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COVID-19 NEUROLOGY SCIENTIFIC ADVISORY BOARD UPDATE

HENRY FORD NEUROSCIENCE INSTITUTE

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COVID-19 PANDEMIC: THE NUMBERS (as of 5/6/20, 5pm EST)

- **World:[1] 3,744,585 confirmed cases. Total deaths: 263,068. Total recovered: 1,287,791.**
- **US:[1] 1,257,157 confirmed cases. Total deaths: 74,142; Total recovered: 205,268**
- **Michigan:[2] 45,054 confirmed cases. Total deaths: 4,250. New cases in the last 24h: 657. New deaths in the last 24h: 71.**
- **Peak resource use in the United States was on April 17, 2020.[3]**
- **Evolution of the pandemic:[4] The US is in the plateau phase of the pandemic with regards to confirmed cases and deaths. The number of deaths doubled in the past 20 days.**

HENRY FORD HEALTH SYSTEM AND COVID-19 (New!)

- **The "Will Hydroxychloroquine Impede or Prevent COVID-19" or WHIP-COVID trial is now enrolling!** Our home-based trial studies the benefit of hydroxychloroquine as prophylaxis for front-line workers. Visit https://www.henryford.com/whip-covid-19 for more information on how to enroll.
- **SARS-CoV-2 testing:** We now have the capacity to test 1000 samples per day with a turnaround time of less than 24 hours. All tests are run in-house, no tests are being sent out.
- **Convalescent Plasma (information contributed by Dr. Ileana Lopez-Plaza): Henry Ford Health System (HFHS) was one of the first Michigan health systems to participate in a convalescent plasma program. As of this date, more than 50 COVID-19 patients have been treated with convalescent plasma. Convalescent plasma is the name given to the plasma of an individual that has been infected with the SARS-CoV-2 and then developed protecting antibodies against that specific infection. The premise for the current investigational treatment is the hope that this plasma infusion will provide some level of protection against the virus in patients with COVID-19. Currently, the FDA considers the convalescent plasma as an investigational product. Convalescent plasma donors must meet regular volunteer blood donor criteria in addition to specific criteria related to the COVID-19 infection. The plasma collection takes place at a blood center collection site. Plasma distribution is provided by the blood center.**

BEST EXPOSURE PREVENTION PRACTICES

- CoV-2 may be aerosolized through talking, toileting and exhaling. Recent data from the University of Nebraska Medical Center showed that viral PCR was detected in air samples inside and outside isolation

rooms even in the absence of coughing and across all degrees of severity of patients' respiratory illnesses.[5] It is however still unclear what proportion of these viral particles are transmitted via aerosolization and whether this route is clinically significant and leads to infection. These findings were relayed in a letter written by the National Academies Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats to the White House on April 1, 2020.[6]

- 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.[7]
- 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).[8]
- 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).[8]
- The CDC now recommends cloth face masks be used in public settings where it is not feasible to exercise appropriate social distancing such as grocery stores.[9] Some experts remain skeptical of this recommendation due to 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.[10]
- 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.[11]
- Temporal Dynamics of SARS-COV2: A group from China investigated temporal dynamics of viral shedding in 94 patients with laboratory confirmed COVID-19 infection, modeled patterns of transmission among 77 transmission pairs and demonstrated that the highest viral load was present at the time of symptom onset, suggesting that infectiousness peaks at or immediately before symptom onset. However, 44% of patients got infected during index cases' presymptomatic phase, highlighting the importance of social distancing even among healthy individuals.[12]
- New! A simulation out of Haifa, Israel provides insight into the imperfect protection conferred by standard PPEs. Using adult and pediatric manikins experiencing respiratory distress and coughing spells and having to be endotracheally intubated, the group was able to show that despite full standard PPE application, all team members (nurses and physicians) had aerosolized particles detected by fluorescence on their uncovered skin, hair and shoes, making the point that "the current recommendations for personal protective equipment may not fully prevent exposures in emergency department settings"**.[13]**
- **Montpellier University Hospital in France performed video study in operating rooms using two types of intubation: direct laryngoscopy (DL) using Macintosh blade, and video laryngoscopy (VL). They concluded that VL-intubation reduced risk of exposure to airway secretion and patient-to-provider transmission, in part because the provider can distance themselves better with VL than DL. Data worldwide shows that 80% of intubations in COVID-19 patients are being performed using VL.[14]**

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.[15] 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.[16]

- 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.[17]
- 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, TNF and IL-1β, all proinflammatory cytokines, are central in this process. The inflammatory state seen in COVID-19 is closely associated with a procoagulant state, caused by consumption of anticoagulant factors, overproduction of prothrombotic factors and endothelial injury. This leads to microthrombosis, DIC and venothrombotic events frequently seen in COVID-19+ patients and associated with a worse prognosis. Thrombin and Factor Xa have pro-inflammatory properties via activation of proteinase-activated receptors (PARs) and therefore their antagonists such as Factor Xa inhibitors (e.g., apixaban, rivaroxaban) and LMWH (e.g., enoxaparin) could not only have anticoagulant properties but anti-inflammatory ones as well.[18]
- 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 vagus nerve stimulation quiesces the immune response.[19] One wonders whether blocking the sympathetic outflow may halt or prevent the development of this exuberant inflammatory response.
- Evidence is mounting around the role of CoV-2 poisoning heme porphyrin. Using bioinformatic analysis, a group from China showed that some viral proteins bind the porphyrin, while others bind the heme (iron-porphyrin complex) component of the hemoglobin beta-1 chain. This binding leads to a dissociation of iron to porphyrin and the hemoglobin loses its oxygen-carrying capacity. This is analogous to carbon monoxide poisoning. This phenomenon can lead to 1) profound hypoxia seen in some COVID-19 patients, 2) heme and iron accumulation which may be toxic to tissues and produce an inflammatory cascade, 3) increased synthesis of ferritin to chelate the excess iron being deposited in tissues and not being utilized for oxygen carrying purposes.[20]
- 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.[21] 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.[22]
  - 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.[21] Patients with underlying cardiovascular disease and elevated troponin were found to have the highest mortality.[23] Autopsies have revealed infiltration of myocardium by interstitial mononuclear inflammatory cells, evidencing a myocarditis.[24] 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.[25]

UPDATES ON SARS-COV2 TESTING

- Per the CDC,[26] 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).[27] HFH has expanded testing sites to NP and tracheal aspirates in intubated patients. BALs are not being done at HFH due to the risk of aerosolization. A recent study, still in print, shows that saliva sampling may be superior than NP sampling. SARS-CoV-2 titers were higher and collection was less variable and more consistent in saliva compared with NP specimens.[28]
- **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.
  - On March 21, the FDA approved a point-of-care (POC) test by Cepheid with a turnaround time of 45 minutes.[29] *Abbott* has been granted emergency use authorization (EUA) 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.[30]
  - **PCR specificity is thought to be 100% (i.e., false positive rate ~0%) due to the specificity of the SARS-CoV-2 genome primer utilized. Sensitivity, however, varies based on the source of the specimen: lowest in pharyngeal swab (32%), nasal swab (63%), sputum (72%), highest in BAL (93%), in one study of 205 patients.[31]**
  - **The virus can usually be isolated from the respiratory tract starting 1 week before to about 1 week after symptom onset (i.e., time of maximal infectivity). Beyond 7-8 days from symptom onset, it is unlikely that a patient remains infectious, unless they get reinfected.[32]**
  - **In some cases, PCR was positive for as long as 6 weeks despite recovery. It is unlikely that these patients were infectious for as long as 6 weeks. The correct interpretation is that a positive PCR means viral RNA detection but not necessarily viral viability. PCR positivity may persist beyond 6 weeks in stool and BAL. In one study, PCR remained positive in stool 4-11 days beyond NP sample.[33]**
- **Serology:** tests that detect IgM and IgG antibodies and provide information about the immune response of the host to the virus antigens.
  - **IgM and IgG antibodies appear as early as 4 days from symptom onset and peak at 2-3 weeks. IgM usually disappears by week 7 whereas IgG persists well beyond week 7.[34] While IgM positivity indicates a recent or current infection, 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 (PCR is usually + during this time). Therefore, serological testing should not be used alone to diagnose active infection.**
  - **Specificity of the available ELISA IgM/IgG tests is roughly 95%. In one study, sensitivity of a single PCR was 52% but improved to 98.6% when combined with an anti-nucleocapsid (NC) IgM ELISA test. The NC protein is the most abundant protein in the SARS-CoV-2. Therefore, tests that detect antibodies directed against it have higher sensitivities but are not as specific due to cross-reactivity with SARS-CoV.[35]**
  - On April 2nd, the FDA approved antibody testing by Cellex which can provide results in 15 min.[36] So far, the FDA has issued four EUAs for serological tests and continues to evaluate their performance. It is important to remember that we still do not know the length of immunity imparted by positive antibodies or whether reinfection is possible.[37]
  - While antibody testing is not full proof at this time, it may become an important tool to transition people out of lockdown and allow them to join the workforce again. Several European countries, such as Italy, Germany and the UK, are planning nationwide antibody testing to determine when to reopen their economies and loosen social distancing policies.[38] In LA county, USC researchers and public health officials are conducting antibody testing, so far showing that the estimate of infected cases is "28 to 55 times

higher than the (number) of confirmed cases at the beginning of the study in early April".[39]

- **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.[40]
- The FDA continues to warn the public against the marketing of at-home COVID-19 test kits.[41]
- 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.[42]
- *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.[43]

SARS-COV2 NEUROLOGICAL SYNDROMES

- **Symptomatology:**
  - **CNS symptoms:**
    - **Stroke:** A case series of 5 COVID-19+ patients younger than 50 years old presenting to Mount Sinai Hospital in NYC over a two-week period was published in NEJM. 4/5 were males, age range was 33-49 and admission NIHSS range was 13-23. All 5 had large vessel occlusions (MCA, ICA, PCA territories). 3/5 had cardiovascular comorbidities (DM, HTN, HLP and one had a prior mild stroke). 3/5 had symptoms consistent with COVID-19. Only one presented within the IV-tPA window and received the thrombolytic. 3/5 had clot retrieval and one of them also had a stent placed in the MCA. 2/5 were treated with aspirin, one of them went from craniectomy, the patient who received the stent was placed on dual antiplatelet and the remaining 2 were anticoagulated with full-dose apixaban. one patient was discharged home, 2 to rehab and the remaining 2 are still hospitalized at this time.[44]
    - In one study, 24.8% of cases (dizziness and headache).[45] In another study of 221 patients at a single center in China, 5% cases had AIS, 0.5% CVST and 0.5% ICH.[46] 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.[47] A group from China reported three cases of ischemic stroke involving various territories associated with positive antiphospholipid antibodies, raising the possibility of a role for COVID19-infection related antiphospholipid syndrome in the pathomechanism of COVID-19 related thrombotic episodes. However, the baseline status of these antibodies is unclear in these patients and a causal relationship remains to be determined.[48] Another series from Italy reported 4 cases with ischemic strokes and 2 cases with hemorrhagic strokes. 5/6 patients had severe COVID pneumonia, while 4/6 patients had disturbed coagulation tests. Poor outcome was noted in the majority of patients as 4/6 patients died, 1 patient was still in coma and 1 patient had severe neurological disability (mRS 4).[49]
    - Seizures: There is a single case report from Italy of focal SE as the initial presentation of COVID-19 infection in a 78-year-old lady with remote history of HSV encephalitis.[50] In another case series from China involving 304 patients with COVID-19 infection, only two patients exhibited seizure like phenomena. The first patient had bilateral body spasms, attributed to acute anxiety disorder, while the 2nd patient had myoclonic movements involving all extremities that were attributed to underlying electrolyte abnormalities. These movements resolved upon correction of

underlying metabolic abnormalities. None had acute symptomatic seizures or SE. However, EEG was not obtained in any of the studied patients.[51]

- **Encephalopathy/encephalitis:** 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.[52] The patient was discharged to rehab after 22 days of hospitalization in improved condition. A group from Japan reported the first case of CSF-proven SARS-COV2 meningo-encephalitis in a 24-year-old gentleman presenting with new-onset seizure and altered consciousness preceded by an 8-day history of fever, malaise and sore throat. CSF PCR was positive for SARS-COV2 while nasopharyngeal swab PCR was negative. MRI showed evidence of restricted diffusion along the wall of the inferior horn of the right lateral ventricle as well as T2 FLAIR hyperintense signal involving right mesial temporal structures.[53]
- **Demyelinating lesions: A report from Italy of a 54 year-old woman with a remote history of anterior communicating aneurysm rupture who underwent presumably clipping, was found unconscious at home and tested positive for COVID-19 on arrival. Of note, she reported anosmia and ageusia for a few day prior to presentation. Initial CT was normal but CXR showed "interstitial pneumonia". A few hours later, she went into hypoxic respiratory failure and was intubated. She later developed two seizures captured on EEG, emanating from the side of her craniotomy, for which she was treated with combination AEDs. MRI brain revealed periventricular and C/T spine T2/FLAIR hyperintense yet non-enhancing lesions, consistent with demyelination. CSF was essentially unremarkable and negative for neurotropic viruses (unspecified which ones were tested) and SARS-CoV-2. Paper does not mention OCB or IgG index. Patient received HCQ, antiviral (not specified) when COVID was diagnosed and high dose dexamethasone after lesion discovery. She received a tracheostomy and was transferred to rehab without sensory or motor deficits on day 12. This case highlights the possible local neuroinflammatory response that results from the more systemic cytokine storm and sHLH. It is unclear from the report if the patient has a history of seizure (from her prior aneurysmal rupture). It remains questionable whether this is a viral encephalitis or a viral-triggered neuroinflammatory response.[54]**
  - In a series of 58 consecutive COVID-19-confirmed patients with ARDS admitted to 2 ICUs in Strasbourg, France, neurological symptoms were found in 14% of cases on admission, and in 67% after sedation and paralytics were weaned. The most common symptom was encephalopathy (69%), closely followed by corticospinal signs (67%) and dysexecutiveness (36%). All 11 patients who were imaged with MRI had bifrontal hypoperfusion and 62% of them had leptomeningeal enhancement. 2/11 patients were found to have small acute strokes. CSF was obtained in 7 patients, none of them positive for CoV-2 PCR. No cells were present in any of the samples and 2 patients had elevated protein levels with only 1 having elevated IgG index.[55]
- **Peripheral symptoms:**
  - In one study, 8.9% of patients (hypogeusia, hyposmia, neuralgia).[45] Myalgias were found in 10.7% of cases.
  - Generalized muscle aching, pain and fatigue are known to be a part of a viral symptom complex. However, rhabdomyolysis has not

been commonly reported. Jin and Tong reported a case who developed rhabdomyolysis during the course of infection. The patient presented with fever and respiratory symptoms initially with normal CPK levels. Nine days into hospitalization, he developed lower extremity weakness and pain and was found to have markedly elevated CPK, myoglobin and LDH. Over the next few days, with treatment, his muscle pain and fatigue improved.[56]

- *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.[57]
- **In** *Neurology*, a group in Spain reported two cases of Miller Fisher syndrome (MFS) and polyneuritis cranialis, respectively. The first patient, a 50 year-old man developed the cardinal features of MFS (ataxia, areflexia and ophthalmoparesis) 5 days after the onset of flu-like illness. He was found to have positive GD1b antibodies and albuminocytologic dissociation. He was treated with IVIG for 5 days on the fifth day of his neurological symptoms, resulting in complete recovery, save for residual anosmia and ageusia. The second patient, a 39 year-old man presented with bilateral abducens palsies, ageusia and areflexia, 3 days after diarrhea and fever. While albuminocytological dissociation was present, anti-ganglioside antibodies testing was not performed. Patient was treated with acetaminophen and made a complete recovery.[58]
- Three hospitals in Northern Italy reported a series of 5 COVID-19 cases who presented with GBS symptoms 5-10 days after onset of respiratory symptoms. Four had paraparesis progressing to tetraparesis/plegia and 1 had facial diplegia. Antiganglioside antibodies were negative in all tested patients. Albuminocytological dissociation was demonstrated in 3/5 patients. CSF was negative for CoV-2 PCR in all patients. Three had an axonal variant whereas 2 had demyelinating features on EMG. All received IVIG, one had plasmapheresis in addition. At 4 weeks, 2 patients were still mechanically ventilated, 1 was discharged and 2 were undergoing physical rehabilitation.[59]
    - **Movement disorders:** so far, none has been reported as a result of the infection.

- **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.[45]

- **Neuroimaging or neuroelectrophysiological characteristics:** nothing specific has been 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.[60] A systematic review including 18 studies of 1065 pediatric cases demonstrated that the majority of children present with mild symptoms or no symptoms at all. Only 1 patient (a 13-month old infant) had severe infection. No deaths were reported.[61] An additional case report published in NEJM not included in the systematic review described severe COVID-19 infection in a 3-week old boy.[62]

- A series from France reported that 4/5 infants <3 months old with COVID-19 infections had neurological manifestations including axial hypotonia, drowsiness and moaning sounds or both upon presentation. CSF analysis was unremarkable and CSF SARS-COV2 PCR was negative. Prognosis was favorable as patients were discharged 1-3 days after admission.[63]
- Despite the concern among many practitioners about the increased risk for severe COVID-19 infections among chronically immunosuppressed patients, a review of pediatric hepatic transplant patients from Bergamo, Italy did not show an increase in COVID-19 severe infections as would have been expected. 3/200 patients being followed there, tested positive for SARS-CoV2 infection, however, none developed pulmonary disease. The authors felt that it is likely that the children are asymptomatic carriers of the infection, despite their suppressed immune status.[64]

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. A small study from China demonstrated markedly elevated levels of serum angiotensin II in 12 patients with COVID-19 infection and its correlation with increased viral load as well as the severity of lung injury, suggesting a possible beneficial role of ACEIs and ARBS in patients with COVID-19 infection.[65]
  - Furthermore, a multi-center retrospective trial from China including 1128 patients with COVID-19 infection which included 188 patients taking ACEI/ARB demonstrated reduced COVID-19 mortality risk in patients receiving ACEI/ARB compared to non-ACEI/ARB group (3.7% vs 9.8%, P=0.01. Further subgroup analysis demonstrated that ACEI/ARB use was associated with reduced mortality risk compared to the use of other anti-HTN therapies in HTN patients.[66] **Another multicenter observational study from 169 hospitals led by Brigham and Women's hospital involving 8910 patients with COVID-19 infection demonstrated that ACEI use was associated with mortality reduction (OR 0.33; 95% CI 0.2-0.54).[67] Authors advised taking these results with extreme caution given the non-randomized nature of the trial.** The American Heart Association recommends at this point continuing ACEi and ARB medications if clinically indicated.[68] 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.[69]
  - 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.[70]
  - 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.[71]
  - 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.[72]

- 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.[73]
- **Recently proposed recommendations for management of large vessel occlusion from Cincinnati was published and highlighted the importance of maintaining safety for health personnel. To preserve hospital resources during this crisis, patients most likely to benefit from thrombectomy, should be prioritized based on AHA/ASA guidelines.[74]**
- **Guidance statement form SVIN also highlighted several aspects of thrombectomy care. The statement suggested to obtain CT chest with initial stroke imaging for patients with positive pulmonary symptoms. An approach of direct transfer to angiography suite should be considered for patients with stroke symptoms onset within 24 h, who are transferred from other hospitals with time from last neuroimaging within 2 h and ASPECTS ≥7. Clinical-core mismatch on ASPECT scores (6-10) on CT overlaps with clinical core mismatch by CT perfusion or MRI using DAWN criteria, this can be used as a substitute for patients in late window and mere absence of advance imaging should not preclude from patients getting thrombectomy.[75]**
- Stroke teams are posed with several challenges to ensure time-sensitive acute therapies. In Veneto (Italy) they implemented a protocol for evaluating COVID positive and suspected patients in a "hot spot" (a pre-triage unit outside ER) and utilized mobile CT units outside ER to perform CT, CTA and CT perfusion studies and triaged acute stroke patients accordingly to keep stroke unit COVID free.[76]

- **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.[77-79]
  - So far, there is no evidence to suggest increased predisposition for acquiring COVID-19 among patients with epilepsy. However, COVID infection can possibly increase risk for breakthrough seizure in a similar fashion to other febrile illnesses. Therefore, the CDC lists epilepsy patients among high risk conditions for COVID. [80] Patients with epilepsy syndromes known to be susceptible to febrile illnesses such as Dravet Syndrome and genetic epilepsy with febrile seizures plus (GEFS+) are likely to be particularly at increased risk for breakthrough seizures or increased seizure frequency in the setting of COVID-19 infection.[81] Consensus recommendations emphasized administrating care at home as much as possible instead of health care facilities to avoid exposure, minimizing seizure exacerbation through adherence, and ensuring a regular supply of medication and rescue therapies.[82]
  - 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.[83] 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.[84]

- 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).[85] 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.[86]

- **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.[87]

- **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.[88] 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.[88]
  - **The AANEM has established guidance for triaging electrodiagnostic studies during COVID-19. Urgent electrodiagnostic testing is appropriate for those neuromuscular conditions presenting with acute, rapidly progressive neurological decline and would be necessary to determine treatment options. Possibly urgent are those that after carefully reviewing the case, an EMG is necessary to make a diagnosis and escalate treatment to prevent the development of a poor patient outcome. Non-urgent are those cases that are mild, chronic, or when electrodiagnostic testing is not necessary to make a diagnosis or determine treatment. These can be deferred to when conditions are safe for practice.[89]**

- **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.

- **Headache**
  - **Large retrospective studies both in the Chinese and European population report an incidence of headache >70.3% in COVID-19 patients; higher percentages are reported in young & female patients with mild-to-moderate disease.[90,91]**
  - **Healthcare professionals also had a high-incidence (81%) of self-reported headache during the COVID-19 pandemic, thought to be related to the PPE and work-related stress.[92]**
  - **Headache management for chronic headache patients not affected by COVID-19 has been significantly altered due to the development of exclusive telehealth measures implementing outpatient management plans and alternative plans for Botox administration.[93] Bridging therapies and use of CGRP antagonists continues to be the upcoming trends to manage Headache patients in the COVID-19 pandemic era.[94]**

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).[95] No mention of severe neurologic sequelae in any of these patients. Currently being investigated along with other therapies in the French-led Discovery trial.[96,97]
  - **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,[98-103] A case series was published of 53 patients with COVID-19 and hypoxia who had received remdesivir via compassionate-use; overall mortality was 13%, and 68% had improvement in need for oxygen support.[103] A randomized placebo-controlled trial including 237 patients with severe COVID-19 infection from 10 centers in Wuhan, China failed to demonstrate clinical benefit for IV remdesivir therapy. However, there was a trend towards shorter duration to recovery among patients with symptom-duration ≤10 days, though this did not reach statistical significance.[104] Preliminary results from a larger NIH-sponsored clinical trial involving 1063 patients released today demonstrated 31% faster time to recovery among patients receiving IV remdesivir compared to placebo (P<0.001). The median time to recovery was 11 days in remdesivir arm compared to 15 days in placebo arm. Mortality was lower among patients receiving remdesivir (8%) compared to those receiving placebo (11.6%), though this was not statistically significant (P=0.059).[105] FDA is currently exploring approving emergency use of the drug in severe COVID-19 infections.[106]
  - **Ribavirin**: guanosine analogue, usually combined with recombinant interferon. Not effective in MERS.[107] 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.[108] 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).[109]

- **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.[110-113]
- **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. A small retrospective cohort study of non-intubated patients in China with COVID-19 showed possible clearing of the virus (negative RT-PCR from NP swabs) more quickly in patients treated with the combination of arbidol and LPV/RTV than with LPV/RTV alone, although the latter group was statistically more likely to have received steroids.[114] The drug is currently being investigated in 4 clinical trials in China.[115-118]
- **Hydroxychloroquine (HCQ) +/- azithromycin (AZT):** In vitro data has demonstrated efficacy of chloroquine and hydroxychloroquine in suppressing SARS-CoV2.[119] 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.[120] 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.[121] The same group from Marseille 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.[122] 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,[123] and a French trial was halted due to emergence of serious cardiac adverse events.[124] 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.[125] 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.[126] Another multicenter open label randomized controlled trial (available as pre-print; not peer reviewed yet) failed to demonstrate significant association between hydroxychloroquine use and viral suppression, while a significant association with 28-day symptom alleviated was only demonstrated in post-hoc analysis after excluding confounding effect of antiviral agents.[127] Another preprint retrospective study involving 368 veterans with COVID-19 infection also failed to demonstrate a significant effect of hydroxychloroquine +/- azithromycin on the rates of ventilation. Surprisingly, all-cause mortality risk was higher in patients in HCQ arm compared to HCQ+AZT and placebo arms (adjusted hazards ration 2.61; 95% CI 1.1 to 6.17; P=0.03).[128] A phase 2 trial investigating the use of high vs low dose chloroquine therapy was halted prematurely due to emergence of evidence of increased risk

for QTc prolongation and increased mortality risk in high dose chloroquine arm upon interim analysis.[129] 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.[130-134] Given the lack of strong evidence supporting its use in the light of potential cardiotoxicity, NIH COVID-19 treatment guidelines panel recommends against the use of HCQ+AZT outside the scope of clinical trials but does not recommend for or against HCQ monotherapy given limited data at this point.[135]

- **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.[136]
- **Ivermectin**: Antiparasitic medication with reported in-vitro activity against multiple RNA viruses including Influenza[137] and West Nile[138] viruses. The mechanism likely involves blocking entry of viral proteins into the cellular nuclei.[138] A recent study demonstrated in-vitro viral suppression within 48 hours of administration.[139] No human trials yet.
- **Nitazoxanide:** Antiparasitic agent with reported in-vitro activity against MERS-COV and SARS-CoV-2.[140,141] No human trials yet.
- **Camostat:** A medication used in Japan for treatment of pancreatitis; shown to have in-vitro activity against SARS-COV2 via inhibiting cellular protease TMPRSS2 which plays an essential role in facilitating viral entry into cells.[142]
- **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 clathrin-mediated endocytosis and subsequently viral entry into cells.[143] One clinical trial is currently underway in Italy investigating its use.[144]
- **Soluble ACE2 molecules:** May play a role in competitively blocking membrane ACE2 viral bindings sites, and subsequently blocking viral entry and replication.[145] 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.[146-149] 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. 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. A retrospective study from China involving 201 patients with COVID-19 related ARDS demonstrated statistically significant association between methylprednisolone use and reduced mortality risk (HR, 0.38; 95% CI, 0.20-0.72).[150] 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.[151] **A preprint study from Henry Ford involving 212 patients with moderate to severe COVID-19 infections demonstrated that the implementation of this protocol has been associated with reduction in mortality, ICU admissions and need for mechanical ventilation. Multivariate regression analysis demonstrated independent association with reduction in reaching primary composite endpoint including mortality, ICU admissions and mechanical ventilation in patients receiving steroids after controlling for other risk factors (OR 0.45; 95% CI: 0.25-0.81).[152]**
  - **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.[153] Preliminary data from a French trial involving 129

patients with moderate to severe infection demonstrated significant benefit on mortality reduction and decreased need for life support interventions.[154] There are two currently ongoing clinical trials in China further investigating this drug.[155]

- **Sarilumab:** Another monoclonal antibody targeting IL6 receptors. A clinical trial evaluating its use is currently enrolling patients in New York (NCT04315298).[156] Preliminary analysis of a phase 2 trial involving 457 patients with severe to critical COVID-19 pneumonia showed no clinical benefit when both severe and critical groups were combined but positive trend towards clinical benefit was noted among the critical patient group. Based on these preliminary data, Sanofi announced amending phase 3 trial to include critical patients only.[157]
- **Siltuximab:** Another monoclonal antibody targeting IL6. A case series from China including 21 patients with COVID pneumonia/ARDS demonstrated clinical improvement in 7/21 (33%) patients, clinical stabilization in 9/21 (43%) patients and clinical worsening in 5/21 (24%) patients.[158] A clinical trial is currently underway investigating its utility.[159]
- **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.[160]
- **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).[161]
- **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.[161]
- **IC14:** A recombinant chimeric monoclonal antibody targeting CD14 (which is thought to play an important role in cellular activation leading to development of ARDS). A compassionate open label trial is currently underway in Italy.[162]
- **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.[163]
- **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.[164] Another case series from China reported resolution of clinical symptoms and radiological improvement of varying degrees in 10 patients with severe COVID-19 infections and conversion of positive to negative RT-PCR in 7/10 patients receiving convalescent plasma.[165] 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.[166] One clinical trial evaluating its role in COVID-19 infection (NCT04292340) is currently underway in China as well.[167]
- **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. [168]
- **IVIG:** Cao et al. reported improvement in 3 cases with severe COVID-19 infection from China.[169] Trials are currently underway to further assess its utility.[170]
- **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.[171]
- **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.[172,173]

- **Vazegepant:** An intranasal CGRP antagonist currently under trial as abortive therapy for migraine. Postulated role in COVID-19 infection therapy involves blocking CGRP-mediated alveolar inflammation. A phase 2 trial is currently underway.[174]
- **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.[96]
  - **Discovery trial:** A European trial similar to Solidarity trial except for exclusion of chloroquine.[96,97]

- **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:[175,176] 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:[175,177] 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:[175,178] 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.[179,181] 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.[182] An Australian clinical trial is currently underway investigating the role of BCG administration in prevention of COVID-19 infections among healthcare workers.[183]

For more information about ongoing clinical trials, visit https://www.av.co/covid for an updated list of currently active trials in diagnostics, therapeutics and vaccines.[184]

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This HFH COVID-19 Update is intended for the members of the Department of Neurology Henry Ford Hospital. Information concerning COVID-19 is rapidly evolving and the present text represents the authors' current interpretation, understanding, and evaluation of data at the time of writing. This update does not represent the official position of Henry Ford Hospital regarding COVID-19. For current updates concerning COVID-19, readers should consult the CDC website.