biochem Mol Biol* 2020; **203**: 105751 [PMID: 32871238 DOI: 10.1016/j.jsbmb.2020.105751]

122 **Murai IH**, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, Silva CBR, Franco AS, Macedo MB, Dalmolin HHH, Baggio J, Balbi GGM, Reis BZ, Antonangelo L, Caparbo VF, Gualano B, Pereira RMR. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial. *JAMA* 2021; **325**: 1053-1060 [PMID: 33595634 DOI: 10.1001/jama.2020.26848]

123 **Deng QF**, Chu H, Wen Z, Cao YS. Vitamin D and Urinary Tract Infection: A Systematic Review and Meta-Analysis. *Ann Clin Lab Sci* 2019; **49**: 134-142 [PMID: 30814089]

124 **Skalny AV**, Rink L, Ajsuvakova OP, Aschner M, Gritsenko VA, Alekseenko SI, Svistunov AA, Petrakis D, Spandidos DA, Aaseth J, Tsatsakis A, Tinkov AA. Zinc and respiratory tract infections: Perspectives for COVID‑19 (Review). *Int J Mol Med* 2020; **46**: 17-26 [PMID: 32319538 DOI: 10.3892/ijmm.2020.4575]

125 **Barffour MA**, Hinnouho GM, Wessells KR, Kounnavong S, Ratsavong K, Sitthideth D, Bounheuang B, Sengnam K, Chanhthavong B, Arnold CD, Brown KH, Larson CP, Hess SY. Effects of therapeutic zinc supplementation for diarrhea and two preventive zinc supplementation regimens on the incidence and duration of diarrhea and acute respiratory tract infections in rural Laotian children: A randomized controlled trial. *J Glob Health* 2020; **10**: 010424 [PMID: 32612816 DOI: 10.7189/jogh.10.010424]

126 **Baum MK**, Lai S, Sales S, Page JB, Campa A. Randomized, controlled clinical trial of zinc supplementation to prevent immunological failure in HIV-infected adults. *Clin Infect Dis* 2010; **50**: 1653-1660 [PMID: 20455705 DOI: 10.1086/652864]

127 **Lassi ZS**, Moin A, Bhutta ZA. Zinc supplementation for the prevention of pneumonia in children aged 2 mo to 59 mo. *Cochrane Database Syst Rev* 2016; **12**: CD005978 [PMID: 27915460 DOI: 10.1002/14651858.CD005978.pub3]

128 **Martinez-Estevez NS**, Alvarez-Guevara AN, Rodriguez-Martinez CE. Effects of zinc supplementation in the prevention of respiratory tract infections and diarrheal disease in Colombian children: A 12-month randomised controlled trial. *Allergol Immunopathol (Madr)* 2016; **44**: 368-375 [PMID: 27255474 DOI: 10.1016/j.aller.2015.12.006]

129 **Lin LC**, Que J, Lin LK, Lin FC. Zinc supplementation to improve mucositis and dermatitis in patients after radiotherapy for head-and-neck cancers: a double-blind, randomized study. *Int J Radiat Oncol Biol Phys* 2006; **65**: 745-750 [PMID: 16751063 DOI: 10.1016/j.ijrobp.2006.01.015]

130 **Pakfetrat M**, Shahroodi JR, Zolgadr AA, Larie HA, Nikoo MH, Malekmakan L. Effects of zinc supplement on plasma homocysteine level in end-stage renal disease patients: a double-blind randomized clinical trial. *Biol Trace Elem Res* 2013; **153**: 11-15 [PMID: 23475369 DOI: 10.1007/s12011-013-9639-2]

131 **Ghaffari J**, Khalilian A, Salehifar E, Khorasani E, Rezaii MS. Effect of zinc supplementation in children with asthma: a randomized, placebo-controlled trial in northern Islamic Republic of Iran. *East Mediterr Health J* 2014; **20**: 391-396 [PMID: 24960516]

132 **Gholipour Baradari A**, Alipour A, Mahdavi A, Sharifi H, Nouraei SM, Emami Zeydi A. The Effect of Zinc Supplementation on Sleep Quality of ICU Nurses: A Double Blinded Randomized Controlled Trial. *Workplace Health Saf* 2018; **66**: 191-200 [PMID: 29241421 DOI: 10.1177/2165079917734880]

133 **Ranasinghe P**, Jayawardena R, Pigera AS, Katulanda P, Constantine GR, Galappaththy P. Zinc supplementation in pre-diabetes: study protocol for a randomized controlled trial. *Trials* 2013; **14**: 52 [PMID: 23421759 DOI: 10.1186/1745-6215-14-52]

134 **Hemilä H**. Zinc lozenges may shorten the duration of colds: a systematic review. *Open Respir Med J* 2011; **5**: 51-58 [PMID: 21769305 DOI: 10.2174/1874306401105010051]

135 **Wei Z**, Burwinkel M, Palissa C, Ephraim E, Schmidt MF. Antiviral activity of zinc salts against transmissible gastroenteritis virus in vitro. *Vet Microbiol* 2012; **160**: 468-472 [PMID: 22818659 DOI: 10.1016/j.vetmic.2012.06.019]

136 **te Velthuis AJ**, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity *in vitro* and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog* 2010; **6**: e1001176 [PMID: 21079686 DOI: 10.1371/journal.ppat.1001176]

137 **Speth R,** Carrera E, Jean-Baptiste M, Joachim A, Linares A. Concentration-dependent effects of zinc on angiotensin-converting enzyme-2 activity (1067.4). *FASEB J* 2014; **28**: 1067. 4 [DOI: 10.1096/fasebj.28.1\_supplement.1067.4]

138 **Read SA**, Obeid S, Ahlenstiel C, Ahlenstiel G. The Role of Zinc in Antiviral Immunity. *Adv Nutr* 2019; **10**: 696-710 [PMID: 31305906 DOI: 10.1093/advances/nmz013]

139 **Jothimani D**, Kailasam E, Danielraj S, Nallathambi B, Ramachandran H, Sekar P, Manoharan S, Ramani V, Narasimhan G, Kaliamoorthy I, Rela M. COVID-19: Poor outcomes in patients with zinc deficiency. *Int J Infect Dis* 2020; **100**: 343-349 [PMID: 32920234 DOI: 10.1016/j.ijid.2020.09.014]

140 **Vogel-González M**, Talló-Parra M, Herrera-Fernández V, Pérez-Vilaró G, Chillón M, Nogués X, Gómez-Zorrilla S, López-Montesinos I, Arnau-Barrés I, Sorli-Redó ML, Horcajada JP, García-Giralt N, Pascual J, Díez J, Vicente R, Güerri-Fernández R. Low Zinc Levels at Admission Associates with Poor Clinical Outcomes in SARS-CoV-2 Infection. *Nutrients* 2021; **13**: 562 [PMID: 33572045 DOI: 10.3390/nu13020562]

141 **Finzi E**. Treatment of SARS-CoV-2 with high dose oral zinc salts: A report on four patients. *Int J Infect Dis* 2020; **99**: 307-309 [PMID: 32522597 DOI: 10.1016/j.ijid.2020.06.006]

142 **Yao JS**, Paguio JA, Dee EC, Tan HC, Moulick A, Milazzo C, Jurado J, Della Penna N, Celi LA. The Minimal Effect of Zinc on the Survival of Hospitalized Patients With COVID-19: An Observational Study. *Chest* 2021; **159**: 108-111 [PMID: 32710890 DOI: 10.1016/j.chest.2020.06.082]

143 **Abd-Elsalam S**, Soliman S, Esmail ES, Khalaf M, Mostafa EF, Medhat MA, Ahmed OA, El Ghafar MSA, Alboraie M, Hassany SM. Do Zinc Supplements Enhance the Clinical Efficacy of Hydroxychloroquine?: a Randomized, Multicenter Trial. *Biol Trace Elem Res* 2021; **199**: 3642-3646 [PMID: 33247380 DOI: 10.1007/s12011-020-02512-1]

144 **Carlucci PM**, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. *J Med Microbiol* 2020; **69**: 1228-1234 [PMID: 32930657 DOI: 10.1099/jmm.0.001250]

145 **Frontera JA**, Rahimian JO, Yaghi S, Liu M, Lewis A, de Havenon A, Mainali S, Huang J, Scher E, Wisniewski T, Troxel AB, Meropol S, Balcer LJ, Galetta SL. Treatment with Zinc is Associated with Reduced In-Hospital Mortality Among COVID-19 Patients: A Multi-Center Cohort Study. *Res Sq* 2020 epub ahead of print [PMID: 33140042 DOI: 10.21203/rs.3.rs-94509/v1]

146 **Derwand R**, Scholz M, Zelenko V. COVID-19 outpatients: early risk-stratified treatment with zinc plus low-dose hydroxychloroquine and azithromycin: a retrospective case series study. *Int J Antimicrob Agents* 2020; **56**: 106214 [PMID: 33122096 DOI: 10.1016/j.ijantimicag.2020.106214]

147 **United States National Library of Medicine**. Coronavirus 2019 (COVID-19)- Using Ascorbic Acid and Zinc Supplementation (COVIDAtoZ). National Institutes of Health. [cited 1 May 2021]. Available from: https://clinicaltrials.gov/ct2/show/NCT04342728

148 **United States National Library of Medicine**. Placebo Controlled Trial to Evaluate Zinc for the Treatment of COVID-19 in the Outpatient Setting. National Institutes of Health. [cited 1 May 2021]. Available from: https://clinicaltrials.gov/ct2/show/NCT04621461

149 **United States National Library of Medicine**. A Study of Hydroxychloroquine and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers (COVID-Milit). National Institutes of Health. [cited 1 May 2021]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT04377646

150 **Iranian Registry of Clinical Trails**. The effect of zinc on the treatment and clinical course of patients with SARS-cov2 (COVID-19). [Accessed 2021 May 1]. In: Iranian Registry of Clinical Trails [Internet]. Available from: https://en.irct.ir/trial/47516 IRCT registration number: IRCT20180425039414N2

151 **Trumbo P**, Yates AA, Schlicker S, Poos M. Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. *J Am Diet Assoc* 2001; **101**: 294-301 [PMID: 11269606 DOI: 10.1016/S0002-8223(01)00078-5]

152 **Magee AC**, Matrone G. Studies on growth, copper metabolism of rats fed high levels of zinc. *J Nutr* 1960; **72**: 233-242 [PMID: 13765181 DOI: 10.1093/jn/72.2.233]

153 **Ogiso T**, Moriyama K, Sasaki S, Ishimura Y, Minato A. Inhibitory effect of high dietary zinc on copper absorption in rats. *Chem Pharm Bull (Tokyo)* 1974; **22**: 55-60 [PMID: 4833375 DOI: 10.1248/cpb.22.55]

154 **Chandra RK**. Excessive intake of zinc impairs immune responses. *JAMA* 1984; **252**: 1443-1446 [PMID: 6471270]

155 **Hooper PL**, Visconti L, Garry PJ, Johnson GE. Zinc lowers high-density lipoprotein-cholesterol levels. *JAMA* 1980; **244**: 1960-1961 [PMID: 7420708 DOI: 10.1001/jama.1980.03310170058030]

156 **Johnson AR**, Munoz A, Gottlieb JL, Jarrard DF. High dose zinc increases hospital admissions due to genitourinary complications. *J Urol* 2007; **177**: 639-643 [PMID: 17222649 DOI: 10.1016/j.juro.2006.09.047]

157 **Leitzmann MF**, Stampfer MJ, Wu K, Colditz GA, Willett WC, Giovannucci EL. Zinc supplement use and risk of prostate cancer. *J Natl Cancer Inst* 2003; **95**: 1004-1007 [PMID: 12837837 DOI: 10.1093/jnci/95.13.1004]

158 **Gavilanes X**, Huaux F, Meyer M, Lebecque P, Marbaix E, Lison D, Scholte B, Wallemacq P, Leal T. Azithromycin fails to reduce increased expression of neutrophil-related cytokines in primary-cultured epithelial cells from cystic fibrosis mice. *J Cyst Fibros* 2009; **8**: 203-210 [PMID: 19345617 DOI: 10.1016/j.jcf.2009.03.003]

159 **Shinkai M**, Foster GH, Rubin BK. Macrolide antibiotics modulate ERK phosphorylation and IL-8 and GM-CSF production by human bronchial epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2006; **290**: L75-L85 [PMID: 16085674 DOI: 10.1152/ajplung.00093.2005]

160 **Yamasawa H**, Oshikawa K, Ohno S, Sugiyama Y. Macrolides inhibit epithelial cell-mediated neutrophil survival by modulating granulocyte macrophage colony-stimulating factor release. *Am J Respir Cell Mol Biol* 2004; **30**: 569-575 [PMID: 14551160 DOI: 10.1165/rcmb.2003-0105OC]

161 **Gielen V**, Johnston SL, Edwards MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. *Eur Respir J* 2010; **36**: 646-654 [PMID: 20150207 DOI: 10.1183/09031936.00095809]

162 **Du X**, Zuo X, Meng F, Wu F, Zhao X, Li C, Cheng G, Qin FX. Combinatorial screening of a panel of FDA-approved drugs identifies several candidates with anti-Ebola activities. *Biochem Biophys Res Commun* 2020; **522**: 862-868 [PMID: 31806372 DOI: 10.1016/j.bbrc.2019.11.065]

163 **Danesi R**, Lupetti A, Barbara C, Ghelardi E, Chella A, Malizia T, Senesi S, Angeletti CA, Del Tacca M, Campa M. Comparative distribution of azithromycin in lung tissue of patients given oral daily doses of 500 and 1000 mg. *J Antimicrob Chemother* 2003; **51**: 939-945 [PMID: 12654753 DOI: 10.1093/jac/dkg138]

164 **Iannetta M**, Ippolito G, Nicastri E. Azithromycin Shows Anti-Zika Virus Activity in Human Glial Cells. *Antimicrob Agents Chemother* 2017; **61**: e01152-17 [PMID: 28839081 DOI: 10.1128/AAC.01152-17]

165 **Kouznetsova J**, Sun W, Martínez-Romero C, Tawa G, Shinn P, Chen CZ, Schimmer A, Sanderson P, McKew JC, Zheng W, García-Sastre A. Identification of 53 compounds that block Ebola virus-like particle entry *via* a repurposing screen of approved drugs. *Emerg Microbes Infect* 2014; **3**: e84 [PMID: 26038505 DOI: 10.1038/emi.2014.88]

166 **Li C**, Zu S, Deng YQ, Li D, Parvatiyar K, Quanquin N, Shang J, Sun N, Su J, Liu Z, Wang M, Aliyari SR, Li XF, Wu A, Ma F, Shi Y, Nielsevn-Saines K, Jung JU, Qin FX, Qin CF, Cheng G. Azithromycin Protects against Zika virus Infection by Upregulating virus-induced Type I and III Interferon Responses. *Antimicrob Agents Chemother* 2019; **63**: e00394-19 [PMID: 31527024 DOI: 10.1128/AAC.00394-19]

167 **Madrid PB**, Panchal RG, Warren TK, Shurtleff AC, Endsley AN, Green CE, Kolokoltsov A, Davey R, Manger ID, Gilfillan L, Bavari S, Tanga MJ. Evaluation of Ebola Virus Inhibitors for Drug Repurposing. *ACS Infect Dis* 2015; **1**: 317-326 [PMID: 27622822 DOI: 10.1021/acsinfecdis.5b00030]

168 **Retallack H**, Di Lullo E, Arias C, Knopp KA, Laurie MT, Sandoval-Espinosa C, Mancia Leon WR, Krencik R, Ullian EM, Spatazza J, Pollen AA, Mandel-Brehm C, Nowakowski TJ, Kriegstein AR, DeRisi JL. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. *Proc Natl Acad Sci U S A* 2016; **113**: 14408-14413 [PMID: 27911847 DOI: 10.1073/pnas.1618029113]

169 **Tran DH**, Sugamata R, Hirose T, Suzuki S, Noguchi Y, Sugawara A, Ito F, Yamamoto T, Kawachi S, Akagawa KS, Ōmura S, Sunazuka T, Ito N, Mimaki M, Suzuki K. Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A(H1N1)pdm09 virus infection by interfering with virus internalization process. *J Antibiot (Tokyo)* 2019; **72**: 759-768 [PMID: 31300721 DOI: 10.1038/s41429-019-0204-x]

170 **Zeng S**, Meng X, Huang Q, Lei N, Zeng L, Jiang X, Guo X. Spiramycin and azithromycin, safe for administration to children, exert antiviral activity against enterovirus A71 *in vitro* and in vivo. *Int J Antimicrob Agents* 2019; **53**: 362-369 [PMID: 30599241 DOI: 10.1016/j.ijantimicag.2018.12.009]

171 **Touret F**, Gilles M, Barral K, Nougairède A, van Helden J, Decroly E, de Lamballerie X, Coutard B. In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication. *Sci Rep* 2020; **10**: 13093 [PMID: 32753646 DOI: 10.1038/s41598-020-70143-6]

172 **Ou X**, Liu Y, Lei X, Li P, Mi D, Ren L, Guo L, Guo R, Chen T, Hu J, Xiang Z, Mu Z, Chen X, Chen J, Hu K, Jin Q, Wang J, Qian Z. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat Commun* 2020; **11**: 1620 [PMID: 32221306 DOI: 10.1038/s41467-020-15562-9]

173 **Sandeep S,** McGregor K. Energetics based modeling of hydroxychloroquine and azithromycin binding to the SARS-CoV-2 spike (S) protein-ACE2 complex. 2020 Preprint. Available from: ChemRxiv [DOI: 10.26434/chemrxiv.12015792.v1]

174 **Nujić K**, Banjanac M, Munić V, Polančec D, Eraković Haber V. Impairment of lysosomal functions by azithromycin and chloroquine contributes to anti-inflammatory phenotype. *Cell Immunol* 2012; **279**: 78-86 [PMID: 23099154 DOI: 10.1016/j.cellimm.2012.09.007]

175 **Beigelman A**, Isaacson-Schmid M, Sajol G, Baty J, Rodriguez OM, Leege E, Lyons K, Schweiger TL, Zheng J, Schechtman KB, Castro M, Bacharier LB. Randomized trial to evaluate azithromycin's effects on serum and upper airway IL-8 Levels and recurrent wheezing in infants with respiratory syncytial virus bronchiolitis. *J Allergy Clin Immunol* 2015; **135**: 1171-8.e1 [PMID: 25458910 DOI: 10.1016/j.jaci.2014.10.001]

176 **Kneyber MC**, van Woensel JB, Uijtendaal E, Uiterwaal CS, Kimpen JL; Dutch Antibiotics in RSV Trial (DART) Research Group. Azithromycin does not improve disease course in hospitalized infants with respiratory syncytial virus (RSV) lower respiratory tract disease: a randomized equivalence trial. *Pediatr Pulmonol* 2008; **43**: 142-149 [PMID: 18085694 DOI: 10.1002/ppul.20748]

177 **Pinto JA**, Capparelli EV, Warshaw M, Zimmer B, Cressey TR, Spector SA, Qin M, Smith B, Siberry GK, Mirochnick M; IMPAACT P1083 Team. A Phase II/III Trial of Lopinavir/Ritonavir Dosed According to the WHO Pediatric Weight Band Dosing Guidelines. *Pediatr Infect Dis J* 2018; **37**: e29-e35 [PMID: 29088027 DOI: 10.1097/INF.0000000000001817]

178 **Ishaqui AA**, Khan AH, Sulaiman SAS, Alsultan MT, Khan I, Naqvi AA. Assessment of efficacy of Oseltamivir-Azithromycin combination therapy in prevention of Influenza-A (H1N1)pdm09 infection complications and rapidity of symptoms relief. *Expert Rev Respir Med* 2020; **14**: 533-541 [PMID: 32053044 DOI: 10.1080/17476348.2020.1730180]

179 **Arabi YM**, Deeb AM, Al-Hameed F, Mandourah Y, Almekhlafi GA, Sindi AA, Al-Omari A, Shalhoub S, Mady A, Alraddadi B, Almotairi A, Al Khatib K, Abdulmomen A, Qushmaq I, Solaiman O, Al-Aithan AM, Al-Raddadi R, Ragab A, Al Harthy A, Kharaba A, Jose J, Dabbagh T, Fowler RA, Balkhy HH, Merson L, Hayden FG; Saudi Critical Care Trials group. Macrolides in critically ill patients with Middle East Respiratory Syndrome. *Int J Infect Dis* 2019; **81**: 184-190 [PMID: 30690213 DOI: 10.1016/j.ijid.2019.01.041]

180 **Kawamura K**, Ichikado K, Takaki M, Eguchi Y, Anan K, Suga M. Adjunctive therapy with azithromycin for moderate and severe acute respiratory distress syndrome: a retrospective, propensity score-matching analysis of prospectively collected data at a single center. *Int J Antimicrob Agents* 2018; **51**: 918-924 [PMID: 29501821 DOI: 10.1016/j.ijantimicag.2018.02.009]

181 **Molina JM**, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, de Castro N. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect* 2020; **50**: 384 [PMID: 32240719 DOI: 10.1016/j.medmal.2020.03.006]

182 **Sekhavati E**, Jafari F, SeyedAlinaghi S, Jamalimoghadamsiahkali S, Sadr S, Tabarestani M, Pirhayati M, Zendehdel A, Manafi N, Hajiabdolbaghi M, Ahmadinejad Z, Kouchak HE, Jafari S, Khalili H, Salehi M, Seifi A, Golestan FS, Ghiasvand F. Safety and effectiveness of azithromycin in patients with COVID-19: An open-label randomised trial. *Int J Antimicrob Agents* 2020; **56**: 106143 [PMID: 32853672 DOI: 10.1016/j.ijantimicag.2020.106143]

183 **Furtado RHM**, Berwanger O, Fonseca HA, Corrêa TD, Ferraz LR, Lapa MG, Zampieri FG, Veiga VC, Azevedo LCP, Rosa RG, Lopes RD, Avezum A, Manoel ALO, Piza FMT, Martins PA, Lisboa TC, Pereira AJ, Olivato GB, Dantas VCS, Milan EP, Gebara OCE, Amazonas RB, Oliveira MB, Soares RVP, Moia DDF, Piano LPA, Castilho K, Momesso RGRAP, Schettino GPP, Rizzo LV, Neto AS, Machado FR, Cavalcanti AB; COALITION COVID-19 Brazil II Investigators. Azithromycin in addition to standard of care *vs* standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet* 2020; **396**: 959-967 [PMID: 32896292 DOI: 10.1016/S0140-6736(20)31862-6]

184 **Deshpande A**, Pasupuleti V, Thota P, Pant C, Rolston DD, Sferra TJ, Hernandez AV, Donskey CJ. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. *J Antimicrob Chemother* 2013; **68**: 1951-1961 [PMID: 23620467 DOI: 10.1093/jac/dkt129]

185 **Brown KA**, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. *Antimicrob Agents Chemother* 2013; **57**: 2326-2332 [PMID: 23478961 DOI: 10.1128/AAC.02176-12]

186 **Owens RC Jr**, Nolin TD. Antimicrobial-associated QT interval prolongation: pointes of interest. *Clin Infect Dis* 2006; **43**: 1603-1611 [PMID: 17109296 DOI: 10.1086/508873]

187 **Ray WA**, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012; **366**: 1881-1890 [PMID: 22591294 DOI: 10.1056/NEJMoa1003833]

188 **Mori F**, Pecorari L, Pantano S, Rossi ME, Pucci N, De Martino M, Novembre E. Azithromycin anaphylaxis in children. *Int J Immunopathol Pharmacol* 2014; **27**: 121-126 [PMID: 24674687 DOI: 10.1177/039463201402700116]

189 **United States Food and Drug Administration**. Azithromycin tablets and (azithromycin for oral suspension). [cited 1 May 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda\_docs/Label/2013/050710s039,050711s036,050784s023Lbl.pdf

190 **Longo G**, Valenti C, Gandini G, Ferrara L, Bertesi M, Emilia G. Azithromycin-induced intrahepatic cholestasis. *Am J Med* 1997; **102**: 217-218 [PMID: 9217574]

191 **Lockwood AM**, Cole S, Rabinovich M. Azithromycin-induced liver injury. *Am J Health Syst Pharm* 2010; **67**: 810-814 [PMID: 20479103 DOI: 10.2146/ajhp080687]

192 **Koffas A**, Murray-Lyon IM, Williams R. Azithromycin-induced cholestatic hepatitis. *Oxf Med Case Reports* 2017; **2017**: omx027 [PMID: 28580159 DOI: 10.1093/omcr/omx027]

193 **Macaigne G**, Mokbel M, Marty O, De La Lande P, Mallet L. [Acute pseudoangiocholitic hepatitis probably induced by azithromycin]. *Gastroenterol Clin Biol* 2000; **24**: 969-970 [PMID: 11084438]

194 **Lane JC,** Weaves J, Kostka K, Duarte-Salles T, Abrahao MTF, Alghoul H, Alser O, Alshammari TM, Biedermann P, Burn E, Casajust P, Conover M, Culhane AC, Davydov A, DuVall SL, Dymshyts D, Fernandez-Bertolin S, Fister K, Hardin J, Hester L, Hripcsak G, Kent S, Khosla S, Kolovos S, Lambert CG, van der Lei J, Lunch KE, Makadia R, Margulis AV, Matheny ME, Mehta P, Morales DR, Morgan-Stewart H, Mosseveldd M, Newby D, Nyberg F, Ostropolets A, Park RW, Prats-Uribe A, Rao GA, Reich C, Reps J, Rijnbeel P, Sathappan SMK, Schuemie M, Seager S, Sena A, Shoaibi A, Spotnitz M, Suchard MA, Swerdel J, Torre CO, Vizcaya D, Wen H, de Wilde M, You SC, Zhang L, Zhuk O, Ryan P, Prieto-Alhambra D. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. 2020 Preprint. Available from: medRxiv [DOI: 10.1101/2020.04.08.20054551]

195 **Mercuro NJ**, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, Gold HS. Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 1036-1041 [PMID: 32936252 DOI: 10.1001/jamacardio.2020.1834]

196 **Schultheiss HP**, Piper C, Sowade O, Waagstein F, Kapp JF, Wegscheider K, Groetzbach G, Pauschinger M, Escher F, Arbustini E, Siedentop H, Kuehl U. Betaferon in chronic viral cardiomyopathy (BICC) trial: Effects of interferon-β treatment in patients with chronic viral cardiomyopathy. *Clin Res Cardiol* 2016; **105**: 763-773 [PMID: 27112783 DOI: 10.1007/s00392-016-0986-9]

197 **Traboulsee A**, Li DKB, Cascione M, Fang J, Dangond F, Miller A. Effect of interferon beta-1a subcutaneously three times weekly on clinical and radiological measures and no evidence of disease activity status in patients with relapsing-remitting multiple sclerosis at year 1. *BMC Neurol* 2018; **18**: 143 [PMID: 30217172 DOI: 10.1186/s12883-018-1145-x]

198 **Fontaine H**, Chaix ML, Lagneau JL, Bréchot C, Pol S. Recovery from chronic hepatitis C in long-term responders to ribavirin plus interferon alfa. *Lancet* 2000; **356**: 41 [PMID: 10892765 DOI: 10.1016/S0140-6736(00)02434-X]

199 **Hoofnagle JH**, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, Peters M, Waggoner JG, Park Y, Jones EA. Treatment of chronic non-A,non-B hepatitis with recombinant human alpha interferon. A preliminary report. *N Engl J Med* 1986; **315**: 1575-1578 [PMID: 3097544 DOI: 10.1056/NEJM198612183152503]

200 **Runkel L**, Pfeffer L, Lewerenz M, Monneron D, Yang CH, Murti A, Pellegrini S, Goelz S, Uzé G, Mogensen K. Differences in activity between alpha and beta type I interferons explored by mutational analysis. *J Biol Chem* 1998; **273**: 8003-8008 [PMID: 9525899 DOI: 10.1074/jbc.273.14.8003]

201 **Hart BJ**, Dyall J, Postnikova E, Zhou H, Kindrachuk J, Johnson RF, Olinger GG, Frieman MB, Holbrook MR, Jahrling PB, Hensley L. Interferon-β and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. *J Gen Virol* 2014; **95**: 571-577 [PMID: 24323636 DOI: 10.1099/vir.0.061911-0]

202 **Sainz B Jr**, Mossel EC, Peters CJ, Garry RF. Interferon-beta and interferon-gamma synergistically inhibit the replication of severe acute respiratory syndrome-associated coronavirus (SARS-CoV). *Virology* 2004; **329**: 11-17 [PMID: 15476870 DOI: 10.1016/j.virol.2004.08.011]

203 **Spiegel M**, Pichlmair A, Mühlberger E, Haller O, Weber F. The antiviral effect of interferon-beta against SARS-coronavirus is not mediated by MxA protein. *J Clin Virol* 2004; **30**: 211-213 [PMID: 15135736 DOI: 10.1016/j.jcv.2003.11.013]

204 **Arabi YM**, Asiri AY, Assiri AM, Balkhy HH, Al Bshabshe A, Al Jeraisy M, Mandourah Y, Azzam MHA, Bin Eshaq AM, Al Johani S, Al Harbi S, Jokhdar HAA, Deeb AM, Memish ZA, Jose J, Ghazal S, Al Faraj S, Al Mekhlafi GA, Sherbeeni NM, Elzein FE, Al-Hameed F, Al Saedi A, Alharbi NK, Fowler RA, Hayden FG, Al-Dawood A, Abdelzaher M, Bajhmom W, AlMutairi BM, Hussein MA, Alothman A; Saudi Critical Care Trials Group. Interferon Beta-1b and Lopinavir-Ritonavir for Middle East Respiratory Syndrome. *N Engl J Med* 2020; **383**: 1645-1656 [PMID: 33026741 DOI: 10.1056/NEJMoa2015294]

205 **Al Ghamdi M**, Alghamdi KM, Ghandoora Y, Alzahrani A, Salah F, Alsulami A, Bawayan MF, Vaidya D, Perl TM, Sood G. Treatment outcomes for patients with Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. *BMC Infect Dis* 2016; **16**: 174 [PMID: 27097824 DOI: 10.1186/s12879-016-1492-4]

206 **Rahmani H**, Davoudi-Monfared E, Nourian A, Khalili H, Hajizadeh N, Jalalabadi NZ, Fazeli MR, Ghazaeian M, Yekaninejad MS. Interferon β-1b in treatment of severe COVID-19: A randomized clinical trial. *Int Immunopharmacol* 2020; **88**: 106903 [PMID: 32862111 DOI: 10.1016/j.intimp.2020.106903]

207 **Hung IF**, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, Ng YY, Lo J, Chan J, Tam AR, Shum HP, Chan V, Wu AK, Sin KM, Leung WS, Law WL, Lung DC, Sin S, Yeung P, Yip CC, Zhang RR, Fung AY, Yan EY, Leung KH, Ip JD, Chu AW, Chan WM, Ng AC, Lee R, Fung K, Yeung A, Wu TC, Chan JW, Yan WW, Chan WM, Chan JF, Lie AK, Tsang OT, Cheng VC, Que TL, Lau CS, Chan KH, To KK, Yuen KY. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 2020; **395**: 1695-1704 [PMID: 32401715 DOI: 10.1016/S0140-6736(20)31042-4]

208 **Davoudi-Monfared E**, Rahmani H, Khalili H, Hajiabdolbaghi M, Salehi M, Abbasian L, Kazemzadeh H, Yekaninejad MS. A Randomized Clinical Trial of the Efficacy and Safety of Interferon β-1a in Treatment of Severe COVID-19. *Antimicrob Agents Chemother* 2020; **64**: e01061-20 [PMID: 32661006 DOI: 10.1128/AAC.01061-20]

209 **Alavi Darazam I**, Shokouhi S, Pourhoseingholi MA, Naghibi Irvani SS, Mokhtari M, Shabani M, Amirdosara M, Torabinavid P, Golmohammadi M, Hashemi S, Azimi A, Jafarazadeh Maivan MH, Rezaei O, Zali A, Hajiesmaeili M, Shabanpour Dehbsneh H, Hoseyni Kusha A, Taleb Shoushtari M, Khalili N, Soleymaninia A, Gachkar L, Khoshkar A. Role of interferon therapy in severe COVID-19: the COVIFERON randomized controlled trial. *Sci Rep* 2021; **11**: 8059 [PMID: 33850184 DOI: 10.1038/s41598-021-86859-y]

210 **Kirkwood JM**, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, Ernstoff MS, Smith TJ, Rao U, Steele M, Blum RH. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. *J Clin Oncol* 2000; **18**: 2444-2458 [PMID: 10856105 DOI: 10.1200/JCO.2000.18.12.2444]

211 **Cameron DA**, Cornbleet MC, Mackie RM, Hunter JA, Gore M, Hancock B, Smyth JF; Scottish Melanoma Group. Adjuvant interferon alpha 2b in high risk melanoma - the Scottish study. *Br J Cancer* 2001; **84**: 1146-1149 [PMID: 11379605 DOI: 10.1054/bjoc.2000.1623]

212 **Motzer RJ**, Murphy BA, Bacik J, Schwartz LH, Nanus DM, Mariani T, Loehrer P, Wilding G, Fairclough DL, Cella D, Mazumdar M. Phase III trial of interferon alfa-2a with or without 13-cis-retinoic acid for patients with advanced renal cell carcinoma. *J Clin Oncol* 2000; **18**: 2972-2980 [PMID: 10944130 DOI: 10.1200/JCO.2000.18.16.2972]

213 **Negrier S**, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, Ravaud A, Mercatello A, Peny J, Mousseau M, Philip T, Tursz T. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Français d'Immunothérapie. *N Engl J Med* 1998; **338**: 1272-1278 [PMID: 9562581 DOI: 10.1056/NEJM199804303381805]

214 **Sleijfer S**, Bannink M, Van Gool AR, Kruit WH, Stoter G. Side effects of interferon-alpha therapy. *Pharm World Sci* 2005; **27**: 423-431 [PMID: 16341948 DOI: 10.1007/s11096-005-1319-7]

215 **Ruan Q**, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; **46**: 846-848 [PMID: 32125452 DOI: 10.1007/s00134-020-05991-x]

216 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]

217 **United States Food and Drug Administration**. ACTEMRA (tocilizumab) Injection label. [cited 1 May 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda\_docs/Label/2013/125276s092Lbl.pdf

218 **United States Food and Drug Administration**. KEVZARA (sarilumab) injection. [cited 1 May 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda\_docs/Label/2017/761037s000Lbl.pdf

219 **United States Food and Drug Administration**. SYLVANT (siltuximab) for Injection. [cited 1 May 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda\_docs/Label/2014/125496s000Lbl.pdf

220 **Le RQ**, Li L, Yuan W, Shord SS, Nie L, Habtemariam BA, Przepiorka D, Farrell AT, Pazdur R. FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. *Oncologist* 2018; **23**: 943-947 [PMID: 29622697 DOI: 10.1634/theoncologist.2018-0028]

221 **Nakaoka Y**, Isobe M, Takei S, Tanaka Y, Ishii T, Yokota S, Nomura A, Yoshida S, Nishimoto N. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). *Ann Rheum Dis* 2018; **77**: 348-354 [PMID: 29191819 DOI: 10.1136/annrheumdis-2017-211878]

222 **Khanna D**, Denton CP, Lin CJF, van Laar JM, Frech TM, Anderson ME, Baron M, Chung L, Fierlbeck G, Lakshminarayanan S, Allanore Y, Pope JE, Riemekasten G, Steen V, Müller-Ladner U, Spotswood H, Burke L, Siegel J, Jahreis A, Furst DE. Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate). *Ann Rheum Dis* 2018; **77**: 212-220 [PMID: 29066464 DOI: 10.1136/annrheumdis-2017-211682]

223 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

224 **Aouba A**, Baldolli A, Geffray L, Verdon R, Bergot E, Martin-Silva N, Justet A. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann Rheum Dis* 2020; **79**: 1381-1382 [PMID: 32376597 DOI: 10.1136/annrheumdis-2020-217706]

225 **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0]

226 **United States Food and Drug Administration**. Kineret (anakinra) for injection. [cited 1 May 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda\_docs/Label/2012/103950s5136Lbl.pdf

227 **Mehta P**, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol* 2020; **2**: e358-e367 [PMID: 32373790 DOI: 10.1016/S2665-9913(20)30096-5]

228 **Shakoory B**, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, Cron RQ, Opal SM. Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. *Crit Care Med* 2016; **44**: 275-281 [PMID: 26584195 DOI: 10.1097/CCM.0000000000001402]

229 **Sönmez HE**, Demir S, Bilginer Y, Özen S. Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature. *Clin Rheumatol* 2018; **37**: 3329-3335 [PMID: 29663156 DOI: 10.1007/s10067-018-4095-1]

230 **United States Food and Drug Administration**. ILARIS (canakinumab) for injection. [cited 1 May 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda\_docs/Label/2016/BLA125319\_858687Lbl.pdf

231 **Sheng F**, Han M, Huang Z, Zhang L. Interleukin 6 receptor inhibitor tocilizumab suppresses cytokine expression, inflammasome activation and phagocytosis in a cell model of sepsis. *Pharmazie* 2016; **71**: 636-639 [PMID: 29441967 DOI: 10.1691/ph.2016.6713]

232 **Radigan KA**, Nicholson TT, Welch LC, Chi M, Amarelle L, Angulo M, Shigemura M, Shigemura A, Runyan CE, Morales-Nebreda L, Perlman H, Ceco E, Lecuona E, Dada LA, Misharin AV, Mutlu GM, Sznajder JI, Budinger GRS. Influenza A Virus Infection Induces Muscle Wasting *via* IL-6 Regulation of the E3 Ubiquitin Ligase Atrogin-1. *J Immunol* 2019; **202**: 484-493 [PMID: 30530483 DOI: 10.4049/jimmunol.1701433]

233 **Ibrahim YF**, Moussa RA, Bayoumi AMA, Ahmed AF. Tocilizumab attenuates acute lung and kidney injuries and improves survival in a rat model of sepsis *via* down-regulation of NF-κB/JNK: a possible role of P-glycoprotein. *Inflammopharmacology* 2020; **28**: 215-230 [PMID: 31440860 DOI: 10.1007/s10787-019-00628-y]

234 **Guo C**, Li B, Ma H, Wang X, Cai P, Yu Q, Zhu L, Jin L, Jiang C, Fang J, Liu Q, Zong D, Zhang W, Lu Y, Li K, Gao X, Fu B, Liu L, Ma X, Weng J, Wei H, Jin T, Lin J, Qu K. Single-cell analysis of two severe COVID-19 patients reveals a monocyte-associated and tocilizumab-responding cytokine storm. *Nat Commun* 2020; **11**: 3924 [PMID: 32764665 DOI: 10.1038/s41467-020-17834-w]

235 **Zhang X**, Song K, Tong F, Fei M, Guo H, Lu Z, Wang J, Zheng C. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Adv* 2020; **4**: 1307-1310 [PMID: 32243501 DOI: 10.1182/bloodadvances.2020001907]

236 **Luo P**, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol* 2020; **92**: 814-818 [PMID: 32253759 DOI: 10.1002/jmv.25801]

237 **Xu X**, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wei H. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A* 2020; **117**: 10970-10975 [PMID: 32350134 DOI: 10.1073/pnas.2005615117]

238 **Guaraldi G**, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, Franceschini E, Cuomo G, Orlando G, Borghi V, Santoro A, Di Gaetano M, Puzzolante C, Carli F, Bedini A, Corradi L, Fantini R, Castaniere I, Tabbì L, Girardis M, Tedeschi S, Giannella M, Bartoletti M, Pascale R, Dolci G, Brugioni L, Pietrangelo A, Cossarizza A, Pea F, Clini E, Salvarani C, Massari M, Viale PL, Mussini C. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020; **2**: e474-e484 [PMID: 32835257 DOI: 10.1016/S2665-9913(20)30173-9]

239 **Mikulska M**, Nicolini LA, Signori A, Di Biagio A, Sepulcri C, Russo C, Dettori S, Berruti M, Sormani MP, Giacobbe DR, Vena A, De Maria A, Dentone C, Taramasso L, Mirabella M, Magnasco L, Mora S, Delfino E, Toscanini F, Balletto E, Alessandrini AI, Baldi F, Briano F, Camera M, Dodi F, Ferrazin A, Labate L, Mazzarello G, Pincino R, Portunato F, Tutino S, Barisione E, Bruzzone B, Orsi A, Schenone E, Rosseti N, Sasso E, Da Rin G, Pelosi P, Beltramini S, Giacomini M, Icardi G, Gratarola A, Bassetti M. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. *PLoS One* 2020; **15**: e0237831 [PMID: 32817707 DOI: 10.1371/journal.pone.0237831]

240 **Salvarani C**, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, Bruzzi P, Boni F, Braglia L, Turrà C, Ballerini PF, Sciascia R, Zammarchi L, Para O, Scotton PG, Inojosa WO, Ravagnani V, Salerno ND, Sainaghi PP, Brignone A, Codeluppi M, Teopompi E, Milesi M, Bertomoro P, Claudio N, Salio M, Falcone M, Cenderello G, Donghi L, Del Bono V, Colombelli PL, Angheben A, Passaro A, Secondo G, Pascale R, Piazza I, Facciolongo N, Costantini M; RCT-TCZ-COVID-19 Study Group. Effect of Tocilizumab *vs* Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med* 2021; **181**: 24-31 [PMID: 33080005 DOI: 10.1001/jamainternmed.2020.6615]

241 **Salama C**, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, Criner GJ, Kaplan-Lewis E, Baden R, Pandit L, Cameron ML, Garcia-Diaz J, Chávez V, Mekebeb-Reuter M, Lima de Menezes F, Shah R, González-Lara MF, Assman B, Freedman J, Mohan SV. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med* 2021; **384**: 20-30 [PMID: 33332779 DOI: 10.1056/NEJMoa2030340]

242 **Stone JH**, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, Woolley AE, Nikiforow S, Lin N, Sagar M, Schrager H, Huckins DS, Axelrod M, Pincus MD, Fleisher J, Sacks CA, Dougan M, North CM, Halvorsen YD, Thurber TK, Dagher Z, Scherer A, Wallwork RS, Kim AY, Schoenfeld S, Sen P, Neilan TG, Perugino CA, Unizony SH, Collier DS, Matza MA, Yinh JM, Bowman KA, Meyerowitz E, Zafar A, Drobni ZD, Bolster MB, Kohler M, D'Silva KM, Dau J, Lockwood MM, Cubbison C, Weber BN, Mansour MK; BACC Bay Tocilizumab Trial Investigators. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *N Engl J Med* 2020; **383**: 2333-2344 [PMID: 33085857 DOI: 10.1056/NEJMoa2028836]

243 **Roche**. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. [cited 1 May 2021]. Available from: https://www.roche.com/investors/updates/inv-update-2020-07-29.html

244 **Roche**. Roche’s phase III EMPACTA study showed Actemra/RoActemra reduced the likelihood of needing mechanical ventilation in hospitalised patients with COVID-19 associated pneumonia. [cited 1 May 2021]. Available from: https://www.roche.com/investors/updates/inv-update-2020-09-18.html

245 **Gordon AC**, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Buzgau A, Cheng AC, Detry MA, Duffy EJ, Estcourt LJ, Fitzgerald M, Goossens H, Haniffa R, Higgins AM, Hills TE, Horvat CM, Lamontagne F, Lawler PR, Leavis HL, Linstrum KM, Litton E, Lorenzi E, Marshall JC, Mayr FB, McAuley DF, McGlothlin A, McGuinness SP, McVerry BJ, Montgomery SK, Morpeth SC, Murthy S, Orr K, Parke RL, Parker JC, Patanwala AE, Pettilä V, Rademaker E, Santos MS, Saunders CT, Seymour CW, Shankar-Hari M, Sligl WI, Turgeon AF, Turner AM, van de Veerdonk FL, Zarychanski R, Green C, Lewis RJ, Angus DC, McArthur CJ, Berry S, Webb SA, Derde LPG; REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med* 2021; **384**: 1491-1502 [PMID: 33631065 DOI: 10.1056/NEJMoa2100433]

246 **Sanofi.** Sanofi provides update on Kevzara® (sarilumab) Phase 3 trial in severe and critically ill COVID-19 patients outside the U.S. Sanofi. [cited 1 May 2021]. Available from: https://www.sanofi.com/en/media-room/press-releases/2020/2020-09-01-07-00-00

247 **Cauchois R**, Koubi M, Delarbre D, Manet C, Carvelli J, Blasco VB, Jean R, Fouche L, Bornet C, Pauly V, Mazodier K, Pestre V, Jarrot PA, Dinarello CA, Kaplanski G. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. *Proc Natl Acad Sci U S A* 2020; **117**: 18951-18953 [PMID: 32699149 DOI: 10.1073/pnas.2009017117]

248 **Cavalli G**, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, Oltolini C, Castiglioni B, Tassan Din C, Boffini N, Tomelleri A, Farina N, Ruggeri A, Rovere-Querini P, Di Lucca G, Martinenghi S, Scotti R, Tresoldi M, Ciceri F, Landoni G, Zangrillo A, Scarpellini P, Dagna L. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020; **2**: e325-e331 [PMID: 32501454 DOI: 10.1016/S2665-9913(20)30127-2]

249 **Huet T**, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, Sacco E, Naccache JM, Bézie Y, Laplanche S, Le Berre A, Le Pavec J, Salmeron S, Emmerich J, Mourad JJ, Chatellier G, Hayem G. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020; **2**: e393-e400 [PMID: 32835245 DOI: 10.1016/S2665-9913(20)30164-8]

250 **Kooistra EJ**, Waalders NJB, Grondman I, Janssen NAF, de Nooijer AH, Netea MG, van de Veerdonk FL, Ewalds E, van der Hoeven JG, Kox M, Pickkers P; RCI-COVID-19 Study Group. Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study. *Crit Care* 2020; **24**: 688 [PMID: 33302991 DOI: 10.1186/s13054-020-03364-w]

251 **Maes B**, Bosteels C, De Leeuw E, Declercq J, Van Damme K, Delporte A, Demeyere B, Vermeersch S, Vuylsteke M, Willaert J, Bollé L, Vanbiervliet Y, Decuypere J, Libeer F, Vandecasteele S, Peene I, Lambrecht B. Treatment of severely ill COVID-19 patients with anti-interleukin drugs (COV-AID): A structured summary of a study protocol for a randomised controlled trial. *Trials* 2020; **21**: 468 [PMID: 32493441 DOI: 10.1186/s13063-020-04453-5]

252 **United States National Library of Medicine**. Anakinra for COVID-19 Respiratory Symptoms (ANACONDA). National Institutes of Health. [cited 1 May 2021]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04364009

253 **Front Line COVID-19 Critical Care**. I-MASK+ Prevention & Early Outpatient Treatment Protocol for COVID-19. Front Line COVID-19 Critical Care. [cited 1 May 2021]. Available from: https://covid19criticalcare.com/covid-19-protocols/i-mask-plus-protocol/

254 **Mastrangelo E**, Pezzullo M, De Burghgraeve T, Kaptein S, Pastorino B, Dallmeier K, de Lamballerie X, Neyts J, Hanson AM, Frick DN, Bolognesi M, Milani M. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. *J Antimicrob Chemother* 2012; **67**: 1884-1894 [PMID: 22535622 DOI: 10.1093/jac/dks147]

255 **Wagstaff KM**, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem J* 2012; **443**: 851-856 [PMID: 22417684 DOI: 10.1042/BJ20120150]

256 **Yang SNY**, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, Jans DA. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. *Antiviral Res* 2020; **177**: 104760 [PMID: 32135219 DOI: 10.1016/j.antiviral.2020.104760]

257 **Tay MY**, Fraser JE, Chan WK, Moreland NJ, Rathore AP, Wang C, Vasudevan SG, Jans DA. Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. *Antiviral Res* 2013; **99**: 301-306 [PMID: 23769930 DOI: 10.1016/j.antiviral.2013.06.002]

258 **Varghese FS**, Kaukinen P, Gläsker S, Bespalov M, Hanski L, Wennerberg K, Kümmerer BM, Ahola T. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. *Antiviral Res* 2016; **126**: 117-124 [PMID: 26752081 DOI: 10.1016/j.antiviral.2015.12.012]

259 **King CR**, Tessier TM, Dodge MJ, Weinberg JB, Mymryk JS. Inhibition of Human Adenovirus Replication by the Importin α/β1 Nuclear Import Inhibitor Ivermectin. *J Virol* 2020; **94** [PMID: 32641484 DOI: 10.1128/JVI.00710-20]

260 **Götz V**, Magar L, Dornfeld D, Giese S, Pohlmann A, Höper D, Kong BW, Jans DA, Beer M, Haller O, Schwemmle M. Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. *Sci Rep* 2016; **6**: 23138 [PMID: 26988202 DOI: 10.1038/srep23138]

261 **Ci X**, Li H, Yu Q, Zhang X, Yu L, Chen N, Song Y, Deng X. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. *Fundam Clin Pharmacol* 2009; **23**: 449-455 [PMID: 19453757 DOI: 10.1111/j.1472-8206.2009.00684.x]

262 **Zhang X**, Song Y, Ci X, An N, Ju Y, Li H, Wang X, Han C, Cui J, Deng X. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. *Inflamm Res* 2008; **57**: 524-529 [PMID: 19109745 DOI: 10.1007/s00011-008-8007-8]

263 **Zhang X**, Song Y, Xiong H, Ci X, Li H, Yu L, Zhang L, Deng X. Inhibitory effects of ivermectin on nitric oxide and prostaglandin E2 production in LPS-stimulated RAW 264.7 macrophages. *Int Immunopharmacol* 2009; **9**: 354-359 [PMID: 19168156 DOI: 10.1016/j.intimp.2008.12.016]

264 **Arévalo AP**, Pagotto R, Pórfido JL, Daghero H, Segovia M, Yamasaki K, Varela B, Hill M, Verdes JM, Duhalde Vega M, Bollati-Fogolín M, Crispo M. Ivermectin reduces *in vivo* coronavirus infection in a mouse experimental model. *Sci Rep* 2021; **11**: 7132 [PMID: 33785846 DOI: 10.1038/s41598-021-86679-0]

265 **Caly L**, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 2020; **178**: 104787 [PMID: 32251768 DOI: 10.1016/j.antiviral.2020.104787]

266 **de Melo GD,** Lazarini F, Larrous F, Feige L, Kergoat L, Marchio A, Pineau P, Lecuit M, Lledo PM, Changeuz JP, Bourhy H. Anti-COVID-19 efficacy of ivermectin in the golden hamster. 2020 Preprint. Available from: bioRxiv [DOI: 10.1101/2020.11.21.392639]

267 **Aguirre Chang G,** Trujillo Figueredo A. COVID-19: Ivermectin prophylaxis in adult contacts. First report on health personnel and post-exposure prophylaxis. 2020 Preprint. Available from: Research Gate [DOI: 10.13140/RG.2.2.11985.35680/3]

268 **Elgazzar A,** Hany B, Youssef SA, Hafez M, Moussa H, Eltaweel A. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. 2020 Preprint. Available from: Research Square [DOI: 10.21203/rs.3.rs-100956/v3]

269 **Rahman MA,** Iqbal SA, Islam MA, Niaz MK, Hssain T, Siddiquee TH. Comparison of viral clearance between ivermectin with doxycycline and hydroxychloroquine with azithromycin in COVID-19 patients. *J Bangladesh Coll Phys Surg* 2020; 5-9 [DOI: 10.3329/jbcps.v38i0.47514]

270 **Alam MT,** Murshed R, Bhiuyan E, Saber S, Alam RF, Robin RC. A case series of 100 COVID-19 positive patients treated with combination of ivermectin and doxycycline. *J Bangladesh Coll Phys Surg* 2020; **38**: 10-15 [DOI: 10.3329/jbcps.v38i0.47512]

271 **Khan MSI**, Khan MSI, Debnath CR, Nath PN, Mahtab MA, Nabeka H, Matsuda S, Akbar SMF. Ivermectin Treatment May Improve the Prognosis of Patients With COVID-19. *Arch Bronconeumol (Engl Ed)* 2020; **56**: 828-830 [PMID: 33994641 DOI: 10.1016/j.arbres.2020.08.007]

272 **Podder CS,** Chowdhury N, Sina MI, Haque WMMU. Outcome of ivermectin treated mild to moderate COVID-19 cases: A single-centre, open-label, randomised controlled study. *IMC J Med Sci* 2020; **14**: 11-18 [DOI: 10.3329/imcjms.v14i2.52826]

273 **Rajter JC**, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ. Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019: The Ivermectin in COVID Nineteen Study. *Chest* 2021; **159**: 85-92 [PMID: 33065103 DOI: 10.1016/j.chest.2020.10.009]

274 **Hashim HA,** Maulood MF, Rasheed AM, Fatak DF, Kabah KK, Abdulamir AS. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. 2020 Preprint. Available from: medRxiv [DOI: 10.1101/2020.10.26.20219345]

275 **Ahmed S**, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, Phru CS, Rahman M, Zaman K, Somani J, Yasmin R, Hasnat MA, Kabir A, Aziz AB, Khan WA. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis* 2021; **103**: 214-216 [PMID: 33278625 DOI: 10.1016/j.ijid.2020.11.191]

276 **López-Medina E**, López P, Hurtado IC, Dávalos DM, Ramirez O, Martínez E, Díazgranados JA, Oñate JM, Chavarriaga H, Herrera S, Parra B, Libreros G, Jaramillo R, Avendaño AC, Toro DF, Torres M, Lesmes MC, Rios CA, Caicedo I. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. *JAMA* 2021; **325**: 1426-1435 [PMID: 33662102 DOI: 10.1001/jama.2021.3071]

277 **United States Food and Drug Administration**. Stromectol (Ivermectin). [cited 1 May 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda\_docs/Label/2009/050742s026Lbl.pdf

278 **Baudou E**, Lespine A, Durrieu G, André F, Gandia P, Durand C, Cunat S. Serious Ivermectin Toxicity and Human *ABCB1* Nonsense Mutations. *N Engl J Med* 2020; **383**: 787-789 [PMID: 32813957 DOI: 10.1056/NEJMc1917344]

279 **Marano G**, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, Grazzini G. Convalescent plasma: new evidence for an old therapeutic tool? *Blood Transfus* 2016; **14**: 152-157 [PMID: 26674811 DOI: 10.2450/2015.0131-15]

280 **Luke TC**, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Ann Intern Med* 2006; **145**: 599-609 [PMID: 16940336 DOI: 10.7326/0003-4819-145-8-200610170-00139]

281 **Zhou B**, Zhong N, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) infection. *N Engl J Med* 2007; **357**: 1450-1451 [PMID: 17914053 DOI: 10.1056/NEJMc070359]

282 **Hung IF**, To KK, Lee CK, Lee KL, Chan K, Yan WW, Liu R, Watt CL, Chan WM, Lai KY, Koo CK, Buckley T, Chow FL, Wong KK, Chan HS, Ching CK, Tang BS, Lau CC, Li IW, Liu SH, Chan KH, Lin CK, Yuen KY. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis* 2011; **52**: 447-456 [PMID: 21248066 DOI: 10.1093/cid/ciq106]

283 **Hung IFN**, To KKW, Lee CK, Lee KL, Yan WW, Chan K, Chan WM, Ngai CW, Law KI, Chow FL, Liu R, Lai KY, Lau CCY, Liu SH, Chan KH, Lin CK, Yuen KY. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. *Chest* 2013; **144**: 464-473 [PMID: 23450336 DOI: 10.1378/chest.12-2907]

284 **Kraft CS**, Hewlett AL, Koepsell S, Winkler AM, Kratochvil CJ, Larson L, Varkey JB, Mehta AK, Lyon GM 3rd, Friedman-Moraco RJ, Marconi VC, Hill CE, Sullivan JN, Johnson DW, Lisco SJ, Mulligan MJ, Uyeki TM, McElroy AK, Sealy T, Campbell S, Spiropoulou C, Ströher U, Crozier I, Sacra R, Connor MJ Jr, Sueblinvong V, Franch HA, Smith PW, Ribner BS; Nebraska Biocontainment Unit and the Emory Serious Communicable Diseases Unit. The Use of TKM-100802 and Convalescent Plasma in 2 Patients With Ebola Virus Disease in the United States. *Clin Infect Dis* 2015; **61**: 496-502 [PMID: 25904375 DOI: 10.1093/cid/civ334]

285 **Mora-Rillo M**, Arsuaga M, Ramírez-Olivencia G, de la Calle F, Borobia AM, Sánchez-Seco P, Lago M, Figueira JC, Fernández-Puntero B, Viejo A, Negredo A, Nuñez C, Flores E, Carcas AJ, Jiménez-Yuste V, Lasala F, García-de-Lorenzo A, Arnalich F, Arribas JR; La Paz-Carlos III University Hospital Isolation Unit. Acute respiratory distress syndrome after convalescent plasma use: treatment of a patient with Ebola virus disease contracted in Madrid, Spain. *Lancet Respir Med* 2015; **3**: 554-562 [PMID: 26041403 DOI: 10.1016/S2213-2600(15)00180-0]

286 **Mupapa K**, Massamba M, Kibadi K, Kuvula K, Bwaka A, Kipasa M, Colebunders R, Muyembe-Tamfum JJ. Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. International Scientific and Technical Committee. *J Infect Dis* 1999; **179 Suppl 1**: S18-S23 [PMID: 9988160 DOI: 10.1086/514298]

287 **van Griensven J**, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, Horby PW, Raoul H, Magassouba N, Antierens A, Lomas C, Faye O, Sall AA, Fransen K, Buyze J, Ravinetto R, Tiberghien P, Claeys Y, De Crop M, Lynen L, Bah EI, Smith PG, Delamou A, De Weggheleire A, Haba N; Ebola-Tx Consortium. Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea. *N Engl J Med* 2016; **374**: 33-42 [PMID: 26735992 DOI: 10.1056/NEJMoa1511812]

288 **Cheng Y**, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, Chan P, Wong KC, Leung CB, Cheng G. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* 2005; **24**: 44-46 [PMID: 15616839 DOI: 10.1007/s10096-004-1271-9]

289 **Soo YO**, Cheng Y, Wong R, Hui DS, Lee CK, Tsang KK, Ng MH, Chan P, Cheng G, Sung JJ. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin Microbiol Infect* 2004; **10**: 676-678 [PMID: 15214887 DOI: 10.1111/j.1469-0691.2004.00956.x]

290 **Chun S**, Chung CR, Ha YE, Han TH, Ki CS, Kang ES, Park JK, Peck KR, Cho D. Possible Transfusion-Related Acute Lung Injury Following Convalescent Plasma Transfusion in a Patient With Middle East Respiratory Syndrome. *Ann Lab Med* 2016; **36**: 393-395 [PMID: 27139619 DOI: 10.3343/alm.2016.36.4.393]

291 **Ko JH**, Seok H, Cho SY, Ha YE, Baek JY, Kim SH, Kim YJ, Park JK, Chung CR, Kang ES, Cho D, Müller MA, Drosten C, Kang CI, Chung DR, Song JH, Peck KR. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. *Antivir Ther* 2018; **23**: 617-622 [PMID: 29923831 DOI: 10.3851/IMP3243]

292 **Tanne JH**. Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. *BMJ* 2020; **368**: m1256 [PMID: 32217555 DOI: 10.1136/bmj.m1256]

293 **Duan K**, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A* 2020; **117**: 9490-9496 [PMID: 32253318 DOI: 10.1073/pnas.2004168117]

294 **Shen C**, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Yang Y, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y, Liu L. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 2020; **323**: 1582-1589 [PMID: 32219428 DOI: 10.1001/jama.2020.4783]

295 **Ye M**, Fu D, Ren Y, Wang F, Wang D, Zhang F, Xia X, Lv T. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol* 2020; **92**: 1890-1901 [PMID: 32293713 DOI: 10.1002/jmv.25882]

296 **Zhang B**, Liu S, Tan T, Huang W, Dong Y, Chen L, Chen Q, Zhang L, Zhong Q, Zhang X, Zou Y, Zhang S. Treatment With Convalescent Plasma for Critically Ill Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *Chest* 2020; **158**: e9-e13 [PMID: 32243945 DOI: 10.1016/j.chest.2020.03.039]

297 **Joyner MJ**, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, Carter RE, Klompas AM, Wiggins CC, Shepherd JR, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Johnson PW, Lesser ER, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Hodge DO, Kunze KL, Buras MR, Vogt MN, Herasevich V, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Van Buskirk CM, Winters JL, Stubbs JR, Paneth NS, Verdun NC, Marks P, Casadevall A. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *J Clin Invest* 2020; **130**: 4791-4797 [PMID: 32525844 DOI: 10.1172/JCI140200]

298 **Liu STH**, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Rahman F, Rodriguez D, Tandon P, Bassily-Marcus A, Bander J, Sanky C, Dupper A, Zheng A, Nguyen FT, Amanat F, Stadlbauer D, Altman DR, Chen BK, Krammer F, Mendu DR, Firpo-Betancourt A, Levin MA, Bagiella E, Casadevall A, Cordon-Cardo C, Jhang JS, Arinsburg SA, Reich DL, Aberg JA, Bouvier NM. Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. *Nat Med* 2020; **26**: 1708-1713 [PMID: 32934372 DOI: 10.1038/s41591-020-1088-9]

299 **Salazar E**, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, Eubank T, Bernard DW, Eagar TN, Long SW, Subedi S, Olsen RJ, Leveque C, Schwartz MR, Dey M, Chavez-East C, Rogers J, Shehabeldin A, Joseph D, Williams G, Thomas K, Masud F, Talley C, Dlouhy KG, Lopez BV, Hampton C, Lavinder J, Gollihar JD, Maranhao AC, Ippolito GC, Saavedra MO, Cantu CC, Yerramilli P, Pruitt L, Musser JM. Treatment of Coronavirus Disease 2019 (COVID-19) Patients with Convalescent Plasma. *Am J Pathol* 2020; **190**: 1680-1690 [PMID: 32473109 DOI: 10.1016/j.ajpath.2020.05.014]

300 **Agarwal A**, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P; PLACID Trial Collaborators. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 2020; **371**: m3939 [PMID: 33093056 DOI: 10.1136/bmj.m3939]

301 **Gharbharan A,** Jordans CCE, GeurtsvanKessel C, *et al* Convalescent plasma for COVID-19. A randomized clinical trial. 2020 Preprint. Available from: medRxiv [DOI: 10.1101/2020.07.01.20139857]

302 **Li L**, Zhang W, Hu Y, Tong X, Zheng S, Yang J, Kong Y, Ren L, Wei Q, Mei H, Hu C, Tao C, Yang R, Wang J, Yu Y, Guo Y, Wu X, Xu Z, Zeng L, Xiong N, Chen L, Wang J, Man N, Liu Y, Xu H, Deng E, Zhang X, Li C, Wang C, Su S, Zhang L, Wang J, Wu Y, Liu Z. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. *JAMA* 2020; **324**: 460-470 [PMID: 32492084 DOI: 10.1001/jama.2020.10044]

303 **Grabowski F**, Preibisch G, Giziński S, Kochańczyk M, Lipniacki T. SARS-CoV-2 Variant of Concern 202012/01 Has about Twofold Replicative Advantage and Acquires Concerning Mutations. *Viruses* 2021; **13**: 392 [PMID: 33804556 DOI: 10.3390/v13030392]

304 **Lv J**, Tu S, Xu L. Detection of Phenotype-Related Mutations of COVID-19 *via* the Whole Genomic Data. *IEEE/ACM Trans Comput Biol Bioinform* 2021; **18**: 1242-1249 [PMID: 33417561 DOI: 10.1109/TCBB.2021.3049836]

**Footnotes**

**Conflict-of-interest statement:** All authors have no conflicts of interest, financial or other, to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:**Unsolicited article; Externally peer reviewed.

**Peer-review started:** June 28, 2021

**First decision:** July 31, 2021

**Article in press:** September 16, 2021

**Specialty type:** Pharmacology and pharmacy

**Country/Territory of origin:** United States

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Cai J **S-Editor:** Liu M **L-Editor:** Kerr C **P-Editor:** Yu HG

**Table 1 Summary of guideline recommendations for COVID-19 treatment**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Organization** | **Dexamethasone** | **Hydroxychloroquine** | **Remdesivir** | **Convalescent plasma** | **Tocilizumab** |
| World Health Organization | Strong recommendation to use in patients with severe/critical illness; Conditional recommendation against use in non-severe/critical patients | Strong recommendation against use | Conditional recommendation against use | No recommendation | No recommendation |
| United States Centers for Disease Control and Prevention/National Institutes of Health | Recommend use in patient requiring supplemental oxygen or mechanical ventilation; Recommend against use in patients not requiring supplemental oxygen | Recommend against | Recommend in hospitalized patients requiring supplemental oxygen; Not routinely recommended for patients requiring mechanical ventilation | Recommends against use in hospitalized patients; No recommendation for non-hospitalized or immunocompromised patients | Recommended for patients requiring mechanical ventilation within 24 h of ICU admission |
| Infectious Disease Society of America | Suggest against use in hospitalized patients not requiring oxygen; Suggest use for patients with severe disease; Recommend use for patients with critical disease | Recommend against use | Suggest against use in hospitalized patients not requiring oxygen; Suggest use for patients with severe/critical disease | Suggest against use | Conditionally suggest use in severe/critical patients  |
| Surviving Sepsis/Society for Critical Care Medicine | Recommend for patients with severe/critical illness | Recommend against use in patients with severe/critical illness | Recommend to use in severe/critical patients not receiving mechanical ventilation; Recommend against starting in patients receiving mechanical ventilation | Recommend against (outside of clinical trial) for patients with severe/critical illness | No recommendation |

**Table 2** **Common adverse reaction of immunomodulators used in treatment of COVID-19**

|  |  |  |
| --- | --- | --- |
| **Drug** | **Class** | **Adverse effects** |
| Anakinra | Interleukin 1 inhibitor | Abdominal painAnaphylaxisElevated liver enzymesFlu-like symptomsHeadacheLocal reactionsNausea/vomiting/diarrheaNeutropeniaSinusitis |
| Canakinumab | Anti-interleukin 1β monoclonal antibody | Abdominal painElevated liver enzymesFlu-like symptomsHematologic cytopeniasHypersensitivity reactionsLocal reactionsNausea/vomiting/diarrheaSinusitis |
| Dexamethasone | Corticosteroid | Bone lossEdema/weight gainHyperglycemiaHypernatremiaHypertensionMyopathyNeuropsychiatric disturbancePeptic ulcer diseaseReactivation of latent infections (*i.e*., TB or strongyloidosis)Secondary infectionsVenous thromboembolism |
| Interferon-α | Interferon | Elevated liver functionsFlu-like symptomsHematological cytopeniaInfusion reactionLocal reactionNausea/vomitingNeuropsychiatric disease |
| Interferon-β | Interferon | Elevated liver functionsFlu-like symptomsHematological cytopeniaInfusion reactionLocal reactionNausea/vomitingNeuropsychiatric disease |
| Siltuximab | Anti-interleukin 6 monoclonal antibody | Elevated liver enzymesGastrointestinal perforationHeadache/dizzinessHyperuricemia Hypersensitivity reactionNeutropeniaPruritis/rashReactivation of latent infection (*i.e.*, HBV)Secondary infections |
| Sirulimab | Anti-interleukin 6 Receptor monoclonal antibody | Elevated liver enzymesGastrointestinal perforationHypersensitivity reactionNeutropeniaReactivation of latent infection (*i.e.*, HBV)Secondary infections |
| Tocilizumab | Anti-interleukin 6 Receptor monoclonal antibody | Elevated liver enzymesGastrointestinal perforationChanges in platelets and lipids Hypersensitivity reactionNeutropeniaReactivation of latent infection (*i.e.*, HBV)Secondary infections |

TB: Tuberculosis; HBV: Hepatitis B vírus



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**