HFH NEUROLOGY COVID-19 SCIENTIFIC ADVISORY BOARD
03/27/20 UPDATE

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COVID-19 PANDEMIC: THE NUMBERS (as of 3/27/20, 10 am EST)

- **World**:[1] **551,337 confirmed cases. Total deaths: 24,906 (CFR 4.51%). Total recovered: 127,564 (CRR 23.13%).**
- **US:[1] 86,012 confirmed cases. Total deaths: 1,301 (CFR 1.51%). 246 new deaths in the past 24 hours. Highest number of deaths in NY: 365 deaths.**
- **Michigan:[2] 2,856 confirmed cases. Total deaths: 60 (CFR 2.1%). 17 new deaths in the past 24 hours.**
- **Evolution of the pandemic:[3] The US is in the acceleration phase of the pandemic with exponential growth of confirmed cases and deaths. Doubling time remains 3 days. In China, the curve has flattened. 111 new cases and only 5 deaths in the last 24 hours.**

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.[4]
- 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).[5]
- 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).[5]
- **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.[6]**

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, 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.[7]
- 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.[8]
- **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.[9] One wonders whether blocking the sympathetic outflow may halt or prevent the development of this exuberant inflammatory response.

- **Important clinical features of the disease: 1) 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. 2) Elevation of several serum inflammatory markers- IL-6, ferritin, LDH, CRP, D-dimer, triglycerides, 3) Neutrophil-to-lymphocyte ratio (NLR) of ≥3.13 predicts disease progression, 4) Lymphopenia, thrombocytopenia.**

UPDATES ON SARS-COV2 TESTING

- Per the CDC,[10] 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).[11] 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.[12]
- **Serology:** IgM and IgG provide information about the immune response of the host to the virus antigens. In one study, antibodies were detected in all patients 5 days after symptom onset. Faster to get results, but less accurate than PCR.
- **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.[13]**
- **FDA has not approved at-home test kits and warns the public against the marketing of fraudulent COVID-19 test kits.[14]**
- **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.[15]**

SARS-COV2 NEUROLOGICAL SYNDROMES

- **Symptomatology:**
  - CNS symptoms: In one study, 24.8% of cases (dizziness and headache).[16] In another study of 221 patients at a single center in China, 5% cases had AIS, 0.5% CVST and 0.5% ICH.[17] Ischemic and hemorrhagic strokes, impaired consciousness and muscle injury were more prevalent in patients with more severe respiratory disease.
  - PNS symptoms: In one study, 8.9% of patients (hypogeusia, hyposmia, neuralgia).[16] 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.
- **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.[16]
- No specific neuroimaging or electrophysiological characteristics described in COVID-19 patients yet.

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 or angiotensin receptor blockers requires further investigation. The American Heart Association recommends at this point continuing ACEi and ARB medications if clinically indicated. [18]
  - 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.[19]
  - 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.
  - **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.[20]**

- **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.[21-23] So far, there have been only rare reports of encephalitis associated with COVID-19 making it an infrequent cause of new onset epilepsy.[24]
  - There is no evidence to suggest that people with epilepsy are at increased risk than others for acquiring COVID-19 infections. However, as with any other viral febrile illnesses, COVID-19 infection may lower seizure threshold and place patients at increased risk for breakthrough seizures. Therefore, the CDC has included epilepsy among conditions associated with increased risk for serious COVID-19 infection.[25] Patients with epilepsy syndromes known to be sensitive to fevers such as Dravet Syndrome and genetic epilepsy with febrile seizures plus (GEFS+) are likely to be particularly at increased risk for breakthrough seizures in the setting of COVID-19 infection.[26] Use of rescue seizure medications can be considered in those patients.
  - 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.[27] 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.[28]
  - 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).[29] **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.[30]

- **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.[31]

- **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.[32]
  - 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.

- **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).[33] 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,[34-36] 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.[37] 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.[38] 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).[39]**
- **Oseltamivir: A drug approved for influenza A and B treatment; it inhibits the viral neuraminidase and, consequently, blocks the release of viral particles from host cells, reducing the spread in the respiratory tract. The use of oseltamivir has been reported during the COVID-19 epidemic in China, either with or without antibiotics and corticosteroids. Oseltamivir is also used in a clinical trial in multiple combinations with chloroquine and favipiravir.[40-43]**
- **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[40,44-48]**
- **Hydroxychloroquine +/- azithromycin**: In vitro data has demonstrated efficacy of chloroquine and hydroxychloroquine in suppressing SARS-CoV2.[49] Based on this data, Gautret et al. studied the antiviral activity in a non-randomized trial that included 20 patients receiving hydroxychloroquine 200 mg q8h compared to 16 non-matched controls receiving standard of care.[50] 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. Interestingly, 6/6 (100%) patients receiving azithromycin in addition to hydroxychloroquine 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.[51] **Another pilot trial from China randomized 30 patients to receiving hydroxychloroquine therapy vs conventional treatment only. Hydroxychloroquine was not superior to standard therapy in achieving viral suppression.[52] However, the small sample size is a significant limitation to this study and larger clinical trials are needed to assess its efficacy. Multiple clinical trials are currently underway assessing the role of hydroxychloroquine +/- azithromycin in treatment of COVID-19 infections of varying severities as well as for pre-exposure and post-exposure prophylaxis of healthcare workers.[52-57]**

- **Immunosuppressive/Immunomodulatory therapies and Passive immunization**
  - **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.[58] There

are two currently ongoing clinical trials in China further investigating this drug.[59]

- **Sarilumab:** Another monoclonal antibody targeting IL6 receptors. A clinical trial evaluating its use is currently enrolling patients in New York (NCT04315298).[60]
- **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.[61]
- **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).[62]
- **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.[62]
- **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.[63]
- **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.[64] 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.[65]** One clinical trial evaluating its role in COVID-19 infection (NCT04292340) is currently underway in China as well.[66]
- **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.[67]**
- **IVIG: Cao et al. reported clinical improvement in three cases with severe COVID-19 infection from China[61]. A clinical trial is currently underway in China to further assess its utility.[68,69]**
- **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.[70]**
- **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.[71,72]**

- **International Clinical Trials: There are two large international clinical trials that are currently underway:**
  - **Solidarity trial: A WHO-funded trial enrolling patients into one of 5 treatment arms: remdesivir, chloroquine/hydroxychloroquine, LPV/RTV, LPV/RTV+ IFN-β or standard of care. Countries participating in the trial include Argentina, Bahrain, Canada, France, Iran, Norway, South Africa, Spain, Switzerland, and Thailand.[73]**
  - **Discovery trial: A European trial similar to Solidarity trial except that hydroxychloroquine is solely used instead of chloroquine. The trial plans to enroll 3200 patients from Belgium, France, Germany, Luxembourg, the Netherlands, Spain, Sweden, and the UK.[73]**

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Glossary

ACE2: angiotensin-converting enzyme-2; AIS: acute ischemic stroke; ARDS: acute respiratory distress syndrome; CNS: central nervous system; CFR: case fatality rate; CKD: chronic kidney disease; CRP: C-reactive peptide; CRR: case recovery rate; CVST: cerebral venous sinus thrombosis; DM: diabetes mellitus; DMT: disease-modifying therapy; HCP: healthcare personnel ; HTN: hypertension; ICH: intracerebral hemorrhage; IVIG: intravenous immunoglobulin; LEMS: Lambert Eaton myasthenic syndrome; MG: myasthenia gravis; PAPR: powered, air-purifying respirator; PLEX: plasma exchange; PNS: peripheral nervous system; PPE: personal protective equipment ; rRT-PCR: real-time reverse transcription-polymerase chain reaction