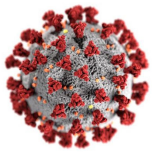

HFH NEUROLOGY COVID-19 SCIENTIFIC ADVISORY BOARD 03/24/20 UPDATE

COVID-19 pandemic: the numbers (as of 3/24/20, 9 am EST)

- **World**:[1] 395,647 confirmed cases. Total deaths:17,241 (CFR 4.35%). Total recovered:103,317 (CRR 26.11%).
- **US**:[1] 46,485 confirmed cases. Total deaths:591 (CFR 1.2%). 119 new deaths in the past 24 hours. Highest number of deaths in NY: 125 deaths.
- **Michigan**:[2] 1,328 confirmed cases. Total deaths:15 (CFR 1.2%). 5 new deaths in the past 25 hours.
- **Evolution of the pandemic**:[3] The US is in the acceleration phase of the pandemic with exponential growth of confirmed cases and deaths. The number of deaths increased 2.3 times in the past 3 days. In China, the curve has almost flattened. Less than 10 new cases per 24 hours in the past 5 days.

Best exposure prevention practices

- **NEW! 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]

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.**[6]
- Cytokine storm, from immune system hyperactivation, leads to multiorgan system dysfunction (MOSD) and failure (MOSF). Lymphopenia appears to be a universal finding in severe disease. IL-6 is central to the pathophysiology.
- Mild disease in 81% cases, severe disease (respiratory failure, ARDS, requiring oxygen +/- ventilatory support) in 14% cases, and critical disease (shock, MOSD, MOSF) in 5% cases.[7]

Updates on SARS-CoV2 testing

- Per the CDC,[8] 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).[9] 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, can take up to 5 days based on 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.**[10]
- **Serology:** IgM and IgG testing important to understand immune response. In one study, antibodies were detected in all patients 5 days after symptom onset.

SARS-CoV2 neurological syndromes

- **Symptomatology:**
  - CNS symptoms: In one study, 24.8% of cases (dizziness and headache).[11] In another study of 221 patients at a single center in China, 5% cases had AIS, 0.5% CVST and 0.5% ICH.[12] 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).[11] 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.[11]
- 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.** [13]
  - 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.[14]
- **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.[15-17] So far, there have been only rare reports of encephalitis associated with COVID-19[18] making it an infrequent cause of new onset epilepsy.
  - 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.[19] 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.[20] 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.**[21] 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.[22]
  - 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 seizure medications.[23]

- **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.[24]
- **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**.[25]
    - 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.
    - 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 cautious social isolation.
- **Movement disorders**
    - **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: what works, what doesn't

- **Therapies targeting viral replication:**
    - **Lopinavir/ritonavir:** not recommended; **not effective** when tested in COVID-19 pneumonia (did not change mortality, discharge, length of stay).[26] 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,[27-29]

except for children and pregnant women with severe disease. Transitioning to an “expanded access program” soon.

- **Ribavirin**: guanosine analogue, usually combined with recombinant interferon. Not effective in MERS.[30] Looks good in vitro with poor in vivo activity (hard to get high enough serum levels in humans/limited by toxicity).
- **Hydroxychloroquine/azithromycin**: In vitro data has demonstrated efficacy of chloroquine and hydroxychloroquine in suppressing SARS-CoV2.[31] Based on this data, Gautret et al.[32] 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. Viral eradication was assessed via repeat PCR 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. Interesting 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 3 patients who were transferred to ICU and 1 patient who died which could have altered the outcome in addition the use of a different PCR cycle threshold for defining positive test than the one adapted by CDC as well.[33]

- **Immunosuppressive and modulatory therapies**
  - **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.[34] There are two currently ongoing clinical trials in China further investigating this drug.[35]
  - **Sarilumab:** another monoclonal antibody targeting IL6 receptors. A clinical trial evaluating its use is currently enrolling patients in New York (NCT04315298).[35]
  - **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.[36]
  - **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).[37]
  - **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.[37]
  - **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.[38]
  - **Convalescent plasma:** Convalescent plasma from recovering patients has been used in SARS-COV with reported success. One clinical trial evaluating its role in COVID-19 infection (NCT04292340) is currently underway in China,[39] and similar ones are planned in the US.

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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