April 4th, 2020

COVID-19 PANDEMIC: THE NUMBERS (as of 4/4/20, 8pm EST)

- **World:[1] 1,192,028 confirmed cases. Total deaths: 64,316. Total recovered: 245,981**
- **US:[1] 305,820 confirmed cases. Total deaths: 8291 (CFR 2.91%); Total recovered: 14,520**
- **Michigan:[2] 14,225 confirmed cases. Total deaths: 540 (CFR 3.79%). New cases in the last 24h: 1,481. New deaths in the last 24h: 61**
- **Peak resource use and peak deaths in the US is projected on April 15, 2020. Visit *covid19.healthdata.org* for prediction on deaths, need for ICU bed and ventilators.**[3]
- **Evolution of the pandemic:[4] The US remains in the acceleration phase of the pandemic with exponential growth of confirmed cases and deaths. The number of deaths increased 2.8 times in the past 4 days.**

BEST EXPOSURE PREVENTION PRACTICES

- CoV-2 was detected in aerosols for up to 3 hours, 4 hours on copper, 24 hours on cardboard and 2-3 days on plastic and stainless steel.[5]
- Continue to perform basic hygiene and apply droplet precautions (cover cough, wash hands for at least 20 sec, do not touch face/eyes, disinfect the surroundings with 60-95% alcohol, social distancing of at least 6 feet).[6]
- Before entering in contact with suspected or known COVID-19 infected patients, familiarize yourself with the donning and doffing procedures. Proper PPE includes: respirator or facemask (N95, P100; or PAPR), gloves, gown, and eye protection (e.g., reusable goggles or disposable face shield).[6]
- **There is an ongoing debate around the recommendation of wearing a facemask by the general asymptomatic public. Antagonists argue the following points: 1) scarcity of PPE, 2) false sense of protection and relaxation of social distancing measures, 3) lack of solid scientific data regarding efficacy.**[7]
- A case of possible vertical mother-to-fetus transmission was reported in China. Infection was confirmed in the symptomatic mother by PCRs. 23 days later, she was delivered by C-section. Two hours post-delivery, the baby had positive IgM and IgG titers but negative PCRs. Importantly, IgM does not cross the placenta so this was not transmitted immunity.[8]

DISCOVERIES IN SARS-COV-2 PATHOGENICITY

- Similarly to CoV (SARS epidemic), CoV-2 uses the ACE2 receptor for entry into cells via its spike protein.
- ACE2 is expressed in human airway epithelia, lung parenchyma, vascular endothelium, kidney cells, and small intestine cells. Also expressed in some

neuronal populations - cardiorespiratory centers in the brainstem, raphe nucleus, hypothalamus and motor cortex.

- CoV-2, like CoV, may gain access to the CNS via the olfactory receptor neurons (may explain anosmia common in these infections), spreading to the olfactory bulbs and then to other parts of the brain via trans-synaptic transfer (e.g., thalamus, hypothalamus, brainstem). The medullary cardiorespiratory centers appear to be highly infected, which may play a role in central respiratory failure in these patients.[9] Coronaviruses infect both neurons and glia. Neuroinfection, along with the systemic inflammatory response, leads to a breakdown of the blood-brain barrier and contributes to the activation of microglia and astroglia.[10]
- Mild disease in 81% of cases, severe disease (respiratory failure, ARDS, requiring oxygen +/- ventilatory support) in 14% cases, and critical disease (shock, MOSD, MOSF) in 5% cases.[11]
- Cytokine storm: A hallmark of severe CoV-2 disease is the development of a potent "cytokine storm". This is not unique to COVID-19 and has been described in MERS and SARS, both of which are closely-related coronaviruses. IL-6, a proinflammatory cytokine, is central in this process.
- Is there a CNS control of the immune system? The answer is yes. The autonomic system is an important modulator of the immune system. Dysregulating the autonomic system stimulates the inflammatory response of both innate and adaptive immune systems. There is strong evidence to support the direct sympathetic innervation of immune organs such as the spleen. Sympathetic activation causes splenic cytokine production (IL-1β, IL-2, IL-5, IL-16 and TGFβ1), whereas vagal nerve stimulation quiesces the immune response.[12] One wonders whether blocking the sympathetic outflow may halt or prevent the development of this exuberant inflammatory response.
- Important clinical features of the disease:
    - A minority of patients will develop hypoxia and deteriorate very quickly, going from oxygen supplementation by oxygen to high flow nasal cannula to intubation within a few hours.
    - Initial CT chest made the right diagnosis in 96.1% of cases in one series.[13] Most common findings were ground glass opacities, consolidations, vascular enlargement, interlobular septal thickening, and air bronchogram sign.
    - 2-10% of COVID-19 presented with GI symptoms, such as diarrhea, abdominal pain, and vomiting in 2% to 10% of cases.[14]
    - Elevation of several serum inflammatory markers- IL-6, ferritin, LDH, CRP, D-dimer, and triglycerides, indicating the presence of a potent cytokine storm and secondary hemophagocytic lymphohistiocytosis.
    - Neutrophil-to-lymphocyte ratio (NLR) of ≥3.13 predicts disease progression
    - Lymphopenia and thrombocytopenia
    - Myocardial injury: in one study of 416 patients admitted with COVID-19, 20% had evidence of cardiac injury as defined as elevated troponin.[15] Patients with underlying cardiovascular disease and elevated troponin were found to have the highest mortality.[16] Autopsies have revealed infiltration of myocardium by interstitial mononuclear inflammatory cells, evidencing a myocarditis.[17] ARDS, myocarditis, sympathetic hyperactivity, hypercoagulable state, and the cytokine storm all contribute to direct myocardial injury, mismatch myocardial oxygen supply/demand and plaque rupture, leading to increase in the risk of myocardial infarction, arrhythmias and heart failure.

UPDATES ON SARS-COV2 TESTING

- Per the CDC,[18] priority for testing goes to 1) hospitalized patients with signs/symptoms compatible with COVID-19, 2) vulnerable patient populations (older adults, immunocompromised state, chronic medical conditions (e.g., HTN, DM, CKD, lung, heart disease), 3) HCP who had close contact with a COVID19 suspect or positive patient within 14 days of symptom onset (*close contact= being within 6 feet for a prolonged period of time or direct contact with secretions of COVID-19 case, while not using recommended PPE*).
- **Methods for sample collection:** nasopharyngeal (NP) swab, tracheal aspirate/BAL (intubated patients, but increases exposure risk), sputum (induction not recommended).[19] At this point, HFH only tests via NP swabs.
- **rRT-PCR:** Almost all diagnostic testing for CoV-2 is done using rRT-PCR. In the US, testing is performed by the CDC, hospital and public health laboratories. Turnaround time varies, continues to take up to 4-5 days due to the low availability of reagents/batching/prioritization. On March 21st, the

FDA approved a point-of-care (POC) test by Cepheid with a turnaround time of 45 minutes, which should be commercially available at the end of March.[20] *Abbott* has been granted emergency use authorization by the FDA for its POC test that will detect CoV-2 in “as little as 5 min” and “negative results in 13 min”, making it the fastest POC test for the virus at this stage. The company claims they will produce 5 million tests per month.[21]

- **Serology: tests that detect IgM and IgG antibodies and provide information about the immune response of the host to the virus antigens. IgM antibodies appear a couple of days after infection whereas IgG antibodies are produced in delayed fashion. IgM positivity indicates a recent or current infection, whereas IgG positivity indicates recent or previous infection (or vaccinated status). Negative IgM and IgG antibodies does not guarantee that the patient is not infected as they could still be in the early phase before seroconversion. Serology offers faster results, but is less accurate than PCR due to potential cross-reactivity with other infections. NEW! On April 2nd, the FDA approved antibody testing by Cellex which can provide results in 15 min.[22]**
- **Immunoassays:** monoclonal antibody tests that detect viral antigens such as the nucleocapsid (N) protein, spike protein of the virus or multiple antigens. Faster results (20-60 min) but longer to develop and less accurate than PCR.[23]
- FDA has not approved at-home test kits and warns the public against the marketing of fraudulent COVID-19 test kits.[24]
- To date, there is no reliable data on the false positive and false negative rates of the various testing methods.
- A South Korea hospital launched a phone-booth-style CoV-2 testing- a row of 4 negative-pressure, single-occupancy plastic booths under a tent outside the hospital. The patient gets inside the booth and a consultation takes place with a HCP who, from outside of the booth, can obtain samples via arm-length rubber gloves built into the plastic panel. Process takes about 7 min to complete and the booth is easy to disinfect.[25]
- *Kinsa Health* smart thermometers are able to track fever across the US via a web-based app. Although it cannot discriminate fever from different etiologies, it can identify new clusters of fever, track fever curve and gauge the response to implemented measures such as social distancing. It was first created to track the spread of the flu and a million thermometers have been sold since the inception of the company.[26]

SARS-COV2 NEUROLOGICAL SYNDROMES

- **Symptomatology:**
    - CNS symptoms: In one study, 24.8% of cases (dizziness and headache).[27] In another study of 221 patients at a single center in China, 5% cases had AIS, 0.5% CVST and 0.5% ICH.[28] Ischemic and hemorrhagic strokes, impaired consciousness and muscle injury were more prevalent in patients with more severe respiratory disease. **A case series from Careggi Hospital in Florence, Italy, mentions that out of 19 cases with LVO acute ischemic strokes, 10 had suspicious respiratory symptoms and 4 (21%) were found to be positive for SARS-CoV2. Out of 6 cases of aneurysmal SAH, 1 (16%) was positive for SARS-CoV2.[29]**
    - Henry Ford Hospital’s Radiology Department published the first reported case of acute hemorrhagic necrotizing encephalopathy in a COVID-19 patient, a 58 year-old female who presented with altered mental status in addition to URI symptoms. Virology studies were negative for influenza and other viruses. CSF could not be tested for CoV-2. Non-contrast head CT revealed bithalamic hypoattenuating lesions while brain MRI revealed T2 FLAIR hyperintense signal with internal hemorrhage in the bilateral thalami and medial temporal lobes. Vessels were patent on CT angiogram and CT venogram.[30]
    - PNS symptoms: In one study, 8.9% of patients (hypogeusia, hyposmia, neuralgia).[27] Myalgias were found in 10.7% of cases. It remains to be seen whether we will encounter cases of motor-predominant peripheral neuropathy, myopathy and rhabdomyolysis, as we saw during the SARS pandemic in 2002. So far, no reported movement disorders as a result of the infection. ***Lancet Neurology* published the first known case of Guillain-Barre syndrome (GBS) in a COVID-19 patient. A 61 year-old female from Wuhan presented with ascending bilateral lower extremity weakness without initial fever, respiratory or GI symptoms. LP showed elevated protein and normal cells. EMG showed absent F-waves. All these findings are consistent with early findings of GBS.**

Patient received an IVIG course. 8 days later, she developed a fever and a dry cough, and tested positive for CoV-2. She was treated with arbidol, lopinavir, and ritonavir. She was discharged on day 30 with full strength and return of reflexes.[31]

- **Laboratory findings:** Patients with CNS symptoms were more likely to have lower lymphocyte and platelet counts, and elevated BUN levels. There were no characteristic laboratory findings in patients with PNS symptoms. Patients with muscle injury had higher neutrophil counts, lower lymphocyte counts and higher CRP levels and D-dimer levels as well as evidence of multiorgan system failure.[27]
- No specific neuroimaging or electrophysiological characteristics described in COVID-19 patients yet.
- **Pediatric population: Children are not completely immune to infection, but infection is usually less severe. 5.9% of children with COVID confirmed or suspected infection had severe to critical presentation in one retrospective study from China including 731 children with confirmed and 1412 suspected COVID infections. Infants in particular were more likely to have severe symptoms than older children.**

CARING FOR THE NEUROLOGICAL PATIENTS INFECTED WITH COVID-19

- **Stroke:**
  - Cardiovascular comorbidities are prevalent in COVID-19 patients, similarly to SARS and MERS. These comorbidities increase the risk of mortality and morbidity from the infection.
  - With ACE2 serving as the portal for infection, the role of ACE inhibitors (ACEi) or angiotensin receptor blockers (ARB) requires further investigation. The American Heart Association recommends at this point continuing ACEi and ARB medications if clinically indicated.[32] In a study of 187 patients hospitalized with COVID-19, use of ACEi and ARB were not associated with increased mortality, even in the group of patients with higher cardiac injury.[33]
  - The extent to which a community outbreak of infection like COVID-19 stresses other parts of the healthcare system is largely unknown. The question is whether our time metrics for tPA and thrombectomy will be affected by the suspected or confirmed infectious status of the patient. A study comparing timeline in STEMI patients at a hospital in Hong Kong showed numerically longer median times in all components when compared with historical data from the prior year. The largest time difference was in the time from symptom onset to first medical contact.[34]
  - COVID-19 pandemic poses a unique challenge in achieving timely treatment of acute stroke patients with thrombolytics and thrombectomy. It remains to be seen what impact the pandemic will have on adherence to time metrics and quality measures.
  - Similarly, with the current strain imposed by the pandemic on staffing beds and other resources, it will be important to study the impact this will have on triaging and disposition of patients from the ED.
  - The Society of neuro-interventional surgeons released a guideline statement recommending screening for fever and respiratory symptoms in all patients undergoing mechanical thrombectomy and having a low threshold for intubation prior to transport to the angiography suite.
  - **AHA/ AHA stroke council leadership published temporary emergency guidance of stroke centers in the US. This document highlighted the challenges which included usage of PPE and availability of hospital beds, healthcare personnel. This guidance recommends treating stroke patients appropriately, encouraging conserving PPE and using telemedicine services (televideo or telephone). Most importantly, it highlighted the importance of teamwork for delivery of care.[35]**
  - **For acute management of stroke patients, a concept of "protected stroke code" PCS is suggested. A pre-code screening based on information from pre-notification (infection screen, close contact with infectious person and travel history) and patients' history and examination (no or positive infection screen, patient unable to communicate or depressed level of consciousness) determines if a PCS is required or not. The cornerstone of PCS is appropriate use of PPE. All PCS are considered to be droplet and contact precautions. This requires a full-sleeved gown, surgical mask, eye protection (face shield and/or goggles), and gloves. Head covering is currently optional in some**

protocols. Precautions are upgraded to include airborne precautions, using N95 respirator when there is an aerosolizing procedure. A surgical mask should be placed on non-intubated patients all the time.[36]

- Alexandria University in Egypt implemented a protocol of obtaining CT chest with CT protocol in stroke patients that are suspected COVID 19 positive.
- Asian tobacco smokers were found to have significantly higher ACE2 expression in their lungs than their non-smoker counterparts. More males than females smoke in China and males were more likely to develop severe and critical COVID. However, this data does not seem to be reproduced in Caucasians. More data is needed to see whether chronic smoking is an independent risk factor for more severe CoV-2 infection.[37]

- **Epilepsy:**
  - Animal and human studies have demonstrated the neuro-invasive potential of SARS-COV as well as coronavirus strains including HCoV-OC43 with preferential involvement of the thalamus and brainstem.[38-40] So far, there has been one case report of acute hemorrhagic encephalitis from Henry Ford. This patient did not have any reported seizures[30]
  - Although there is no evidence pointing to an increased seizure susceptibility in patients with epilepsy who are infected with CoV-2, seizure threshold may be lowered as it usually is with viral febrile illnesses. The CDC has therefore included epilepsy among conditions associated with increased risk for serious COVID-19 infection.[41] Patients with epilepsy syndromes may be at increased risk for breakthrough seizures in the setting of COVID-19 infection.[42]
  - The American Epilepsy Society released a statement recommending the prescriptions be refilled 1 week in advance for 30-day refills and 2 weeks in advance for 90-day refills.[43] CMS has made healthcare plans more flexible which included removing prior authorization requirements, waiving prescription refill limits, allowing mail delivery of prescription medications and supporting tele visits.[44]
  - Prescribers are advised to review drug interaction profiles of medications currently used for treatment of COVID-19 such as hydroxychloroquine with seizure medications and use caution when prescribing along with hepatically metabolized or hepatotoxic anti-seizure medications (ASMs).[45] A list of the known drug interactions between ASMs and drugs used for COVID-19 treatment is available on the ILAE website as a useful reference for prescribing clinicians and clinical pharmacists.[46]

- **Multiple sclerosis and demyelinating diseases:**
  - It is important here to distinguish between immunosuppressive and immunomodulatory DMTs. While it is usually ok to continue immunomodulatory DMTs including IFNs, glatiramer acetate, teriflunomide and dimethyl fumarate, patients on cell depleting therapies including alemtuzumab, ocrelizumab and cladribine are at increased risk for severe infections including COVID-19 infections. National MS Society recommends that the decision of continuing or discontinuing DMTs be taken on an individualized basis, taking into account the higher risk of infections associated with cell depleting agents and the higher risk of worsening disability among medications including natalizumab and fingolimod.[47]

- **MG and LEMS**
  - There is no available data yet on the COVID-19 infection risk in MG patients. However, many patients with MG are already on various immunosuppressive/immunomodulatory therapies and may also have underlying respiratory muscle weakness which theoretically places them at increased risk for severe COVID-19 infections.
  - A group of International MG experts formed MG/COVID-19 work group which recently released a guideline statement which recommends continuing existing medications for patients who are already on them.[48]
  - They also stated that symptomatic therapies such as pyridostigmine and 3,4 diaminopyridine do not increase the risk for infection and thus should be continued as well.
  - As for patients receiving infusion therapies requiring transport to hospitals or infusion centers, the decision on whether to continue the infusion therapy or not should be individualized

based on the regional incidence of COVID-19 and the risk vs benefit of treatment for the individual patient.
  - They also state that there is no evidence of increased risk for COVID infection with eculizumab therapy. There is also no evidence of any increased risk of COVID infection from PLEX or IVIG therapy, but the risk derived from visits to healthcare facilities should be considered.
  - The decision to switch patients to an alternative immunosuppressive therapy should take into account the presence of other comorbid conditions and the risk of viral infection should be balanced against the risk of developing MG crisis when discussing initiating Rituximab therapy. Blood draws should be done judiciously in order to avoid unnecessary hospital visits and patients on immunosuppressive therapies are advised to practice extra cautious social isolation[48].

- **Movement disorders**
  - Movement disorders as a complication COVID-19: none reported in the literature.
  - **Parkinson disease:** Patients admitted to the hospital or ICU must continue with their outpatient regimen of medications. If intubated carbidopa/levodopa must be crushed and given via NG tube.
  - **Huntington disease**: Patients admitted to the hospital or ICU must continue with their outpatient regimen of medications. If intubated contact movement disorders physician to determine if medication (or alternative) should be continued inpatient.
  - **Essential tremor**: Those patients treated with primidone may potentially have a drug-interaction with Remdesivir (there are no known drug interactions for this medication reported) Primidone is a strong CYP3A4 inducer and a week CYP1A2, CYP2A6, CYP2B6 inducer that is relatively contraindicated with several other antiviral therapies. If pharmacist raises concerns for drug-drug interaction it is reasonable to hold primidone for the duration of antiviral therapy
  - **Other:** General recommendations are to continue all outpatient regimens as prescribed.

THERAPIES: YES, MAYBE, NO

- **Therapies targeting viral replication:**
  - **Lopinavir/ritonavir (LPV/RTV):** not recommended; not effective when tested in COVID-19 pneumonia (did not change mortality, discharge, length of stay).[49] No mention of severe neurologic sequelae in any of these patients
  - **Remdesivir ("GS5734"):** prodrug of adenosine analog, promising in cell and animal models against CoV, crosses BBB in rhesus monkeys [tested in Ebola - also neuro-invasive]; in phase 2 and 3 human trials,[50-53] except for children and pregnant women with severe disease. Remdisivir is no longer available for compassionate use but should be available for expanded access use soon.
  - **Ribavirin**: guanosine analogue, usually combined with recombinant interferon. Not effective in MERS.[54] Looks good in vitro with poor in vivo activity (hard to get high enough serum levels in humans/limited by toxicity).
  - **Favipiravir:** A viral RNA polymerase inhibitor used to treat influenza in Japan.[55] A non-randomized open label trial evaluated its use in SARS-COV2 infection in addition to inhaled interferon-α compared to LPV/RTV therapy. 35 patients received favipiravir compared to 45 patients receiving LPV/RTV. Favipiravir therapy was associated with shorter viral clearance time (median 4 days (IQR 2.5-9) than LPV/RTV (median 11 days (IQR 8-13) ($P<0.001$). In addition, 91.4% of patients receiving favipiravir demonstrated chest CT improvement compared to 62.2% of patients receiving LPV/RTV ($P=0.004$).[56]
  - **Oseltamivir:** A drug commonly used to treat influenza infections; it works by blocking viral neuraminidase enzyme, therefore preventing shedding of viral particles in the respiratory tract. Oseltamivir is is being studies in clinical trials among combination therapies involving chloroquine and famipiravir .[57-59]
  - **Arbidol (also known as umifenovir) :** Approved in Russia and China for the treatment of influenza virus infections. Arbidol's antiviral mechanism against influenza A and B involves viral fusion inhibition with the targeted membrane, which blocks virus entry into the cell. The drug is currently being investigated in 4 clinical trials in China.[60-63]
  - **Hydroxychloroquine (HCQ) +/- azithromycin (AZT):** In vitro data has demonstrated efficacy of

chloroquine and hydroxychloroquine in suppressing SARS-CoV2.[64] Based on this data, Gautret et al. studied the antiviral activity in a non-randomized trial that included 20 patients receiving HCQ 200 mg q8h compared to 16 non-matched controls receiving standard of care.[60] Viral eradication was assessed via repeat PRC nasopharyngeal swab on day 6. Viral eradication was achieved in 14/20 (70%) of patients in the treatment arm compared to 2/16 (12.5%) control patients. 6/6 (100%) patients receiving AZT in addition to HCQ achieved viral eradication. However, this study was criticized by the lack of randomization and lack of blinding as well as the exclusion of three patients who were transferred to ICU and one patient who died which could have altered the outcome, in addition use of a different PCR cycle threshold for defining positive test than the one adapted by CDC.[65] **The same group from Marseille recently reported updated results from a larger cohort including 80 patients admitted to the ID ward, who received daily HCQ+AZT regimen (HCQ= 200 mg t.i.d. for 10 days; AZT= 500 mg on day 1, followed by 250 mg qd for 4 days). 65/80 (81.3%) achieved a favorable outcome. Only 15% required oxygen supplementation. 3 patients required ICU transfer, 2 of which managed to be stepped down back to the ward. One patient who was not transferred to the ICU died. 83 % of PCR results turned negative on day 7 and 93% turned negative on day 8 of treatment. However, comparison with a control group was lacking in this trial. Surprisingly, only 15% of included patients had fever and 4 patients were asymptomatic carriers.[66] The inclusion of these patients in this trial, in addition to the lack of a control group, limit the validity of these results.** A more recent pilot trial from another French group failed to demonstrate clinical benefit or evidence of viral suppression in 10 patients receiving HCQ+AZT therapy[67]. Another pilot trial from China randomized 30 patients to receiving HCQ therapy vs conventional treatment only. HCQ was not superior to standard therapy in achieving viral suppression.[68] A larger clinical trial from China randomized 60 patients to receiving HCQ vs placebo and demonstrated significant shortening of body temperature recovery and cough remission times in HCQ arm. In addition, 80.6% of patients in the HCQ arm demonstrated radiologic improvement of pneumonia compared to 54.8% in the control arm.[69] Multiple larger clinical trials are currently underway assessing the role of hydroxychloroquine +/- azithromycin treatment of COVID-19 infections of varying severities as well as for pre-exposure and post-exposure prophylaxis of healthcare workers.[70-74]

- **Teicoplanin:** A glycopeptide antibiotic used to treat gram positive infections, active *in vitro* against SARS-CoV2 & other viruses, prevents release of genomic viral RNA and stops viral replication at doses lower than reached in human blood. No human trials yet.[75]
- **Ivermectin: Antiparasitic medication with reported in-vitro activity against multiple RNA viruses including Influenza[76] and West Nile viruses[77]. The mechanism likely involves blocking entry of viral proteins into the cellular nuclei.[77] A recent study demonstrated in-vitro viral suppression within 48 hours of administration.[78] No human trials yet.**
- Baricitinib: JAK1 and JAK2 inhibitor approved for treatment of rheumatoid arthritis. Artificial intelligence-based algorithms identified this medication as a potential treatment for COVID-19 infections via inhibition of clarithrin-mediated endocystosis and subsequently viral entry into cells.[79] One clinical trial is currently underway in Italy investigating its use.[80]
- Soluble ACE2 molecules: May play a role in competitively blocking membrane ACE2 viral bindings sites, and subsequently blocking viral entry and replication.[81] No clinical trials yet.

- **Immunosuppressive/modulatory therapies**
  - **Methylprednisolone: The use of corticosteroids in the management of ARDS of various etiologies has been evaluated in multiple studies with mixed results.[82-85] Two studies demonstrated the association of corticosteroid administration with improvement in respiratory and cardiovascular function in patients with ARDS and one study demonstrated that early introduction of IV steroids was associated shortened ICU stay and reduced ICU mortality in patients with ARDS as well.[85,86] In addition,**

the use of corticosteroids in patients with acute hypoxic respiratory failure related to COVID infection may ameliorate the development of cytokine storm which is thought to be the main driver of morbidity and mortality. Current Henry Ford protocol recommends a 3-7-day course of IV Steroids in all patients with hypoxic respiratory failure related to COVID infection. A clinical trial is currently underway in Italy evaluating the role of IV methylprednisolone in management of ARDS in the setting of COVID-19 infection.[86]

- **Tocilizumab:** humanized monoclonal antibody targeting IL6 receptors. A preprint non peer-reviewed case series from China demonstrated clinical improvement in 20/20 and radiologic improvement in 19/20 (90.5%) patients with severe to critical COVID-19 infection.[87] There are two currently ongoing clinical trials in China further investigating this drug.[88]
- **Sarilumab:** Another monoclonal antibody targeting IL6 receptors. A clinical trial evaluating its use is currently enrolling patients in New York (NCT04315298).[89]
- **Eculizumab:** Humanized monoclonal antibody targeting complement protein C5, thus preventing the formation of membrane attack complex (MAC). A clinical trial sponsored by Hudson Medical is currently underway investigating its use in COVID-19 infections of various severities.[90]
- **Anakinra:** recombinant form of IL1 receptor antagonist. This drug is proposed to ameliorate the cytokine storm. There are no active trials at this point investigating this particular drug, but one clinical trial is planned in Italy (sponsored by SOBI).[91]
- **Emapalumab:** monoclonal antibody targeting IFN-γ, a proinflammatory cytokine with a central role in various inflammatory processes. No clinical trials are currently underway evaluating this drug, but one trial is planned in Italy.[91]
- **Bevacizumab:** recombinant humanized monoclonal antibody blocking angiogenesis by targeting VEGF receptors. Based on promising data from ARDS trials, a clinical trial was initiated in China to assess its utility in management of severe or critical COVID-19 pneumonia.[92]
- **Convalescent plasma:** Convalescent plasma from recovering patients has been used in SARS-COV with reported success. One case series from China demonstrated clinical improvement and viral suppression in 5 patients with COVID-19 infection and ARDS. ARDS resolved in 4/5 patients and three patients were weaned from mechanical ventilation and were successfully discharged from the hospital.[93] Based on these data and the state of the current public health crisis, the FDA allowed access to this treatment through single patient emergency IND.[94] One clinical trial evaluating its role in COVID-19 infection (NCT04292340) is currently underway in China as well.[95]
- **Neutralizing antibodies:** Neutralizing antibodies can recognize a wide variety of glycoproteins (GPs) in virus surfaces or the protein shell of a non-enveloped virus. A trial utilizing human immunoglobulin in patients with pneumonia caused by 2019-nCoV who recovered is currently underway. [96]
- **IVIG:** Cao et al. reported improvement in 3 cases with severe COVID-19 infection from China[94]. Trials are currently underway to further assess its utility.[97,98]
- **Fingolimod:** A sphingosine-1-phosphate receptor regulator (FTY720) with an effective immunology modulator that is used in multiple sclerosis. Study NCT04280588 aims to determine the efficacy of fingolimod for COVID-19. Currently Phase 2.[99]
- **Thalidomide:** has an anti-inflammatory action due to its ability to speed up the degradation of messenger RNA in blood cells and thus reduce tumor necrosis factor-α (TNFα). Furthermore, thalidomide can increase the secretion of interleukins, such as IL-12, and activate natural killer cells. Currently phase 2.[100,101]
- **International Clinical Trials**: There are two large international clinical trials that are currently underway:
  - **Solidarity trial:** A WHO-funded trial evaluating various therapies including remdesivir, chloroquine/hydroxychloroquine, LPV/RTV, and IFN-β.[102]
  - **Discovery trial:** A European trial similar to Solidarity trial except for exclusion of chloroquine.[102]

- **Vaccines**
  - COVID Vaccines Phase 1 clinical trials: To date, there are no vaccines for COVID-19. The

projected time for the development of a commercially available vaccine is 12-18 months. We will mention the phase 1 clinical trials here.

- mRNA-1273:[103,104] This investigational vaccine was developed by NIAID scientists and *Moderna* (biotechnological company) using a mRNA that undergoes translation into the synthesis of the viral spike protein. As a result, the immune system produces antibodies against the spike protein attacking the virus prior to it entering the host cells.
- Ad5-nCoV:[103,105] Developed by CanSino Biologics (China), this vaccine is a genetically engineered CoV-2 virus that incorporates the adenovirus type 5 vector to express the viral spike protein, while having lost its virulence.
- ChAdOx1:[103,106] Similarly to the Ad5-nCoV vaccine, this vaccine instead incorporates the chimpanzee adenovirus vaccine vector ChAdOx1. It is being developed by the UK company, Vaccitech (University of Oxford)
- **BCG vaccine: A live attenuated vaccine used in certain countries to protect against the development of pulmonary tuberculosis. BCG vaccine administration may enhance the development of innate immune response which targets various infections, and multiple studies have demonstrated a lower risk for respiratory tract infections and lower infantile mortality among those receiving BCG vaccine.[107-109] In addition, most countries with large number of fatalities including USA, Italy and Spain either do not routinely administer BCG vaccinate or only had BCG vaccines introduced in 1980s which is the case with Iran, leaving many elderly unvaccinated patients susceptible to severe infections based on this theory.[110] An Australian clinical trial is currently underway investigating the role of BCG administration in prevention of COVID-19 infections among healthcare workers.[111]**

References

1. Dong et al, An Interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. Published February 19, 2020. doi:10.1016/S1473-3099(20)30120-1.
2. Coronavirus. *Michigan.gov*. Published online March 24, 2020. Available www.Michigan.gov/coronavirus
3. COVID-19 projections. *IHME.* Published online April 1, 2020. http://covid19.healthdata.org/
4. Coronavirus Disease (COVID-19) - statistics and research. *Our World in Data*. Published online March 24, 2020. ourworldindata.org/coronavirus
5. N van Doremalen, *et al*. Aerosol and surface stability of HCoV-19 (SARS-CoV-2) compared to SARS-CoV-1. *NEJM*. Published online March 17, 2020. doi:10.1056/NEJMc2004973
6. Infection Control: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Centers for Disease Control and Prevention*, Published online March 19, 2020. www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html
7. Brosseau L, *et al*. Commentary: masks-for-all for COVID-19 not based on sound data. *Center for Infectious Disease Research and Policy*. Published online April 1, 2020. https://www.cidrap.umn.edu/news-perspective/2020/04/commentary-masks-all-covid-19-not-based-sound-data
8. Dong L, *et al*. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. *JAMA*. Published online March 26, 2020. doi:10.1001/jama.2020.4621.
9. Li, Y-C, Bai, W-Z, Hashikawa, T. The neuroinvasive potential of SARS‐CoV2 may play a role in the respiratory failure of COVID‐19 patients. *J Med Virol*. 2020;1-4.
10. Steardo L, *et al*. Neuroinfection may potentially contribute to pathophysiology and clinical manifestations of COVID-19. *Acta Physiol (Oxf).* Published online Mar 29, 2020. https://doi: 10.1111/apha.13473
11. 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.* Published online February 24, 2020. doi:10.1001/jama.2020.2648.
12. Abboud F, *et al*.Autonomic neural regulation of the immune system: implications for hypertension and cardiovascular disease.*Hypertension*. 2012 Apr;59(4):755-62.
13. Li Y, *et al.* Coronavirus disease 2019 (COVID-19): role of chest CT in diagnosis and management. *AJR Am J Roentgenol*. Published online Mar 4, 2020. https://doi: 10.2214/AJR.20.22954.
14. YeoC, et al. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? *Lancet Gastroenterol Hepatol*. 2020;5(4):335-337.
15. Shi S, *et al*. Cardiac injury in patients with coronavirus disease 2019. *JAMA Cardiol*. Published online March 25, 2020. doi:10. 1001/jamacardio.2020.0950
16. Guo T, *et al*. Association of cardiovascular disease and myocardial injury with outcomes of patients hospitalized with 2019-coronavirus disease (COVID-19). *JAMA Cardiol*.

Published online March 27, 2020. doi:10.1001/jamacardio.2020.1017
17. Xu Z, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020:S2213-2600(20)30076-X.
18. Evaluating and testing persons for Coronavirus Disease 2019 (COVID-19). *Centers for Disease Control and Prevention*, Published online March 9, 2020 www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html
19. Interim guidelines for collecting, handling, and testing clinical specimens from persons for Coronavirus Disease 2019 (COVID-19). *Centers for Disease Control and Prevention*, Published online March 19, 2020. www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html
20. FDA approves first rapid COVID-19 test. *NPR*. Published online March 21, 2020. www.npr.org/sections/coronavirus-live-updates/2020/03/21/819629909/fda-approves-first-rapid-covid-19-test
21. Detect COVID-19 in as little as 5 minutes. *Abbott*. Published online March 27, 2020. https://www.abbott.com/corpnewsroom/product-and-innovation/detect-covid-19-in-as-little-as-5-minutes.html
22. Mandavilli A. FDA approves first coronavirus antibody test in U.S. *The New York Times*. Published online April 2, 2020. https://www.nytimes.com/2020/04/02/health/coronavirus-antibody-test.html
23. Sheridan C. Fast, portable tests come online to curb coronavirus pandemic. *Nat Biotechnol*. Published online March 23, 2020. https://www.nature.com/articles/d41587-020-00010-2
24. Coronavirus (COVID-19) update: FDA alerts consumers about unauthorized fraudulent COVID-19 test kits. Published online March 20, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-alerts-consumers-about-unauthorized-fraudulent-covid-19-test-kits
25. South Korea dials up coronavirus testing with hospital 'phone booths'. Published online March 17, 2020. https://www.straitstimes.com/asia/east-asia/south-korea-dials-up-coronavirus-testing-with-hospital-phone-booths.
26. McNeil Jr, D. Can Smart Thermometers Track the Spread of the Coronavirus? *The New York Times.* Published online March 18, 2020. https://www.nytimes.com/2020/03/18/health/coronavirus-fever-thermometers.html
27. Mao, *et al.* Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *Lancet Neurol (Preprint)*. Published online February 25, 2020. dx.doi.org/10.2139/ssrn.3544840
28. Li, *et al.* Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Lancet Neurol (Preprint)*. Published online March 13, 2020. dx.doi.org/10.2139/ssrn.3550025
29. Hong T, *et al*. SNIS Special Webinar: Neurointerventional Guidance for COVID-19. *Society of Neurointerventional Surgery*. Published online April 2, 2020. https://www.snisonline.org/meetings/covid19webinar.
30. Poyiadji N, *et al*. COVID-19–associated acute hemorrhagic necrotizing encephalopathy: CT and MRI Features. RSNA. Published online Mar 31, 2020. https://doi.org/10.1148/radiol.2020201187
31. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol. Published online April 01, 2020. https://doi.org/10.1016/S1474-4422(20)30109-5
32. HFSA/ACC/AHA statement addresses concerns Re: Using RAAS Antagonists in COVID-19. Published online Mar 17, 2020.https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19.
33. Madjid M, et al. Potential Effects of Coronaviruses on the Cardiovascular System. *JAMA Cardiol*. Published online Mar 27, 2020. https//doi: 10.1001/jamacardio.2020.1286.
34. Tam Chor-Cheung F, *et al*. Impact of Coronavirus Disease 2019 (COVID-19) outbreak on ST-segment–elevation myocardial infarction care in Hong Kong, China. *Circulation: Cardiovascular Quality and Outcomes*.0(0):CIRCOUTCOMES.120.006631.
35. Lyden P, *et al.* Temporary emergency guidance to US stroke centers during the COVID-19 pandemic. *Stroke*. Published online April 1, 2020. https://doi.org/10.1161/STROKEAHA.120.030023
36. Khosravani H, *et al*. Protected code stroke: hyperacute stroke management during the coronavirus disease 2019 (COVID-19) pandemic. *Stroke*. Published online Apr 2020. https://doi.org/10.1161/STROKEAHA.120.029838
37. Cai H. Sex difference and smoking predisposition in patients with COVID-19. *Lancet Respir Med*. Published online March 11, 2020. https://doi.org/10.1016/S2213-2600(20)30117-X1Lancet Respir Med 2020Published OnlineMarch 11, 2020 https://doi.org/10.1016/ PI
38. Morfopoulou S, *et al*. Human Coronavirus OC43 Associated with Fatal Encephalitis. *New England Journal of Medicine.* 2016;375(5):497-498.
39. Li Y, *et al*. Coronavirus Infections in the Central Nervous System and Respiratory Tract Show Distinct Features in Hospitalized Children. *Intervirology*. 2016;59(3):163-169.
40. Netland J, *et al.* Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol.* 2008;82(15):7264-7275.
41. https://www.cdc.gov/coronavirus/2019-ncov/downloads/community-mitigation-strategy.pdf. Accessed 03/24/2020.
42. https://www.dravetfoundation.org/covid19-dsf-conference-update-3-18-20/. Accessed 03/24/2020.
43. https://www.aesnet.org/about_aes/position_statements/covid-19. Accessed 03/24/2020.
44. https://www.cms.gov/newsroom/press-releases/cms-issues-guidance-help-medicare-advantage-and-part-d-plans-respond-covid-19, archived 3/23/20. Accessed 03/24/2020.
45. Plaquenil (hydroxychloroquine) package insert. St. Michael, Barbados: Concordia Pharmaceuticals, Inc.; 2017 Jan.
46. Italian League against Epilepsy. Clinically relevant Drug-Drug interaction between AEDs and medications used in the treatment of COVID-19 patients. https://www.ilae.org/files/dmfile/Antiepileptic-drugs-interactions_in_COVID-19.pdf. Accessed March 27th, 2020.
47. https://www.nationalmssociety.org/What-you-need-to-know-about-Coronavirus-(COVID-19)/DMT-Guidelines-for-Coronavirus-(COVID-19)-and. Accessed 03/24/2020.
48. https://myasthenia.org/Portals/0/MG%20COVID19%20guidelines%20FINAL%203_23_20_1.pdf. Accessed 03/24/2020.
49. Cao, B *et al*. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. NEJM. 2020.
50. https://clinicaltrials.gov/ct2/show/NCT04280705 - Phase 2 trial - double-blind, placebo-controlled trial of remdesivir in

SARS-CoV-2 with pulmonary disease in hospitalized patients; 200 mg IV once on day 1, followed by 100 mg IV daily up to 10 days
51. https://clinicaltrials.gov/ct2/show/NCT04292899 - Phase 3 trial of remdesivir in severe pulmonary SARS-CoV-2 – 5 day versus 10 day treatment
52. https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-access-to-remdesivir-outside-of-clinical-trials. Accessed 3/24/2020.
53. Chong YP, *et al.* Rapid Response T. Antiviral Treatment Guidelines for Middle East Respiratory Syndrome. *Infect Chemother.* 2015;47(3):212-222.
54. Furuta Y, et al. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proc Jpn Acad Ser B Phys Biol Sc*i. 2017;93(7):449-463.
55. Cai Q, *et al*. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering.* 2020
56. Rosa SGV, *et al.* Clinical trials on drug repositioning for COVID-19 treatment. Rev Panam Salud Publica. 2020;44:e40. https://doi.org/10.26633/RPSP.2020.40
57. Uyeki TM. Oseltamivir Treatment of Influenza in Children. *Clin Infect Dis*. 2018;66(10):1501–3.
58. Wang D, *et al*. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020;Feb7:1–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32031570
59. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2020 Mar 12 – Identifier NCT04303299, Various combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquine for Treatment of COVID-19: A Randomized Control Trial (THDMS-COVID19)
60. Blaising J, *et al.* Arbidol as a broad-spectrum antiviral: an update. *Antiviral Res*. 2014;107(1):84–94. Available from: http://dx.doi.org/10.1016/j.antiviral.2014.04.006
61. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2020 Mar 12 – Identifier NCT04260594, Clinical Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia Caused by Novel Coronavirus. Available from: https://clinicaltrials.gov/ct2/show/NCT04260594.
62. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2020 Mar 12 – Identifier NCT04255017, A prospective, randomized controlled clinical study of antiviral therapy in the 2019-nCoV pneumonia. Available from https://www.clinicaltrials.gov/ct2/show/NCT04255017.
63. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2020 Mar 12 – Identifier NCT04252885, The efficacy of lopinavir plus ritonavir and arbidol against novel coronavirus infection (ELACOI). Available from: https://clinicaltrials.gov/ct2/show/study/NCT04252885.
64. Liu J, *et al*. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discovery.* 2020;6(1):16.
65. Gautret P, *et al*. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents.* 2020:105949.
66. Gautret J-CL, *et al*. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. 2020.
67. Molina JM, Delaugerre C, Goff JL, et al. No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. *Médecine et Maladies Infectieuses.* 2020
68. Dandan, *et al.* A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ (Med Sci).* 2020;49(1):0-0.
69. Chen Z, *et al*. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv.* 2020:2020.2003.2022.20040758.
70. Proactive Prophylaxis With Azithromycin and Chloroquine in Hospitalized Patients With COVID-19 (ProPAC-COVID) ClinicalTrials.gov Identifier: NCT04322396. 2020; https://clinicaltrials.gov/ct2/show/NCT04322396?term=SARS+COV2&cond=covid&intr=Hydroxychloroquine&draw=3&rank=11. Accessed March 27th, 2020.
71. Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial) (PHYDRA) ClinicalTrials.gov Identifier: NCT04318015. 2020; https://clinicaltrials.gov/ct2/show/NCT04318015?term=SARS+COV2&cond=covid&intr=Hydroxychloroquine&draw=2&rank=2. Accessed March 27, 2020.
72. Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting (COPCOV) ClinicalTrials.gov Identifier: NCT04303507. 2020; https://clinicaltrials.gov/ct2/show/NCT04303507?term=SARS+COV2&cond=covid&intr=Hydroxychloroquine&draw=2&rank=6. Accessed March 27, 2020.
73. Safety and Efficacy of Hydroxychloroquine Associated With Azithromycin in SARS-CoV2 Virus (Alliance Covid-19 Brasil II) ClinicalTrials.gov Identifier: NCT04321278. 2020; https://clinicaltrials.gov/ct2/show/NCT04321278?term=SARS+COV2&cond=covid&intr=Hydroxychloroquine&draw=2&rank=7. Accessed March 27, 2020.
74. Hydroxychloroquine Treatment for Severe COVID-19 Pulmonary Infection (HYDRA Trial) (HYDRA) ClinicalTrials.gov Identifier: NCT04315896. 2020; https://clinicaltrials.gov/ct2/show/NCT04315896?term=SARS+COV2&cond=covid&intr=Hydroxychloroquine&draw=4&rank=4. Accessed March 27, 2020
75. Baron SA, *et al*. Teicoplanin: an alternative drug for the treatment of COVID-19? *International Journal of Antimicrobial Agents* 2020;18:epub ahead of print.
76. Yip T-F, Selim ASM, Lian I, Lee SM-Y. Advancements in Host-Based Interventions for Influenza Treatment. *Front Immunol.* 2018;9:1547-1547.
77. Mastrangelo E, Pezzullo M, De Burghgraeve T, et al. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. *J Antimicrob Chemother.* 2012;67(8):1884-1894.
78. 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 Research.* 2020:104787.
79. Richardson P, *et al*. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *The Lancet.* 2020;395(10223):e30-e31.
80. Baricitinib in symptomatic patients Infected by COVID-19: an open-label, pilot study. (BARI-COVID) ClinicalTrials.gov Identifier: NCT04320277. 2020; https://www.clinicaltrials.gov/ct2/show/NCT04320277. Accessed March 31, 2020.
81. Batlle D, *et al*. Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy? *Clinical Science.* 2020;134(5):543-545.
82. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest.* 2007;131(4):954-963.
83. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med.* 2006;354(16):1671-1684.
84. Sessler CN, Gay PC. Are corticosteroids useful in late-stage acute respiratory distress syndrome? *Respiratory care.* 2010;55(1):43-55.
85. Deal EN, Hollands JM, Schramm GE, Micek ST. Role of corticosteroids in the management of acute respiratory distress syndrome. *Clinical therapeutics.* 2008;30(5):787-799
86. Efficacy of Methylprednisolone for Patients With COVID-19 Severe Acute Respiratory Syndrome (MP-C19) ClinicalTrials.gov Identifier: NCT04323592. 2020;

https://www.clinicaltrials.gov/ct2/show/NCT04323592. Accessed April 4, 2020.
87. Xu X ea. Effective treatment of severe COVID-19 patients with tocilizumab. *Pre Print*. Available online: http://chinaxiv.org/abs/202003.00026. Accessed 24 Mar 2020
88. Tocilizumab in COVID-19 Pneumonia (TOCIVID-19) (TOCIVID-19). https://clinicaltrials.gov/ct2/show/NCT04317092. Accessed 03/24/2020.
89. Evaluation of the efficacy and safety of sarilumab in hospitalized patients with COVID-19. https://www.clinicaltrials.gov/ct2/show/NCT04315298. Accessed 03/24/2020.
90. Eculizumab (Soliris) in Covid-19 infected patients (SOLID-C19). https://clinicaltrials.gov/ct2/show/NCT04288713
91. Efficacy and safety of emapalumab and Anakinra in reducing hyperinflammation and respiratory distress in patients with COVID-19 infection. ClinicalTrials.gov Identifier: NCT04324021. 2020; https://www.clinicaltrials.gov/ct2/show/NCT04324021?term=intravenous+immunoglobulin&cond=covid&draw=2&rank=1. Accessed March 27, 2020.
92. Bevacizumab in severe or critical patients with COVID-19 pneumonia (BEST-CP). https://clinicaltrials.gov/ct2/show/NCT04275414. Accessed 03/24/2020.
93. Shen C, *et al*. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA.* 2020.
94. Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19. https://clinicaltrials.gov/ct2/show/NCT04292340. Accessed 03/24/2020.
95. FDA. Investigational COVID-19 Convalescent Plasma - Emergency INDs. 2020; https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds. Accessed March 27, 2020
96. Varadarajan R, *et al*. Broadly neutralizing antibodies for therapy of viral infections. *Antib Technol J.* 2016;1.
97. Cao W, *et al.* High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with Coronavirus Disease 2019. *Open Forum Infectious Diseases.* 2020.
98. The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia ClinicalTrials.gov Identifier: NCT04261426. 2020; https://www.clinicaltrials.gov/ct2/show/NCT04261426?term=immune+globulin&cond=sars+cov2&draw=2&rank=1. Accessed March 27, 2020.
99. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2020 Mar 12 – Identifier NCT04280588, Fingolimod in COVID-19. Available from: https://clinicaltrials.gov/ct2/show/NCT04280588?term=NCT04280588&draw=2&rank=1
100. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2020 Mar 12 – Identifier NCT04273529, The efficacy and safety of thalidomide in the adjuvant treatment of moderate new coronavirus (Covid-19) pneumonia. Available from: https://clinicaltrials.gov/ct2/show/NCT04273529?term=NCT04273529&draw=2&rank=1
101. Newfield C. New Medical Indications for Thalidomide and its Derivatives New Medical Indications for Thalidomide and its Derivatives. *The Science Journal of the Lander College of Arts and Sciences*. 2018;12(1).
102. Sayburn A. Covid-19: trials of four potential treatments to generate “robust data” of what works. *BMJ.* 2020;368:m1206.
103. https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker. Accessed March 30, 2020
104. https://www.nih.gov/news-events/news-releases/nih-clinical-trial-investigational-vaccine-covid-19-begins. . Accessed March 30, 2020
105. https://statnano.com/news/67536/China%E2%80%99s-First-Coronavirus-Vaccine-Delivered-for-Human-Trials. . Accessed March 30, 2020.
106. https://www.clinicaltrialsarena.com/news/oxford-university-covid-19-vaccine-trial/ Accessed March 30, 2020
107. Moorlag SJCFM, Arts RJW, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. *Clinical Microbiology and Infection.* 2019;25(12):1473-1478.
108. Hollm-Delgado M-G, Stuart EA, Black RE. Acute Lower Respiratory Infection Among Bacille Calmette-Guérin (BCG)–Vaccinated Children. *Pediatrics.* 2014;133(1):e73.
109. Covián C, Fernández-Fierro A, Retamal-Díaz A, et al. BCG-Induced Cross-Protection and Development of Trained Immunity: Implication for Vaccine Design. *Front Immunol.* 2019;10:2806-2806.
110. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. *medRxiv.* 2020:2020.2003.2024.20042937.
111. BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE). 2020; https://clinicaltrials.gov/ct2/show/NCT04327206. Accessed April 4, 2020