



The Time to Offer Treatments for COVID-19

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The Time to Offer Treatments for COVID-19

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Abstract

Introduction: COVID-19 has several overlapping phases. Treatment has focused on the late stage of the disease in hospital. Yet, the continuation of the pandemic is by propagation of the disease in outpatients. The current public health strategy relies solely on vaccines to prevent disease.

Areas Covered: We searched the major national registries, pubmed.org, and the preprint servers for all ongoing, completed and published trial results with subject numbers of 100 or more on, and used a targeted search to find announcements of unpublished trial results. As of 2/15/2021, we found 111 publications reporting findings in human studies on 14 classes of agents, and on 9 vaccines. There were 62 randomized controlled studies, the rest retrospective observational analyses. Only 21 publications dealt with outpatient care, the rest all in hospitalized patients. Remdesivir and convalescent plasma have emergency use authorization for hospitalized patients in the U.S.A. There is also support for glucocorticoid

treatment of the COVID-19 respiratory distress syndrome. Monoclonal antibodies are authorized for outpatients, but the supply is inadequate to treat all at time of diagnosis. Favipiravir, ivermectin, and interferons are approved in certain countries.

Expert Opinion: Worldwide vaccination is now underway. Vaccines and antibodies are highly antigen specific and new variants are appearing. There is a need for treatment of outpatients who contract the disease, in addition to mass immunization. We call on public health authorities to authorize treatments with known low risk and potential benefit for use in parallel with mass immunization.

Keywords: SARS-CoV-2, COVID-19, HCQ, Remdesivir, Favipiravir, Interferon- λ , Interferon- β -1, Convalescent plasma, Synthetic anti spike protein antibodies, Ivermectin

Article Highlights

- COVID-19 has characteristic phases, beginning as a viral influenza like illness which may then deteriorate to an inflammatory phase with a subsequent hyperinflammatory reaction characterized by cytokine release; Acute respiratory distress syndrome and a coagulopathy are responsible for mortality.
- The focus of treatment of COVID-19 has been on very ill hospitalized patients. Outpatients who do not require hospitalization are told to home quarantine with no effective treatment.
- The public health authorities have pursued universal immunization to prevent the disease, and several vaccines are now being administered to the population of the entire world. However, vaccination alone may not be sufficient to stop the disease as the virus continues to propagate with newly developing variants.

- We reviewed treatments now available to use in parallel with vaccination to fight COVID-19. We found a number of agents, some already approved and in use in a number of countries.
- We recommend that agents with known safety profile and preliminary evidence of possible benefit be used together with universal vaccination while long term studies proceed in parallel to prove efficacy.

1. INTRODUCTION

SARS-Cov-2 was first identified in December 2019 in Wuhan, China and spread with extraordinary speed. As of February 15, 2021, there have been 108,579,352 confirmed cases of COVID-19, including 2,396,408 deaths worldwide affecting 220 countries and territories (1). Symptomatic COVID-19 exhibits a characteristic sequence of phases beginning with a primary viral attack, manifesting as an influenza-like illness. Then, within seven to 10 days of onset of symptoms, an inflammatory phase develops in up to 20% of infected individuals, typically heralded by an organizing pneumonia (2). In up to 5% of patients, the situation can deteriorate to a hyperinflammatory phase with acute respiratory distress syndrome. Elevated cytokines and a coagulopathy in this hyperinflammatory stage suggest an immune reaction as probable cause (FIGURE 1, 2-6). Secondary infections often develop. In a number of patients who survive, a “tail phase” ensues with prolonged disability.

In mainland China, vigorous efforts to contain the spread of COVID-19 by home isolation, mandatory masking, closure of business activity, travel bans, and tracking and control of contacts succeeded. As of February 15, 2021, China has had 101,536 confirmed cases and 4,838 deaths, but the number of new cases has been low since April, 2020 (1). Similar measures contained the epidemic in Taiwan and in New Zealand (1). However, the disease has not been controlled in the rest of the World, particularly Europe where there have been 36,668,163 cases with 814,455 deaths and the United States (USA) where, despite only a fifth of the population of China, there have been 27,309,503 confirmed cases of COVID-19 and 480,464 deaths. (1). In the Western World, as in China, the response to the pandemic was through reduction of person-to-person contact. Beginning

in early March, social gatherings and meetings ended; schools and businesses were closed along with recreation areas, parks, and beaches. These social distancing efforts blunted the spread of the disease, but not with the results achieved in China. Due to economic pressures, epidemiologic containment was relaxed resulting in a significant ongoing surge well surpassing the original April peak. Facing the growing crisis in early January, Chinese health authorities began treating patients empirically with agents with demonstrated in vitro antiviral activity against coronaviruses and those used during prior outbreaks of SARS 2003, H1N1 influenza of 2009 and MERS 2015(7). The medications included the antimalarial drugs hydroxychloroquine (HCQ) and chloroquine, the human immunodeficiency virus (HIV) protease inhibitor lopinavir-ritanovir (LPV/r), the Russian antiviral umifenovir, and traditional Chinese medical approaches (8). Subsequently, HCQ was widely used to treat COVID-19 throughout the world, despite cautions from numerous regulatory bodies. The scientific basis for their use was in vitro evidence of an effect on blocking viral endosomal penetration, as well as a known suppressive benefit on undesirable autoimmune effects (9).

The primary current focus of treatment of COVID-19 has been on patients with disease sufficiently severe to require hospitalization. Outpatients who are diagnosed are initially told to self-quarantine at home. The major industrialized countries have made an unprecedented effort to rapidly develop vaccines to prevent SARS-Cov-2 infection. Two mRNA vaccines and several adenovirus vector vaccines have shown effectiveness at two months post immunization, and thankfully mass vaccination has begun. However, in view of the continuing daily increase in new cases and deaths, we believe that it is unwise to rely on immunization alone. Gaining control of the pandemic depends largely on the interruption of transmission chains until protective herd immunity arises from prior cases and vaccine administration. Until that time or if acceptable levels of immunity are not reached in the community, medications will be needed for prevention and treatment of cases.. Our goal was to explore the landscape of existing pharmacologic agents to prevent and treat COVID-19 while vigorously pursuing the goal of universal vaccination in 2021.

2. METHODS

2.1 CLINICAL TRIALS: We reviewed up-to-date information from multiple different sources to identify potential treatments for COVID-19: The Reagan-Udall Expanded Access Navigator COVID-19 Treatment Hub was used to track the efforts of companies to develop therapeutic interventions. We actively searched for agents thus identified. We further searched for investigational trials for COVID-19 in active recruitment and those that have completed enrollment. We used (A) covid-trials.org, a registry to collate all trials in real time with data pulled from the International Clinical Trials Registry Platform and all major national registries (10). We cross validated this information on (B) clinicaltrials.gov, the registry of clinical trials information maintained by the United States National Library of Medicine and further cross referenced the trials on (C) the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP), and (D) (Cochrane COVID-19 Study Register. We excluded studies which were clearly observational with multiple different treatments, with no means of comparison. We further set a cutoff of 100 for numbers of subjects since smaller trial size typically lacks statistical power to enable regulatory approval. For each trial selected, we documented the setting of patient contact, either hospital or outpatient, the type of control procedure, the date the trial was initially registered, and the proposed date of completion of enrollment.

2.2 PUBLISHED TRIAL RESULTS: Our search was carried on the week of February 1, 2021. We identified all publications on pubmed.gov to find peer reviewed articles, on medRxiv to find preprint reports and the WHO Global Literature on Coronavirus Disease. We further carried out daily Google™ searches on each potential treatment to find preliminary reports, typically presented as press releases, reviewed by a journalist. We included all publications in our results as well as trial results posted as complete on Clinicaltrials.gov. We did not exclude trials with less than 100 subjects, since many reports were interim, with trials ongoing.

2.3 VIRTUAL DISCUSSIONS AMONG CO-AUTHORS: We used the preprint server medRxiv to post a systematic analysis of the development of therapeutic interventions for COVID-19 in order to stimulate diffusion of the manuscript and allow widespread “open source” input from co-authors (11,12). Successive versions of the preprint article have been posted periodically as a chronicle beginning in late May, 2020 and continuing to date. This process led to the present multinational consensus process.

3. RESULTS

3.1 REVIEW OF CURRENT TRIALS: As of February 1, 2021, we identified 835 trials currently in recruitment phase with subject size of 100 or more. These trials have been listed as a Supplementary Table 1 in our preprint article (9). Of these, 150 were directed at prevention in healthy individuals, 126 were classified as treatment of outpatients with documented infection, and 487 were for treatment of hospitalized inpatients. There were 11 trials focusing on the post discharge Tail phase. The remaining trials were unclear or mixed as to intended subjects. Among the trials, there were 79 vaccine trials, 151 trials involving hydroxychloroquine (HCQ), 41 trials of alternative therapy, 15 trials of colchicine, 48 trials of anticoagulants, 25 trials of the intravenous RNA polymerase inhibitor remdesivir and 23 trials of the oral RNA polymerase inhibitor favipiravir (FVP), 21 trials of interferons, 25 trials of glucocorticoid, and 69 trials of plasma based products

3.2 COMPLETED TRIALS: As of February 1,2021, there were 104 trials reporting completion with 100 or more subjects. These trials have been listed as Supplementary Table 2 in our preprint article (12). There were 65 trials in hospitalized patients, 9 directed at outpatients, and 13 prevention studies, rest unclear.

3.3 PUBLISHED RESULTS ON COVID-19 TRIALS: As of February 15, 2021 we found 111 publications reporting findings in human studies on 14 classes of agents, and on 9 vaccines). There were 62 random-

ized or active controlled studies. The rest were retrospective observational analyses. Only 21 publications dealt with outpatient care, including 9 vaccine reports; the rest were all in hospitalized patients. We have listed certain key studies with high potential impact in TABLE 1

3.3.1 ANTIVIRAL AGENTS

3.3.1.1 Remdesivir In the group of antiviral agents, the largest published randomized, controlled trials were with the intravenously administered RNA polymerase inhibitor remdesivir (13-17). An initial double blind randomized study on 237 patients in China showed no benefit on viral clearance nor mortality (13, TABLE 1). A double blind, randomized placebo controlled trial of remdesivir, in 1062 moderate to severely ill patients was carried out by the National Institute of Allergy and Infectious Disease (NIAID) (14, TABLE 1). The patients who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; $P < 0.001$). The Kaplan-Meier estimates of mortality by 29 days after randomization were 11.4% with remdesivir and 15.2% with placebo (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). On the basis of this trial, the Food and Drug Administration (FDA) approved the use of remdesivir for COVID-19 hospitalized patients. A different study of remdesivir in hospitalized patients with moderate COVID-19 clinical status showed improved clinical status by day 11 compared to standard of care for a 5 day course of remdesivir, but not for a 10 day course (15). There has been no data provided on viral clearance for the U.S. remdesivir studies. In early April, 2020, the WHO organized a megatrial, appropriately named Solidarity, to assess four separate treatment options only in hospitalized patients: (a) Remdesivir, an intravenously administered inhibitor of RNA polymerase; (b) The HIV agent lopinavir/ritonavir (LPV/R); (c) LPV/R plus Interferon β -1a; and (d) the antimalarials hydroxychloroquine (HCQ) and chloroquine (17). Results of the Solidarity Trial were initially reported by the World Health Organization on October 15, 2020. They found no effect of remdesivir on 28 day mortality, need for mechanical ventilation nor duration of hospitalization in a study including 5451 hospitalized patients (17, TABLE 1).

3.3.1.2 Favipiravir There were two positive randomized, active control clinical trials in China of the orally administered RNA polymerase inhibitor favipiravir (FVP) (18,19). In a trial comparing 116 patients on FVP to 120 on umifenovir, the 7 day clinical recovery rate was 55.9% for the umifenovir group and 71% in the FVP group (19, TABLE 1). In Japan, a clinical registry containing 1918 hospitalized patients receiving FVP on a compassionate use basis was released on June 2, 2020 (20). There was no control group nor data on viral clearance. Patients were treated on average 3 days post admission to the hospital. The 30 day overall mortality was 11.6%. In Russia, a preliminary study of FVP showed reduced duration of viral shedding, and the drug was approved for clinical treatment beginning in multiple hospitals on June 12, 2020 (21). In a follow-up phase 3 study, they reported 27% clinical improvement at day 10 compared to 15% for standard care with 98% clearance of SARS-COV-2 compared to 79% (22). In India, a study of 150 mild to moderate COVID-19 patients showed median time to clinical cure of 3 days (95% CI: 3 days, 4 days) for FVP versus 5 days (95% CI: 4 days, 6 days) for control, P=0.030, and FVP received approval in July, 2020 to treat COVID-19 (23). In late September, a report, still unpublished, of a randomized controlled study in Japan announced more rapid viral clearance in FVP treated patients.

3.3.1.3. Hydroxychloroquine There have been many studies of HCQ (24-51). A group in Marseille reported their experience with 3737 patients screened positive for SARS-Cov-2 and immediately treated with HCQ and azithromycin (AZM), after excluding patients at risk of QT prolongation (24, TABLE 1). They showed clearance of viral shedding in 89.4% of the patients by ten days. The overall mortality in their population was 0.9%, none in patients under 60 years old, and no sudden cardiac deaths. They had no randomized control population, but their study prompted immediate widespread use of HCQ throughout the world for treatment of COVID-19 patients.

Most subsequent observational or randomized controlled studies in hospitalized patients have shown no clinical nor mortality benefit of HCQ. In the randomized RECOVERY trial in 1542 hospitalized patients in the United Kingdom, there was no significant difference in the primary endpoint of 28-day mortality (26.8% HCQ vs. 25% usual care; hazard ratio 1.09 [95% confidence interval 0.96-1.23]; $p=0.18$) (38, TABLE 1). In the Solidarity Trial, there was no benefit of HCQ on mortality (HCQ RR=1.19 (0.89-1.59, $p=0.23$; 104/947 vs 84/906), need for mechanical ventilation, nor duration of hospitalization (17, TABLE 1). However, in a retrospective comparison study at NYU Langone Health for all patients admitted between March 2 and April 5, 2020, there was a move to add zinc 100 mg daily to their standard HCQ plus AZM regimen (39, TABLE 1). There was a significantly lower mortality (13.1%) among the zinc treated patients compared to those who did not receive zinc (22.8%).

There has been limited study of HCQ in outpatients. In one internet-based prevention study, with HCQ given for 5 days to healthy individuals with a significant exposure to SARS-Cov-2, the incidence of new illness compatible with COVID-19 did not differ significantly between participants receiving HCQ (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]); absolute difference -2.4 percentage points (95% confidence interval, -7.0 to 2.2 ; $p=0.35$) (40). The same group also treated 423 patients with mild symptoms imputed to COVID-19 (41). At 14 days, 24% (49 of 201) of participants receiving HCQ had ongoing symptoms compared with 30% (59 of 194) receiving placebo ($p = 0.21$).

A study in Spain of 293 patients with PCR-confirmed mild COVID-19, found no difference in viral load nor risk of hospitalization following 6 days HCQ treatment compared to untreated patients (42, TABLE 1). The same group treated 1,116 healthy contacts of 672 Covid-19 index cases with HCQ while 1,198 were randomly allocated to usual care (43, TABLE 1). There was no significant difference in the primary outcome of PCR-confirmed, symptomatic Covid-19 disease (6.2% usual care vs. 5.7% HCQ; risk ratio 0.89 [95% confidence interval 0.54-1.46]), nor evidence of prevention of SARS-CoV-2 transmission (17.8% usual care vs. 18.7% HCQ).

A large population study in Portugal surveyed all patients on chronic HCQ treatment and cross-verified against a mandatory database of patients registered with COVID-19 (44). The incidence of a positive PCR test for SARS-CoV-2 infection in patients receiving HCQ was 5.96%, compared to 7.45% in those not so treated, adjusted odds ratio 0.51 (0.37-0.70). However, two separate randomized controlled studies found no evidence of benefit of two months prophylactic treatment of hospital workers with HCQ (45,46, TABLE 1).

3.3.1.4. Lopinavir/ritonavir. Published results with Lopinavir/ritonavir (LPV/r) have been disappointing (17, 47-50). In a randomized trial with 99 patients on LPV/r and 100 receiving standard care, there was no difference in time to clinical improvement, mortality nor viral clearance (48). In the RECOVERY trial in 1,596 hospitalized patients there was no significant difference in the primary endpoint of 28-day mortality (22.1% LPV/r vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91-1.18]; ($p=0.58$) (49, TABLE 1). In the Solidarity Study, there was no effect of LPV/r on 28 day mortality LPV/r RR=1.00 (0.79-1.25, $p=0.97$; 148/1399 vs 146/1372), need for mechanical ventilation nor duration of hospitalization (17, TABLE 1).

A possibly more favorable result was obtained in Hong Kong in a study of 86 patients assigned to triple combination therapy with LPV/r plus ribavirin plus interferon β -1 (50, TABLE 1). Compared to a control group of 41 patients receiving LPV/r alone, the combination group had a significantly shorter median time from start of study treatment to negative SARS-Cov-2 nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; hazard ratio 4.37 [95% CI 1.86–10.24], $p=0.0010$). The time to complete alleviation of symptoms was 4 days [IQR 3–8] in the combination group vs 8 days [7–9] in the control group; HR 3.92 [95% CI 1.66–9.23]. This study was interpreted not as supporting LPV/r therapy, but rather focusing on interferon β -1 as the primary treatment modality.

3.3.1.5 Interferons Several interferon studies have been more encouraging (51-56). In Cuba, a combination of interferon- α -2b and interferon γ on background therapy of LPV/r and chloroquine was successful in achieving viral clearance in 4 days in 78.6% of the patients compared to 40.6% of those receiving interferon- α -2b alone (53). A trial of prophylactic nasal interferon in 2944 Chinese health workers demonstrated no cases compared to a historical control population (54, TABLE 1). In the Solidarity Study in hospitalized patients, there was no effect of injected interferon on 28 day mortality (IFN RR=1.16 (0.96-1.39, p=0.11; 243/2050 vs 216/2050), need for mechanical ventilation nor duration of hospitalization (17, TABLE 1). However, a trial of nebulized interferon β -1 in the U.K. reported positive improvement in clinical status (56, TABLE 1).

3.3.1.6 Passive immunization Infusion of COVID-19 convalescent plasma has yielded mixed results (57-63). A trial in China of 103 patients did not achieve its primary endpoint before termination due to declining number of cases (57). A study of 464 patients in India showed no benefit in progression to severe disease nor all cause mortality at 28 days after enrollment (58). However, several studies quantitating antibody titers suggest a reduction of mortality of 50% in patients treated within 3 days of diagnosis with high titer plasma (62,63, TABLE 1). Based on evidence of safety in over 20,000 patients in an expanded access program coordinated by the Mayo Clinic, the U.S. FDA issued an emergency authorization for use of convalescent plasma (64). Passive immunization in the early viral replication phase of COVID-19 has been further pursued with synthetic monoclonal antibodies to the SARS-COV-2 spike protein. Treatment of ambulatory patients with the LY-CoV555 neutralizing antibody and the Regeneron combination of two antibodies early in the course of infection but not later has shown success in reducing the frequency of hospitalization, and the FDA issued an emergency authorization for use in outpatients (65-67, TABLE 1).

3.3.1.7 Agents Not Usually Considered Antivirals There have been a number of favorable reports on agents not ordinarily considered as antivirals. These include famotidine, nitazoxanide, fluvoxamine, and ivermectin (68-75). A small randomized control study of fluvoxamine in outpatients showed no clinical deterioration versus 8.7% placebo (70). There have now been a number of trials including several randomized controlled studies

suggesting benefit with ivermectin both in prevention and in treatment of COVID-19 (75). In a matched case control study in India ivermectin prophylaxis yielded a 73% reduction in infection of health care workers (71). Ivermectin has now been authorized as treatment in several countries.

3.3.2 Immunomodulatory Treatment

3.3.2.1 Glucocorticoids There have been many observational studies of immunomodulatory therapy for the inflammatory and hyperinflammatory phases of COVID-19. Pre-COVID-19, glucocorticoid treatment had been a recognized treatment with mortality benefit for acute respiratory distress syndrome (76-78). Dexamethasone has now demonstrated benefit in several COVID-19 hospital trials (79-80). In the RECOVERY trial, 2104 patients were randomly allocated to receive dexamethasone for ten days compared to 4321 patients concurrently allocated to usual care (79, TABLE 1). Overall, 454 (21.6%) patients randomized to dexamethasone and 1065 (24.6%) patients receiving usual care died within 28 days (age adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; $p < 0.001$). Dexamethasone reduced deaths by one-third in the subgroup of patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; $p < 0.001$) and by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; $p = 0.002$), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; $p = 0.14$). Most trials of other glucocorticoids have shown similar benefits in COVID-19 patients with acute respiratory failure (80-87). Methylprednisolone, in particular, has been successful in reducing mortality (80, TABLE 1). There has been ongoing concern about potential harm by suppression of the immune response by utilizing glucocorticoids during the early viral replication phase of COVID-19. High viral load is associated with greater risk of respiratory deterioration and mortality (88). However, it was recently shown that inhaled budesonide was beneficial in cases of early mild COVID-19 (89, TABLE 1). To be sure, the initial viral load in these patients was fairly low (Mean Ct 32).

3.3.3 Anti-cytokine Antibodies Many observational studies of targeted anti-cytokine treatment with the IL-6 inhibitors tocilizumab and sarilumab, the GM-CSF inhibitor mavrilimumab, and the IL-1 inhibitor anakinra suggested reduction of mortality and need for intubation in the hyperinflammatory phase of COVID-19 (32, 87-106). However, several randomized control studies showed no apparent benefit with tocilizumab nor with sarilumab (107-109). In the COVACTA trial, there was no benefit of tocilizumab in clinical status, mortality (19.7% tocilizumab vs placebo = 19.4%), nor in ventilator free days (108), and in the Cor-Immuno-Toci trial, no decrease in mortality at day 28 (109). Sarilumab studies were ended early after an interim analysis failed to show benefit (110). However, the results in these randomized controlled trials were confounded by a higher frequency of glucocorticoid use in the control groups. The REMAP-CAP Study was performed after general acceptance of glucocorticoid treatment for severely ill COVID-19 patients. In their cohort, of whom 93% were steroid treated, there was clear superiority of tocilizumab and sarilumab in organ support free days, time to discharge and 90 day mortality (111, TABLE 1). Similarly, the RECOVERY TRIAL recently reported that tocilizumab treatment reduced mortality from 33% to 29% in a cohort of patients of whom 82% were receiving glucocorticoids (112, TABLE 1).

3.3.4. Colchicine. Early studies of colchicine pointed to a beneficial effect in both hospitalized and ambulatory patients (113,114). In the GRECCO, placebo-controlled, randomized clinical trial of 105 hospitalized patients The primary clinical end point of deterioration to mechanical ventilation or death was 14% in the control group (7 of 50 patients) and 1.8% in the colchicine group (1 of 55 patients) (odds ratio, 0.11; 95% CI, 0.01-0.96; p = 0.02) (115, TABLE 1). The ColCorona study recently reported on 4159 outpatients with PCR-confirmed COVID-19; the primary endpoint of hospitalization or death occurred in 4.6% and 6.0% of patients in the colchicine and placebo groups, respectively (odds ratio, 0.75; 95% CI, 0.57 to 0.99; P=0.04) (116, TABLE 1).

3.3.5 Stem Cells In patients who recover from COVID19 respiratory failure, there is often a prolonged tail phase of slow recovery, with lingering shortness of breath and decreased exercise tolerance. There have been

several pilot studies suggesting initial benefit with introduction of mesenchymal stem cells into the lungs during the inflammatory and hyperinflammatory phases of COVID-19 (111-115). In a small randomized control study comparing 12 patients who received umbilical cord derived stem cells with 12 who receive placebo, there was improved survival (92% vs 42%). in the stem cell group (117, TABLE 1).

3.3.10 There are currently more than 60 vaccines in clinical development worldwide. Nine vaccines are either authorized or shortly will be (122-131, TABLE 2). The Moderna and Pfizer Biontech mRNA spike protein vaccines released phase 3 data showed 95% effectiveness at preventing symptomatic infection in a 2 month post immunization observation period, and emergency authorization for immunization has been given in many countries. These vaccines have relatively stringent temperature requirements for transport and storage. Recombinant adenovirus vectored vaccines, one nanoparticle protein vaccine and several inactivated virus vaccines have also demonstrated protection in short term studies. Large scale vaccination programs are underway in the United States, the United Kingdom, India, Russia, China, and the European Union. At the same time, a different approach was suggested to stimulate non-specific immunity using oral polio or BCG vaccine (132). None of these studies of non-specific immunizations has yet reported results.

4. CONCLUSION

SARS-Cov-2 fueled by modern day jet travel overwhelmed medical preparedness for the pandemic. Current projections are for a continuation of new cases and deaths continuing in 2021 (133,134). Clinical trials to date have targeted predominantly hospitalized patients to try to prevent death. It is hoped that the use of remdesivir, convalescent plasma, glucocorticoids, specific immunomodulator therapy, and anticoagulation will lower the present rate of in hospital mortality which in some series has been as low as 6% but in most hospitals still approaches 20% (83). However, it is essential to change the present dynamic of attempted therapeutic responses to recognize and treat the specific phases of the disease that our group has previously defined (2, 135). In particular, efforts must now focus on prevention and treatment of the initial viral infection so that hospitalization

can be avoided. We face a dilemma with inadequate current prevention and treatment for outpatients with mild to moderate disease, constituting 80% of the infected population and the primary mode of spread of SARS-Cov-2. The lessons learned in very sick hospitalized patients do not necessarily apply to the earlier viremic phase. Antiviral agents, such as remdesivir and favipiravir, interferon, convalescent plasma, and monoclonal antibodies are likely to be most effective during the early stage of viremia, which is prior to the inflammatory pulmonary phase requiring hospitalization.

There has been very little emphasis on outpatient antiviral trials. Vaccines have been the solitary hope held out by public health authorities to arrest SARS-Cov-2. Progress on vaccine development has been rapid, but the speed of development does not reduce the challenges of developing a vaccine to be administered to the population of the entire World. Although neutralizing antibodies and memory T cells can be produced by the vaccine candidate, the demonstration of true protection requires long-term follow-up of an exposed vaccinated population. The current vaccines are released for emergency use after only a short two month period of observation. No matter how rapidly a vaccine advances to Phase III testing, the duration of follow-up cannot be shortened, and for SARS-Cov-2 possibly prolonged due to several factors. First, there is a risk of immune enhancement of infection which occurs when induced antibodies increase entry and internalization of virus into myeloid cells (136). This major complication struck the newly developed dengue vaccine in 2017 (137). Second, the sinister autoimmune pathogenicity of SARS-Cov-2 raises the risk of delayed long-term harm if the virus is not fully and immediately eradicated by the initial immune response to the vaccine. Furthermore, studies of recurrent coronavirus infections suggest that infection may confer immunity for less than a year (138). Vaccines are highly specific to targeted antigens. There is the risk that the virus will mutate to a form for which the new vaccine may not be fully protective. Already a number of variants have emerged and caused major outbreaks (139,140). The incidence of possible reinfection by the Brazilian P1 variant in Manaus has raised great concern (141).

After release of the current vaccines, efforts to find volunteers for trials of new, more effective vaccines will be hampered if there is no treatment available for placebo treated patients who become infected. Finally, the degree of acceptance of the COVID-19 vaccines by the general population is questionable. Seasonal influenza vaccination coverage was only 48% in 2019 (142). Children typically have limited COVID-19 symptoms. However, they may serve as a reservoir of ongoing infectivity (143). Currently there have been no clinical trial results of vaccine in children.

5. EXPERT OPINION

It also follows that totally new viruses may emerge just as did SARS-Cov-2. COVID-19 is now the sixth severe viral epidemic to hit mankind in the past 20 years; certainly it has been more widespread than SARS-Cov-1, H1N1 influenza, MERS, Zika, and Ebola, but that does not diminish the gravity of these repeated viral threats. Development of antigen specific vaccines takes a long time during which disease takes a large toll as has been the case for SARS-Cov-2. The succession of viral afflictions points to the need to implement widespread use of antiviral agents. The current recommendation for COVID-19 is home quarantine with no specific treatment for patients with suspicious symptoms. What is needed is therapeutic intervention which can be used to treat all outpatients with positive COVID-19 tests at the time of initial symptoms, not waiting for deterioration requiring hospital care. Hydroxychloroquine has not succeeded. Remdesivir administered intravenously for five days is not a practical daily outpatient treatment; Gilead© is attempting to develop an inhaled remdesivir formulation, but those efforts are only now beginning. Favipiravir, a tablet, could be used in early stages of infection and has now been released in Russia, Hungary, and in India, but not in the United States and the European Union. It has known embryogenic risks, so its use requires restrictions on women of childbearing potential, as is the case with tretinoin for acne and thalidomide for multiple myeloma. Convalescent plasma is used primarily in hospital patients. Monoclonal antiviral neutralizing antibodies have received emergency use authorization for ambulatory patients. However, the scale of production of these monoclonal antibodies is far too limited to offer to all outpatients. Interferon formulations have shown promise in several studies. Colchicine has successfully miti-

gated the course of COVID-19 in the ColCorona Study. There have been several randomized controlled studies suggesting benefit with ivermectin both for prophylaxis and treatment.

Yet, at this time, no outpatient therapy has been absolutely proven safe and effective in large scale phase III randomized, placebo-controlled studies. There are strong arguments to avoid emergency use of agents until trials are completed and analyzed, but the agents suggested are not new. Most are drugs like zinc, ivermectin, colchicine, inhaled glucocorticoids, and the interferons, marketed and available for other conditions and with well-known safety profiles. There is a clear need to offer outpatient therapeutic intervention now to the World population. It is also imperative to treat COVID-19 specific to the disease phase. Antiviral treatments are appropriate during the incubation and viremic period. They are not necessarily beneficial during the inflammatory and hyperinflammatory phases. Just as glucocorticoids and anti-cytokine treatment could be potentially harmful during the phase of viral replication. In Figure 2, we have outlined a schematic of potential phase specific treatment.

We should remember that the greatest success in fighting a pandemic occurred over the past two decades in the battle against the HIV virus which causes AIDS. AIDS was first recognized in 1981 in the MSM (men who have sex with men) community (144). The disease was considered a death sentence. There was widespread fear because there was no treatment, and projections of infection escalated into the millions. The first AIDS remedy was azidothymidine (AZT), synthesized in 1964 in the hope that it would combat cancer. Twenty years later Dr. Samuel Broder, head of the National Cancer Institute, showed that the drug had activity against the HIV virus in vitro (145). Burroughs Wellcome launched a rapidly conceived trial with just 300 patients. They stopped the trial in 16 weeks claiming that more patients survived on AZT. The FDA came under enormous pressure from AIDS activists to make the drug available, and it was approved on March 19, 1987, with only that one trial. It had taken 20 months for the FDA to give approval to release the drug. To this day, the design and results of the trial remain controversial.

The LGBT community continued to battle for early release of other medications to combat the AIDS pandemic. On October 11, 1988, a massive protest occurred at the FDA. It was back then Dr. Anthony Fauci who publicly advanced the idea of a parallel track to make drugs widely available even while studies are progressing: *“Clearly, the standard approach to the design of clinical trials—that is, rigid eligibility criteria as well as the strict regulatory aspects that attend clinical trial investigations and drug approval—was not well-suited to a novel, largely fatal disease such as this with no effective treatments, and we had many intense discussions about how to make that approach more flexible and ethically sound. One example, which I and others worked closely with the AIDS activists to develop, was called a parallel track for clinical trials. The parallel track concept, which the United States Food and Drug Administration ultimately came to support, meant that there would be the standard type of highly controlled admission criteria and data collection for the clinical trial of a particular drug. In parallel, however, the drug also could be made available to those who did not meet the trial’s strict admission criteria but were still in dire need of any potentially effective intervention, however unproven, for this deadly disease”* (146).

The parallel track advocated by Dr. Fauci was adopted. Today, there are 41 drugs or combinations approved by the FDA to treat and to prevent HIV infection. There is still no vaccine. There are now an estimated 1.1 million patients with HIV in the United States, most enjoying near normal life expectancy thanks to the antiviral agents. The CDC has contributed greatly to limit the spread of HIV by advocating safe sex practices, but social distancing is not the norm for HIV. Rather “treatment as prevention” for people with HIV using highly active antiretroviral regimens to prevent transmission as well as pre-exposure prophylaxis with a daily antiviral combination pill are currently endorsed by the CDC and adopted in wide segments of the at risk population (147).

In this pandemic crisis, we appeal to public health authorities to change the dynamic to outpatient care to use agents with low risk and potential benefit like inhaled glucocorticoids, ivermectin, interferon, favipiravir, and

colchicine. There is also promising data on several investigational agents including molnupiravir, cysteine protease inhibitors, mTORC inhibitors, and CD24Fc agents (148-155). There must be a collective effort to cross institutional, commercial and international boundaries to collate and combine all randomized controlled data submitted for all new agents in Europe, China, Russia, Japan, India and other countries, and by competing companies, whether officially published, posted on line, or unpublished to finalize confirmatory results. The Solidarity Trial is a model of what could and should be done to unify a worldwide effort to pursue randomized controlled studies in outpatients. At the same time, agents with favorable preliminary results and no safety issues should be made immediately available through a parallel track. In Russia and India, the parallel track has been fully implemented, with FVP now offered as treatment throughout both countries, even as further confirmatory controlled trials proceed. Interferon formulations are now approved treatments in China and Cuba. At this time, with no other option available, vaccination must be rapid and universal, despite the need to perform controlled studies to develop improved vaccines. However, it is unwise to rely solely on the hope for eventual mass vaccination to stop SARS-Cov2. Antiviral medication has succeeded in limiting HIV and hepatitis, and antivirals are just as important as annual vaccination for control of influenza. It is necessary for public health authorities to make hard decisions now despite limited current data and offer outpatient treatments on a broad front with no further delay.

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REFERENCES

1) WHO Coronavirus Disease (COVID-19) Dashboard

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2) Griffin DO, Brennan-Rieder D, Ngo B et al. The importance of understanding the stages of COVID-19 in treatment and trials. AIDS Rev. 2021 Feb 8. doi: 10.24875/AIDSRev.200001261. Online ahead of print.

- 3) Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; 323(13): 1239-1242
- 4) Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091.
- 5) Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. *J Thromb Haemost*. 2020 Apr 17 <https://doi.org/10.1111/jth.14849>.
- 6) Ricardo J, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation storm: *Lancet Respir Med* 2020; 8(6): e46-e47
- 7) Park M, Ryan S, Thwaites RS, et al. COVID - 19: Lessons from SARS and MERS *Eur J Immun* 2020; 50(3): 308-311
- 8) China National Health Commission. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition 2020-03-16 12:00:32
- 9) Liu J, Cao R, Xu M, et al. *Cell Discovery*. 2020; 6:16 *Cell Discovery* <https://doi.org/10.1038/s41421-020-0156-0>www.nature.com/celldisc
- 10) Thorlund KT, Dron L, Park J et al. A real-time dashboard of clinical trials for COVID-19. *Lancet Digital Health* 2020; 2: e86-e87 published on line 24 Apr 20 [https://doi.org/10.1016/S2589-7500\(20\)30086-8](https://doi.org/10.1016/S2589-7500(20)30086-8)

- 11) Ngo BT, Rendell M. A systematic analysis of the time course to develop treatments for COVID-19 medRxiv 2020.05.27.20115238; doi: <https://doi.org/10.1101/2020.05.27.20115238>
- (12) Ngo BT, Marik P, Pierre Kory P, et al. The time to offer treatments for COVID-19. medRxiv, 16 Dec20
doi: <https://doi.org/10.1101/2020.05.27.20115238>
- 13) Wang Y, Zhang D, Guanhua Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; 395 (10236): 1569-1578
- 14) Beigel JH, Tomashek KM, Dodd LE et al. Remdesivir for the Treatment of Covid-19 — final Report. October 8, 2020 DOI: 10.1056/NEJMoa2007764
- 15) Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *New Engl J Med* May 27, 2020 DOI: 10.1056/NEJMoa2015301
- 16) Spinner CD, Gottlieb RL, Criner GJ et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19. A randomized clinical trial. *JAMA*. Published online August 21, 2020. doi:10.1001/jama.2020.16349
- 17) WHO Solidarity Trial Consortium, “Repurposed Antiviral Drugs for Covid-19 Interim WHO Solidarity Trial Results”, *New England Journal of Medicine*, Dec. 2020, doi: 10.1056/nejmoa2023184.
<https://doi.org/10.1056/nejmoa2023184>
- 18) Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: An open-label control study *Engineering (Beijing)*. 2020;10.1016/j.eng.2020.03.007. doi:10.1016/j.eng.2020.03.007

- 19) Chen C, Huang J, Zhenshun Cheng Z, et al. Favipiravir versus Arbidol for COVID-19: A randomized clinical trial. medRxiv preprint doi: <https://doi.org/10.1101/2020.03.17.20037432>.this version posted March 20, 2020.
- 20) Preliminary Report of the Favipiravir Observational Study in Japan Favipiravir Observational Study Group. http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_casereport_en_200529.pdf Accessed 19 June 2020
- 21) Ivashchenko AA, Dmitriev KA, Vostokova NV, et al. AVIFAVIR for treatment of patients with moderate COVID-19: Interim results of a Phase II/III multicenter randomized clinical trial. *Clinical Infectious Diseases*, ciaa1176, <https://doi.org/10.1093/cid/ciaa1176>
- 22) <https://clinicaltrials.gov/ct2/show/NCT04542694>: Study of Favipiravir Compared to Standard of Care in Hospitalized Patients With COVID-19. Results posted 9 Nov 2020
- 23) Udwardia ZF, Singh P, Barkate H, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial. *Int J Infect Disease* (In Press)
- 24) Lagier JC, Million M, Gautret P, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. *Travel Med Infect Dis*. 2020 July-August; 36: 101791. Available on line 25 June 2020

- 25) Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv preprint doi:<https://doi.org/10.1101/2020.03.22.20040758>.this version posted March 30, 2020.
- 26) Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19) J Zhejiang Univ (Med Sci) 2020, Vol. 49 Issue (1): 0-0 DOI: 10.3785/j.issn.1008-9292.2020.03.03
- 27) Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients mainly with mild to moderate COVID-19: an open-label, randomized, controlled trial. BMJ 2020;369:m1849
- 28) Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. Med (2020), <https://doi.org/10.1016/j.medj.2020.06.001>
- 29) Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. New Engl J Med 2020 ;382(25):2411-2418
- 30) Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020; 323(24): 2493-2502.
- 31) Mahévas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ 2020;369:m1844
- 32) Ip A, Berry DA, Hansen E, et al, Hydroxychloroquine and tocilizumab therapy in COVID-19 patients - An observational study. PLoS ONE 15(8): e0237693.

- 33) Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Inf Dis.* 2020 ; 97: 396–403
- 34) Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *New Eng J Med* published on line July 23, 2020 DOI: 10.1056/NEJMoa2019014
- 35) Furtado RHM, Berwanger O*, Fonseca HA, et al. Azithromycin in addition to standard of care versus 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: 959–67
- 36) Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: A randomized clinical trial. *JAMA Netw Open* . 2020;3(4):e208857
- 37) Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19. A randomized clinical trial. *JAMA*. Published online November 9, 2020. doi:10.1001/jama.2020.22240
- 38) RECOVERY Collaborative Group. Effect of Hydroxychloroquine in hospitalized patients with COVID-19. *New Engl J Med* October 8, 2020 DOI: 10.1056/NEJMoa2022926

- 39) Carlucci P, Tania Ahuja T, Petrilli CM, et al. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients medRxiv doi: <https://doi.org/10.1101/2020.05.02.20080036>
- 40) Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *N Engl J Med* 2020; 383:517-525
- 41) Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19. A randomized trial. *Ann Int Med* 2020 Jul 16 : M20-4207
- 42) Mitjà O, Corbacho-Monné M, Ubals M, et al. Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. *Clinical Infectious Diseases*, ciaa1009, <https://doi.org/10.1093/cid/ciaa1009> Published: 16 July 2020
- 43) Mitjà O, Ubals M, Corbacho-Monné M, et al. A cluster-randomized trial of hydroxychloroquine as prevention of Covid-19 transmission and disease. *N Engl J Med* 2021; 384:417-427
- 44) Ferreira A, Oliveira-e-Silva A, Bettencourt P. Chronic treatment with hydroxychloroquine and SARS-CoV-2 infection. *J Med Virol* 2020:1-5
- 45) Abella BS, Jolkovsky EL, Biney BT, et al. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers. A randomized clinical trial. *JAMA Intern Med*. doi:10.1001/jamainternmed.2020.6319 Published online September 30, 2020.

46) Rajasingham R, Bangdiwala AS, Nicol MR, et al. Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial. Preprint. medRxiv. 2020;2020.09.18.20197327. Published 2020 Sep 18. doi:10.1101/2020.09.18.20197327

47) Li Y, Xie Z, Lin W, et al. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI.Med (N Y)). 2020 May 19 doi: 10.1016/j.medj.2020.04.001

48) Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir–Ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020;382(19):1787-1799.

49) RECOVERY Collaborative Group. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet Published Online October 5, 2020 [https://doi.org/10.1016/S0140-6736\(20\)32013-4](https://doi.org/10.1016/S0140-6736(20)32013-4).

50) Hung IFN, Lung KC, Tso EYK et al 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 May 30;395(10238):1695-1704.

51) Estebanez M, Ramirez-Olivencia G, Mata T, et al. Clinical evaluation of IFN beta-1-b in COVID-19 pneumonia: a retrospective study. MedRxiv doi: <https://doi.org/10.1101/2020.05.15.20084293>

52) Pereda R, González D, Rivero HB, et al. Therapeutic effectiveness of interferon-alpha 2b against COVID-19: the Cuban experience. medRxiv preprint doi: <https://doi.org/10.1101/2020.05.29.20109199>.

53) Idelsis PE, Perez-Escribano J, Duncan-Robert Y, et al Effect and safety of combination of interferon alpha-2b and gamma or interferon alpha-2b for negativization of SARS-CoV-2 viral RNA medRxiv <https://doi.org/10.1101/2020.07.29.20164251>

54) Rahmani H, Davoudi-Monfared E, Nourian A, et al. Interferon β -1b in treatment of severe COVID-19: A randomized clinical trial. *Int Immunopharmacol.* 2020 Nov; 88: 106903.

55) Meng Z, Wang T, Chen L, et al. An experimental trial of recombinant human interferon alpha nasal drops to prevent COVID-19 in medical staff in an epidemic area. medRxiv .<https://doi.org/10.1101/2020.04.11.20061473>

56) Monk PD, Marsden RJ, Tear VJ, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2020Published OnlineNovember 12, 2020 [https://doi.org/10.1016/S2213-2600\(20\)30511-7](https://doi.org/10.1016/S2213-2600(20)30511-7)

57) Li L, Zhang W, Hu Y, et al. 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.

58) Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicenthttp://dx.doi.org/10.1136/bmj.m3939re randomised controlled trial (PLACID Trial) *BMJ* 2020;371:m3939 <http://dx.doi.org/10.1136/bmj.m3939>

- 59) Perotti C, Baldanti F, Bruno R, et al. Mortality reduction in 46 severe Covid-19 patients treated with hyperimmune plasma. A proof of concept single arm multicenter interventional trial. *Haematologica*. 2020 Jul 23;haematol.2020.261784. doi: 10.3324/haematol.2020.261784
- 60) Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E, et al. Convalescent Plasma for COVID-19: A multicenter, randomized clinical trial. *MedRxiv* September 1, 2020.
.https://doi.org/10.1101/2020.08.26.20182444doi:
- 61) Rogers R, Shehadeh F, Mylona E, et al. Convalescent plasma for patients with severe COVID-19: a matched cohort study medRxiv 2020.08.18.20177402; doi: https://doi.org/10.1101/2020.08.18.20177402
- 62) Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent plasma antibody levels and the risk of death from Covid-19. *N Engl J Med*. DOI: 10.1056/NEJMoa2031893.
- 63) Libster R, Pérez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med*. DOI: 10.1056/NEJMoa2033700
- 64) Joyner MJ, Bruno KA, Klassen SA, et al, Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients *Mayo Clin Proc*. 2020;95 (9):1888-1897
- 65) ACTIV-3/TICO LY-CoV555 Study Group, Lundgren JD, Grund B, Barkauskas CE et al. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. *N Engl J Med*. 2020 Dec 22:NEJMoa2033130.

- 66) Chen P, Nirula A, Heller B, et al SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med*. 2021;384:229-237
- 67) Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med* 2021;384:238-251.
- 68) Freedberg DE, Conigliaro J, Sobieszczyk ME, et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. *Gastroenterology*. 2020 May 22
- 69) Rocco PRM, Silva PL, Cruz FF, et al. Early use of nitazoxanide in mild Covid-19 disease: randomized, placebo-controlled trial *medRxiv* 2020.10.21.20217208; doi: <https://doi.org/10.1101/2020.10.21.20217208>
- 70) Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19. A randomized clinical trial. *JAMA*. Published online November 12, 2020. doi:10.1001/jama.2020.22760
- 71) Behera P, Patro BK, Singh AK, et al. Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: A matched case-control study *medRxiv* 2020.10.29.20222661;
- 72) Khan MSI, Khan MSI, Debnath CR, et al. Ivermectin treatment may improve the prognosis of patients with COVID-19. *Archivos de Bronconeumología*. 2020
- 73) Shouman W. <https://ClinicalTrials.gov/show/NCT04422561> Results posted 27 Aug 20

74) Rajter JC, Sherman M, Fattah N, et al. ICON (Ivermectin in COvid Nineteen) study: Use of ivermectin is associated with lower mortality in hospitalized patients with COVID19. medRxiv doi:

<https://doi.org/10.1101/2020.06.06.20124461>

75) Kory P, GU Meduri, Iglesias J, et al. Review of the emerging evidence demonstrating the efficacy of ivermectin in the prophylaxis and treatment of COVID-19. *Frontiers in Pharmacology*, doi:10.3389/fphar.2021.10.31219/osf.io/wx3zn

76) Meduri GU, Stacey Headley S, Elizabeth Tolley E et al. Plasma and BAL cytokine response to corticosteroid rescue treatment in late ARDS. *Chest* 1995;108;1315-1325

77) Villar J, Ferrando C, Martínez D et al. Dexamethasone treatment for the acute respiratory distress syndrome: A multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276

77) Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX Randomized Clinical Trial. 2020 ;324:1307-1316.

79) RECOVERY Collaborative Group. Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report. July 17, 2020 DOI: 10.1056/NEJMoa2021436

80) Salton F, Confalonieri P, Santus P, et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. *Open Forum Infectious Diseases*, Volume 7, Issue 10, October 2020, ofaa421

- 81) Fadel R, Morrison AR, Vahia A, et al. Early short-course corticosteroids in hospitalized patients with COVID-19. *Clinical Infectious Diseases* 2020; ciaa601, <https://doi.org/10.1093/cid/ciaa601>
- 82) Villar J, Confalonieri, M, Pastore, SM, et al. Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome caused by Coronavirus Disease 2019. *Crit Care Explor* April 2020;2 :e0111
- 83) Marik PE, Kory P, Varon J, et al. MATH+ protocol for the treatment of SARS-CoV-2 infection: the scientific rationale, *Expert Review of Anti-infective Therapy* <https://doi.org/10.1080/14787210.2020.1808462> published on line 18 aug 2020
- 84) Chroboczek T, Lacoste L, Wackenheim C, et al. Beneficial effect of corticosteroids in severe COVID-19 pneumonia: a propensity score matching analysis. *MedRxiv*: doi: <https://doi.org/10.1101/2020.05.08.20094755>
- 85) Jeronimo CMP, Farias MEL, BSc, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): A randomised, double-blind, phase iib, placebo-controlled trial. *Clinical Infectious Diseases*, ciaa1177, <https://doi.org/10.1093/cid/ciaa1177>
- 86) Dequin PF, Heming NMD, Mezian F, et al; Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19, A randomized clinical trial *JAMA*. 2020;324(13):1298-1306. doi:10.1001/jama.2020.16761

- 87) Angus DC , Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA . 2020 Oct 6;324(13):1317-1329. doi: 10.1001/jama.2020.17022
- 88) Magleby R, Westblade LF, Trzebucki A, et al. Impact of SARS-CoV-2 viral load on risk of intubation and mortality among hospitalized patients with Coronavirus disease 2019. Clin Infect Dis. 2020 Jun 30:ciaa851.
- 89) Ramakrishnan S, Nicolau DV Jr, Langford BL et al. Inhaled budesonide in the treatment of early COVID-19 illness: a randomised controlled trial medRxiv preprint doi: <https://doi.org/10.1101/2021.02.04.21251134>
- 90) Xua X, Hanb M, Lia T, et al. Effective treatment of severe COVID-19 patients with tocilizumab 10970–10975 | Proc Natl Acad Sci | May 19, 2020 | vol. 117 | no. 20 www.pnas.org/cgi/doi/10.1073/pnas.2005615117
- 91) Somers EC, Eschenauer GA, Troost JP. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clin Infect Dis. 2020 Jul 11 : ciaa954.
- 92) Rossi B, Nguyen LS, Zimmermann, et al. Effect of tocilizumab in hospitalized patients with severe pneumonia COVID-19: a cohort study Pharmaceuticals (Basel) 2020; 13: 317.
- 93) Martinez-Sanz J, Muriel A, l Ron R, et al. Effects of tocilizumab on mortality in hospitalized patients with COVID-19: A Multicenter Cohort Study. MedRxiv doi: <https://doi.org/10.1101/2020.06.08.20125245>
- 94) Petrak R, Skorodin N, Van Hise N, et al. Tocilizumab as a therapeutic agent for critically ill patients infected with SARS-CoV-2. Clin Transl Sci . 2020 Sep 12.

- 95) Perrone P, Piccirillo MC, Ascierio PA, et al. Tocilizumab for patients with COVID-19 pneumonia. The TOCIVID-19 phase 2 trial. *J Transl Med.* 2020;18: 405.
- 96) Garcia EM, Caballero VR, Albiach L, et al. Tocilizumab is associated with reduction of the risk of ICU admission and mortality in patients with SARS-CoV-2 infection medRxiv doi: <https://doi.org/10.1101/2020.06.05.20113738>
- 97) Wadud N, Ahmed N, Shergil M, et al. Improved survival outcome in SARS-CoV-2 (COVID-19) acute respiratory distress syndrome patients with tocilizumab administration. *MedRxiv* doi: <https://doi.org/10.1101/2020.05.13.20100081>
- 98) Sanchez-Montalva A, Selares-Nadal J, Espinosa-Pereiro J, et al. Early outcomes of tocilizumab in adults hospitalized with severe COVID19. An initial report from the Vall d'Hebron COVID19 prospective cohort study. doi: <https://doi.org/10.1101/2020.05.07.20094599>
- 99) Ramaswamy M, Mannam P, Comer R, et al. Off-label real world experience using tocilizumab for patients hospitalized with COVID-19 disease in a regional community health system: A case-control study medRxiv. doi: <https://doi.org/10.1101/2020.05.14.20099234>
- 100) Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020; 2(8): 2, e474-e484

- 101) Cavalli G, De Luca G, Campochiaro C, et al. 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: e325–31
- 102) Cauchois R, Koubia M, Delarbrec D, et al. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. *Proc Nat Acad Sci* 2020; 117: 18951-18953
- 103) Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020; 2: e393-e400
- 104) Kyriazopoulou E, Panagopoulos P, Metallidis S, et al. Anakinra to prevent respiratory failure in COVID-19. medRxiv preprint doi: <https://doi.org/10.1101/2020.10.28.20217455>; this version posted October 29, 2020.
- 105) De Luca G, Cavalli G, Campochiaro C, et al. GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatol*. 2020 Aug;2(8):e465-e473.
- 106) Della-Torre E, Campochiaro C, Cavalli G, et al Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study. *Ann Rheum Dis*. 2020 Oct;79(10):1277-1285.
- 107) Salvarani C, Dolci G, Massari M et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia *JAMA Intern Med*. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615

- 108) Rosas IO, Bräu N,, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia posted September 12, 2020. medRxiv.<https://doi.org/10.1101/2020.08.27.20183442>doi:
- 109) Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia. A randomized clinical trial Published Online: October 20, 2020. doi:10.1001/jamainternmed.2020.6820
- 110) Sarilumab studies ended early. <https://www.sanofi.com/en/media-room/press-releases/2020/2020-09-01-07-00-00>
- 111) The REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19 – Preliminary report preprint ; <https://doi.org/10.1101/2021.01.07.21249390>doi: medRxiv preprint
- 112) RECOVERY Collaborative Group. COVID-19 (RECOVERY): preliminary results of a 4 randomised, controlled, open-label, platform trial medRxiv preprint doi: <https://doi.org/10.1101/2021.02.11.21249258>; this version posted February 11, 2021
- 113) Scarsi M, Piantoni S, Colombo E, et al. Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome. *Ann Rheum Dis.* 2020;79:1286-1289.
- 114) Della-Torre E, Della-Torre F, Kusanovic M, et al Treating COVID-19 with colchicine in community healthcare setting. *Clin Immunol.* 2020;217:108490.

- 115) Deftereos SG, Giannopoulos G, Dimitrios A, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with Coronavirus Disease 2019. The GRECCO-19 randomized clinical trial. *JAMA Network Open*. 2020;3:e2013136.
- 116) Tardif JC, Bouabdallaoui N, L'Allier PL et al. Efficacy of colchicine in non-hospitalized patients with COVID-19. *medRxiv* 2021 <https://doi.org/10.1101/2021.01.26.21250494>
- 117) Gentile P, Sterodimas A, Pizzicannella J, et al. Research progress on mesenchymal stem cells (MSCs)' Adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease. *Aging Dis*. 2020;11:1191-1201.
- 118) Gentile P, Sterodimas A. Adipose-derived stromal stem cells (ASCs) as a new regenerative immediate therapy combating coronavirus (COVID-19)-induced pneumonia. *Expert Opin Biol Ther*. 2020;20:711-716
- 119) Gentile P, Sterodimas A. Adipose stem cells (ASCs) and stromal vascular fraction (SVF) as a potential therapy in combating (COVID-19)-disease. *Aging Dis*. 2020 May 9;11(3):465-469. doi: 10.14336/AD.2020.0
- 120) Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2- Mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging Dis*. 2020;11:216-228.
- 121) Lanzoni G, Linetsky E, Correa D, et al . Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, phase 1/2a, randomized controlled trial. *Stem Cells Transl Med*.

- 122) Polack FP, Stephen J. Thomas SJ, Nicholas Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; 383:2603-2615
- 123) Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021; 384:403-416
- 124) Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia www.thelancet.com Published online February 2, 2021
- 125) Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; 397: 99–111
- 126) Zhu FC, Guan XH*, Hua Y, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet*. 2020 Aug 15;396(10249):479-488
- 127) Sadoff J, Le Gars M, Shukarev G, Heerwegh D et al. Interim results of a phase 1–2a trial of Ad26.COV2.S Covid-19 vaccine. *N Engl J Med*. 2021; <https://doi.org/10.1056/NEJMoa2034201>
- 128) Keech C, Albert G, Cho I, et al. Phase 1–2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine *N Engl J Med* 2020; 383:2320-2332

- 129) Zhao J, Zhao S, Ou J, et al. COVID-19: Coronavirus vaccine development updates. *Front Immunol.* 2020; 11: 602256.
- 130) Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial *Lancet* 2021; 21: 181-192
- 131) Ella R, Vadrevu KM, Jogdand H et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. *Lancet Infect Dis.* 2021; (published online Jan 21)
- 132) Chumakov K, Benn CS, Aaby P, et al. Can existing live vaccines prevent COVID-19? *Science* 2020; 368: 1187-1188
- 133) Liu, M, Thomadsen, R, Yao, S. Forecasting the spread of COVID-19 under different reopening strategies. *Sci Rep* 2020; 10, 20367
- 134) Institute for Health Metrics and Evaluation. COVID-9 projections . Covid 19.healthdata.org
- 135) Marik PE, Varon J, Kory P. Treatment of Covid-19 is critically phase specific. *Crit Care Shock* 2020;23 :10-12
- 136) Wan Y, Shang J, Sun S, et al. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. *J Virol* 2020;94:e02015-19.

- 137) Fatima K, Syed NI. Dengvaxia controversy: impact on vaccine hesitancy. *J Glob Health*. 2018; 8(2): 020312.
- 138) Edridge AWD, Kaczorowska J, Hoste ACR et al. Coronavirus protective immunity is short-lasting. *Nat Med* 2020; 26, 1691–1693
- 139) Makoni M. South Africa responds to new SARS-CoV-2 variant. *Lancet*. 2021;;397:267
- 140) Zhang W, Davis BD, Chen S et al. Emergence of a novel SARS-CoV-2 variant in Southern California. *JAMA*. Published online February 11, 2021
- 141) Sabino EC, Bussa LF, Carvalho MPS et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence *The Lancet* 2021; 397: 452-455
- 142) Flu Vaccination Coverage, United States, 2019–20 Influenza Season. FluVaxView webpage report posted online October 1, 2020 <https://www.cdc.gov/flu/fluvoxview/coverage-1920estimates.htm>
- 143) Zimmermann P, Nigam SK. Coronavirus infections in children including COVID-19. An overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. *The Pediatric Infectious Disease Journal* 2020;39 : 355-368
- 144) Sepkowitz KA. AIDS-The first 20 years. *N Engl J Med* 2001; 344 (23):1764-1772

- 145) Broder S. The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. *Antiviral Res.* 2010; 85: 1-18
- 146) Fauci AS. Preface: Evolving ethical issues over the course of the AIDS pandemic. *Public Health Rev* 34, 2 (2012)
- 147) Harris NS, Johnson AS, Huang YA, et al. Vital Signs: Status of human immunodeficiency virus testing, viral suppression, and HIV pre-exposure prophylaxis - United States, 2013-2018. *MMWR Morb Mortal Wkly Rep.* 2019; 68 (11):1117-1123
- 148) Urakova N, Kuznetsova V, Crossman DK et al. β -d-N⁴-Hydroxycytidine is a potent anti-alphavirus compound that induces a high level of mutations in the viral genome. *Journal of Virology* 2018; 92 e01965-17
- 149) Sheahan TP, ASims AC, Zhou S, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. *Science Translational Medicine* 2020; 12, eabb5883
- 150) Zhang L, Lin D, Sun X, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α -ketoamide inhibitors. *Science* 2020; 368(6489):409-412.
- 151) Gadlage MJ, Denison MR. Exchange of the coronavirus replicase polyprotein cleavage sites alters protease specificity and processing. *J. Virol* 2010; 84, 6894-6898.

152) de Vries M, Mohamed A S, Prescott R A, et al. Comparative study of a 3CLpro inhibitor and remdesivir against both major SARS-CoV-2 clades in human airway models. bioRxiv preprint doi: <https://doi.org/10.1101/2020.08.28.272880>doi:

153) Dai W, Zhang B, Jiang XM, et al. Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. *Science* 2020; 368 :1331-1335.

154) Mannick JB, Morris M, Hockey HP, et al. TORC1 inhibition enhances immune function and reduces infections in the elderly. *Science Translational Medicine* 2018; 10: eaaq1564

155) Kim PS, Read SW, Fauci AS. Therapy for Early COVID-19: A Critical Need. *JAMA*. 2020;324(21):2149–2150.

ACCEPTED MANUSCRIPT

TABLE 1. PUBLISHED STUDIES of HIGH IMPACT AS OF FEBRUARY 15, 2021. Each agent is listed along with the country originating the publication. We have listed studies with 100 or more subjects. The type of control procedure: RCT: Randomized controlled study PLAC: Placebo, soc: standard of care which is variable depending on each location. AC: Active control: the control options are listed in parenthesis. OBS: retrospective observation study. LPV/R: lopanovir/ritonavir; HCQ: hydroxychloroquine; AZM: azithromycin; IFN: interferon; tocilizumab: TCZ. SEV: severe; CRIT: critical; MOD: moderate. W.H.O.: World Health Organization

TREATMENT	LOCATION	TYPE OF CONTROL	NUMBER SUBJECTS	SETTING	SEVERITY	RESULTS
Remdesivir ¹³	China	RCTPLAC vs soc	273	HOSP	SEV	mortality in remdesivir group 14%, control 13% 11% in remdesivir group with <10 days symptoms Vs 14% in placebo group, no difference in viral clearance
Remdesivir ¹⁴	U.S.A.	RCTPLAC	1062	HOSP	SEV,CRIT	29 day mortality 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03)
Remdesivir ¹⁷	W.H.O.	AC(10 day, vs soc)	5451	HOSP	MOD,SEV	Mortality Remdesivir RR=0.95 (0.81-1.11, p=0.50 301/2743 active vs 303/2708 control
FVP ¹⁹	China	AC (umifenovir vs favipiravir)	240	HOSP	MOD,SEV	Clinical recovery rate 56%umifenovir vs 71% fvp
HCQ ²⁴	France	OBS(hcq+azm, noncomparable control group)	3737	MIXED	MILD,MOD	0.9% overall mortality, no sudden death, no cardiac arrhythmias
HCQ ³⁸	U.K.	RCT (HCQ vs soc)	1542	HOSP	MOD,SEV	no significant difference in 28-day mortality (26.8% hydroxychloroquine vs. 25% usual care; hazard ratio 1.09 [95% confidence interval 0.96-1.23]; p=0.18) (Mortality

						RR=1.19 (0.89-1.59, p=0.23; 104/947 HCQ vs 84/906 control)
HCQ ¹⁷	W.H.O.	AC(HCQ vs soc)	1853	HOSP	MOD, SEV	Mortality RR=1.19 (0.89-1.59, p=0.23; 104/947 HCQ vs 84/906 control)
HCQ ³⁹	U.S.A.	OBS (hcq+azm +zinc vs hzq +azm)	932	HOSP	MOD,SEV	Reduction in mortality with addition of zinc OR 0.449, 95% CI 0.271-0.744).
HCQ ⁴²	Spain	RCTPLAC	293	OUTPAT	MILD	no difference in viral load at 7 days after 6 days HCQ treatment nor risk of hospitalization compared to untreated patients
HCQ ⁴³	Spain	RCTPLAC	2324	OUTPAT	HEALTHY	no significant difference in the primary outcome of PCR-confirmed, symptomatic Covid-19 disease (6.2% usual care vs. 5.7% HCQ; risk ratio 0.89 [95% confidence interval 0.54-1.46]), nor evidence of prevention of SARS-CoV-2 transmission (17.8% usual care vs. 18.7% HCQ)
HCQ ⁴⁶	Canada	RCTPLAC	1483	OUTPAT	HEALTHY	3 month treatment with HCQ in hospital workers no significant difference in SARS-Cov-2 infection rate HCQ 0.27 events per person/year vs placebo 0.38% (p=0.18)

LPV/r ⁴⁹	U.K.	RCT(soc)	1596	HOSP	MOD,SEV	no significant difference in the primary endpoint of 28-day mortality (22.1% LPV/r vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91-1.18]; (p=0.58)
LPV/r ¹⁷	W.H.O.	AC(LPV/r vs soc)	2771	HOSP	MOD,SEV	Mortality LPV/r (RR=1.00 (0.79-1.25, p=0.97; 148/1399 vs 146/1372)
LPV/r ⁵⁰	Hong Kong	AC(lpv/r+ribavirin+beta interferon vs lpv/r+ribavirin)	127	HOSP	MOD,SEV	Triple combination of interferon beta-1b, lpv/r, and ribavirin yielded more rapid viral clearance but attributable primarily to interferon
IFN ¹⁷	W.H.O.	AC(vs soc)	4100	HOSP	MOD,SEV	Mortality IFNRR=1.16 (0.96-1.39, p=0.11; 243/2050 vs 216/2050)
IFN- α nasal drops ⁵⁴	China	OBS	2944	OUTPAT	HEALTHY	No cases of COVID-19 compared to historical control
IFN- β -1a(nebulized) ⁵⁶	U.K.	RCT(soc)	101	HOSP	MOD,SEV	OR for clinical improvement 2.32 (1.07-5.04)
Convalescent plasma ⁵⁷	China	RCT(soc)	103	HOSP	SEV.CRIT	time to clinical improvement at 28 days was 4.9 days shorter (95% CI, -9.33 to -0.54 days) in convalescent plasma group (HR, 2.15 [95% CI, 1.07-4.32]; P = .03). No

						significant difference in critically ill patients. Mortality 28-day mortality (15.7% convalescent plasma vs 24.0% control ; P = .30)
Convalescent plasma ⁶²	U.S.A.	OBS	3,082	HOSP	MOD,SEV	adjusted 30-35 day mortality was 30% in patients treated with plasma with low antibody levels (IgG) 35 or more days after COVID-19 diagnosis. By contrast 30-day mortality was 20% in 353 patients treated within 3 days of diagnosis with plasma with high antibody levels.
Convalescent plasma ⁶³	U.S.A.	OBS	160	HOSP	MOD,SEV	severe respiratory disease developed in 13 of 80 patients (16%) who received convalescent plasma and 25 of 80 patients (31%) who received placebo (relative risk, 0.52; 95% confidence interval [CI], 0.29 to 0.94; P=0.03).
Convalescent plasma ⁶⁴	U.S.A.	OBS	21,987	HOSP	MOD,SEV	7 day mortality 13%
LY-CoV555 ⁶⁶	U.S.A.	RCT(soc)	452	OUTPAT	MILD,MOD	6.2% of patients receiving placebo had emergency room visit or hospitalization vs 1.6% patients who received antibody
RGN-Cov2 ⁶⁷	U.S.A.	RCT(soc)	275	OUTPAT	MILD,MOD	Decreased viral load vs placebo; 6% medical visits for placebo patients vs 3% for those receiving monoclonal antibody cocktail

Fluvoxamine ⁷⁰	U.S.A.	RCT(fluvoxamine vs soc)	152	OUTPAT	MILD,MOD	Clinical deterioration in 0 patients on fluvoxamine, 8.7% placebo (p<0.009)
Ivermectin ⁷¹	India	Case Control (Ivermectin vs placebo)	115	OUTPAT	HEALTHY	Two doses of ivermectin yielded 73% reduction in COVID_19 cases
Dexamethasone ⁷⁹	U.K.	RCT(soc)	6119	HOSP	MOD,SEV	Dexamethasone reduced 28-day mortality by 35% in patients receiving invasive mechanical ventilation (rate ratio 0.65 [95% CI 0.51 to 0.82]; p<0.001) and by 20% in patients receiving oxygen without invasive mechanical ventilation (rate ratio 0.80 [95% CI 0.70 to 0.92]; p=0.002)
Methylprednisolone ⁸⁰	Italy	RCT(soc)	173	HOSP	SEV	Mehtylprednisolone group had fewer deaths (6 vs. 21, adjusted HR=0.29; 95% CI: 0.12-0.73) and more days off invasive mechanical ventilation (24.0 ±9.0 vs. 17.5± 12.8; p=0.001)
Anakinra ¹⁰⁴	Greece	OBS(vs soc)	130	HOSP	SEV	Incidence of severe respiratory failure 22% anakinra patients vs 59% soc., 30 day mortality 11.5% anakinra vs 22.3% soc).
TCZ ¹¹¹	U.S.A.	RCTPLAC (TCZvs soc)	803	HOSP	SEV,CRIT	Mortality 28% tocilizumab vs 36% control
TCZ ¹¹²	U.K.	RCTPLAC (TCZvs soc)	4116	HOSP	SEV,CRIT	Mortality 29% tocilizumab vs 33% control

Colchicine ¹¹⁵	Greece	RCT(colchicine vs soc)	105	HOSP	MOD,SEV	The clinical primary end point rate was 14.0% in the control group (7 of 50 patients) and 1.8% in the colchicine group (1 of 55 patients) (odds ratio, 0.11; 95%CI, 0.01-0.96; P = .02).
Colchicine ¹¹⁶	Canada	RCT(colchicine vs soc)	4159	OUTPAT	MILD,MOD	The clinical primary end point rate was 6% in the control group and 4% in the colchicine group (odds ratio, 0.75; 95% CI, 0.57 to 0.99; P=0.04)
Mesenchymal Stem Cells ¹²⁰	China	RCTPLAC	101	HOSP	SEV WITH LUNG DAMAGE	Lesion volume decreased compared to placebo (p<0.05)

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Vaccine	Commercial sponsor	Country	Vaccination Schedule	Vaccine Technology	Reported Effectiveness	Authorization for Use
BNT162b2 (122)	Pfizer/Biontech	U.S.A.	2 shots	mRNA	95%	U.S.A., European Union, U.K., Israel
mRNA1273 (123)	Moderna	U.S.A.	2 shots	mRNA	<u>94%</u>	<u>U.S.A, U.K. E.U</u>
Sputnik 5 (124)	Gamelaya Institute	Russia	2 shots	Adenovirus vector	91%	Russia
CHadOx1 (125)	Astra Zeneca	U.K.	2 shots	Adenovirus vector	70%	U.K., E.U.
Ad5-nCoV (126)	Cansino	China	One shot	Adenovirus vector	66%	China
Ad26.COV2.S (127)	Janssen	U.S.A.	One shot	Adenovirus vector	72%	South Africa
NVX-CoV2373 (128)	Novavax	U.S.A.	Two shots	Recombinant spike protein	89%	-----
BBIP B-CorV(129)	Sinopharm	China	Two shots	Alum precipitated inactivated virus	86%	China, Bahrain, United Arab Emirates, Egypt
Coronavac (130)	Sinovac	China	Two shots	Inactivated virus	50%	China, Brazil
Covaxin (131)	Bharat Biotech	India	2 shots	Inactivated virus	-----	India

TABLE 2: SARSCov2 VACCINES EITHER CURRENTLY OR SOON TO BE AUTHORIZED

Time Period	Pre-Exposure Period	Incubation Period (post exposure)	Viral Replication Period	Inflammatory Period	Hyperinflammatory Period	Tail Phase
Phase Specific Treatment -->	ANTIVIRAL	ANTIVIRAL	ANTIVIRAL	ANTI-INFLAMMATORY, ANTICOAGULANT	ANTI-INFLAMMATORY, ANTICOAGULANT, ANTIBACTERIAL	ANTI-INFLAMMATORY, ANTICOAGULANT
Administration			Remdesivir	Glucocorticoid	Glucocorticoid	Glucocorticoid
INTRAVENOUS		Monoclonal Antibodies	Monoclonal Antibodies Interferon alpha, beta, gamma Convalescent Plasma	Anti-cytokine agents Heparin	Anti-cytokine agents Heparin	Anti-cytokine agents Heparin
INJECTION	VACCINES	Interferon alpha, beta, gamma			Antibiotics Mesenchymal Stem Cells	Antibiotics Mesenchymal Stem Cells
ORAL	Zinc Ivermectin	Favipiravir Zinc Ivermectin	Favipiravir Zinc Ivermectin	Ivermectin Colchicine Glucocorticoid	Ivermectin Conchicine	
INHALATION		Interferon beta	budesonide for mild infections Interferon beta	Budesonide		
INHALATION INHALATION						

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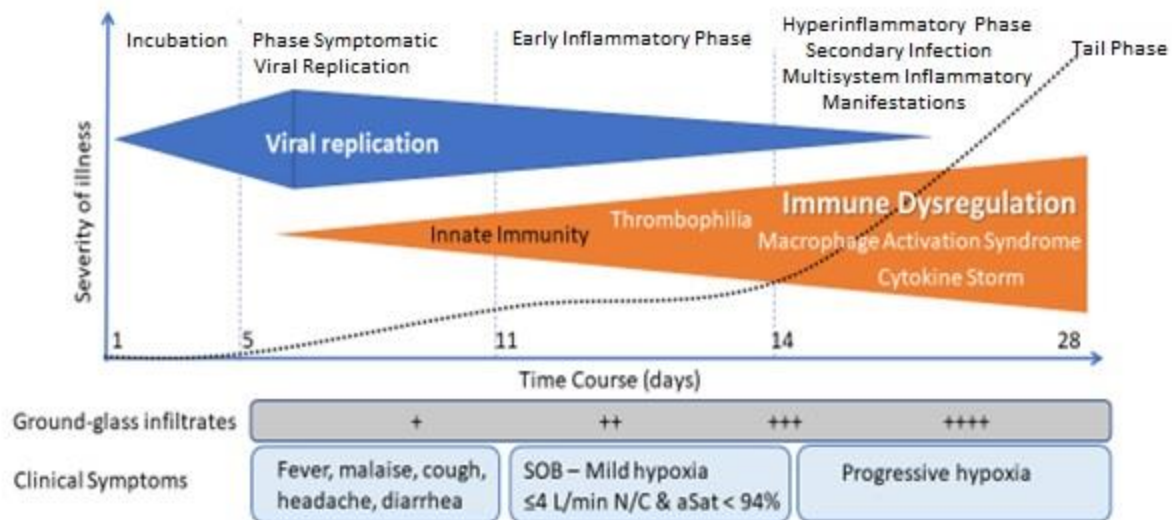


Fig 1

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