

# Develop – DeVos Cardiovascular Research Program’s Emergency Letter on the Pandemic

Scientific Stream Update on the COVID-19 Pandemic – 4.14.20, 1400

Spectrum Health contact: Stefan Jovinge, MD

## 1/3 of COVID-19 Patients Do Have Neurological Signs – Half of Them If They Are Severely Ill In COVID-19

Article Title: Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China

<https://jamanetwork.com/journals/jamaneurology/fullarticle/2764549>

Source: JAMA

Clinical Field: Neurology

Article Type: Clinical Study

Study Type: Retrospective Study

Patient Group: COVID-19 patients

Intervention: Observational

Reviewer	Andrea Little
Study Design	
Study Design Concerns	Retrospective, observational study with data abstracted from EMR of 214 patients in one geographic location (Wuhan, China). Mild neurologic manifestations (taste, smell disturbance) may have been overlooked if not explicitly stated in EMR. Unable to distinguish whether neurologic manifestations are caused by virus directly or by the pulmonary disease or other organ damage indirectly.
Main Results	78/214 (36.4%) consecutive Covid-19 + patients had nervous system manifestations: CNS (53 [24.8%]), PNS (19 [8.9%]), and skeletal muscle injury (23 [10.7%]). Categories of included CNS manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), PNS manifestations (taste impairment, smell impairment, vision impairment, and nerve pain), and skeletal muscular injury manifestations. Nervous system manifestations were significantly more common in severe infections compared with nonsevere infections (40 [45.5%] vs 38 [30.2%], P = .02). They included acute cerebrovascular disease (5 [5.7%]; 4 patients with ischemic stroke and 1 with cerebral hemorrhage who died later of respiratory failure; vs 1 [0.8%]; 1 patient with ischemic stroke;

	<p>P = .03), impaired consciousness (13 [14.8%] vs 3 [2.4%]; P &lt; .001), and skeletal muscle injury (17 [19.3%] vs 6 [4.8%]; P &lt; .001).</p> <p>Some patients without typical symptoms (fever, cough, anorexia, and diarrhea) of COVID-19 came to the hospital with only neurologic manifestation as their presenting symptoms.</p>
Comments	<p>During the epidemic period of COVID-19, when seeing patients with these neurologic manifestations, physicians should consider SARS-CoV-2 infection as a differential diagnosis to avoid delayed diagnosis or misdiagnosis and prevention of transmission.</p>

### As Above

**Article Title: *The Spectrum of Neurologic Disease in the Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic Infection***

<https://jamanetwork.com/journals/jamaneurology/fullarticle/2764548>

Source: JAMA

Clinical Field: Neurology

Article Type: Other

Study Type: Other

Patient Group: N/A

Intervention: N/A

Reviewer	Meredith Busman
Study Design	Minor concerns
Study Design Concerns	<p>Findings are based on a consecutive case series. Results may be more correlation than causation; patients with medical co-morbidities that place them at elevated risk for stroke at baseline (eg, diabetes, hypertension) are also more likely to develop severe disease. Researchers could not perform electromyography or nerve conduction studies in patients due to concern of contracting the COVID-19 infection.</p>
Main Results	<p>This is a retrospective consecutive case series of 214 patients from Wuhan, China with moderate to severe COVID-19 infection. Authors report that 36.4% of patients had some nervous system-related clinical finding, and these findings were most prevalent in patients with severe disease (45.5%). While some symptoms were quite specific (eg, anosmia, ageusia), it was unclear whether more nonspecific symptoms (eg, headache, dizziness) were disease-specific manifestations or part of a systemic inflammatory response in critical ill patients. Specific neurological symptoms tended to occur early in patients' clinical course. A very limited number of pathologic brainstem specimens demonstrated viral infiltration,</p>

	suggesting a possible central nervous system component in patients with severe respiratory failure.
Comments	This study builds on research from the 2002 SARS epidemic regarding the development of neuromuscular complications (myopathy, peripheral neuropathy, vasculitis etc) that appeared to be clinical manifestations specific to the virus itself rather than nonspecific effects of a critical illness. Thus, the neurological manifestations of COVID-19 likely exist across a spectrum.

### Management/Treatment Guidelines for Critical Ill COVID-19 Patients

Article Title: Management of Critically Ill Adults With COVID-19

<https://jamanetwork.com/journals/jama/fullarticle/2763879>

Source: JAMA

Clinical Field: Infectious Disease

Article Type: Other

Study Type: \_\_\_\_\_

Patient Group: Critical Ill COVID-19

Intervention: N/A

Reviewer	Disha Geriani
Study Design	N/A
Study Design Concerns	Clinical guidelines synopsis
Main Results	<p>Infection Control and Testing</p> <ul style="list-style-type: none"> <li>-All health care workers performing aerosol-generating procedures (intubation, nebulized treatments, open suctioning) should wear fitted respirator masks (N95, FFP2) with other PPE.</li> <li>-For usual care of non-vented patients and non-aerosolizing procedures on vented patients, use medical masks instead of fitted respirators, with other PPE.</li> <li>-Endotracheal aspirates are preferred over bronchial washings, BAL and upper respiratory tract samples.</li> </ul> <p>Hemodynamic Support:</p> <ul style="list-style-type: none"> <li>-Use conservative fluid administration strategy after assessing fluid responsiveness.</li> <li>-Use crystalloids over colloids for resuscitation. Balanced crystalloids are preferred over unbalanced.</li> <li>-Vasopressor choice: First-line is norepinephrine. If unavailable, can use vasopressin or epinephrine. Dopamine not recommended even when</li> </ul>

	<p>norepinephrine is unavailable.          Second-line: Vasopressin as an add-on to target MAP 60-65.</p> <p>Ventilatory Support:</p> <ul style="list-style-type: none"> <li>-Start supplemental oxygen if SpO<sub>2</sub>&lt;90%. Upper limit of SpO<sub>2</sub> -96%</li> <li>-For acute hypoxemic respiratory failure, use of high-flow nasal cannula (HFNC) is suggested as compared to conventional oxygen or non-invasive positive pressure ventilation (NIPPV).</li> <li>If HFNC not available, can try NIPPV (weak recommendation) with close monitoring for worsening and early intubation if needed.</li> <li>-For adults on ventilator with acute respiratory distress syndrome (ARDS), use low-tidal volume ventilation (4-8 ml/kg) with target plateau pressures of &lt;30 cmH<sub>2</sub>O. Use of higher PEEP over lower PEEP strategy recommended (weak recommendation, low-quality evidence)</li> <li>-For those on vent with moderate-severe ARDS, prone ventilation for 12-16 hours suggested. Using as-needed neuromuscular blocker instead of continuous is recommended.</li> <li>-For vent patients with severe ARDS and hypoxemia despite optimizing ventilation, trial of inhaled pulmonary vasodilator is suggested. If no rapid improvement in oxygenation, then taper the treatment.</li> <li>Use of lung recruitment maneuvers to open otherwise closed lung segments (such as 40 cm H<sub>2</sub>O inspiratory hold for 40 seconds) is suggested over not using lung recruitment maneuvers. Using staircase (incremental PEEP) recruitment maneuvers is not recommended (strong recommendation, moderate-quality evidence).</li> <li>Use of veno-venous ECMO or referral to ECMO center suggested for selected patients.</li> </ul> <p>Therapy:</p> <ul style="list-style-type: none"> <li>-In vented patients with ARDS, use of corticosteroids is recommended. In those without ARDS, routine use of corticosteroids is not suggested.</li> <li>-In COVID-19 patients on vents who have respiratory failure, use of antimicrobial agents is suggested with assessment with deescalation.</li> <li>-In critically ill patients with fever, use of pharmacologic agents suggested over nonpharmacologic agents or no treatment.</li> <li>Routine use of IV immunoglobulins is not suggested.</li> <li>Convalescent plasma is not suggested.</li> <li>There is insufficient evidence to issue recommendation on use of antiviral agents, recombinant interferons, chloroquine/hydroxychloroquine, or tocilizumab.</li> </ul>
<p>Comments</p>	<p>This paper was published on March 26, 2020 by Surviving Sepsis Campaign.</p> <p>There continues to be rapid synthesis of heterogenous and rapidly evolving data and clinical experience shared by physicians.</p> <p>A small single-center clinical trial (n=83) has suggested decreased intubation and mortality in patients using helmet NIPPV. It could be useful to spare patients from invasive mechanical ventilation while limiting exposure to health care workers. If ventilators are in short supply, it is possible to deliver helmet NIPPV using a flow generator (&gt;60L/min) to</p>

	<p>deliver oxygen and an expiratory pressure valve to maintain PEEP. Given uncertainty regarding its safety and efficacy in COVID-19, the guideline panel was unable to make recommendations.</p> <p>Additionally, there may be different institutional protocols on management based on response of patients noted to the above mentioned therapies given the rapidly evolving data.</p>
--	---

### Quarantine On Population Level Reduces the Spread of SARS-CoV-2 and R<sub>1</sub>

Article Title: Association of Public Health Interventions With the Epidemiology of the COVID-19 Outbreak in Wuhan, China

<https://jamanetwork.com/journals/jama/fullarticle/2764658>

Source: JAMA

Clinical Field: Other

Article Type: Other

Study Type: Retrospective Study

Patient Group: COVID-19+

Intervention: Correlation Public Health Interventions with disease

Reviewer	Vinu Perinjilil
Study Design	N/A
Study Design Concerns	<p>1) Low availability of testing and capability in the early/1st period of observation could skew case rate. Therefore case rate per million people of 2 before January 10th is an underestimate when compared to case rate per million people of 45.9 in the second period starting January 10 until January 22. This flaw could be corrected across the 3rd, 4th, and 5th observation period as testing and detection increased.</p> <p>2) cases occurring in early days of a new period included infections acquired during the previous period, so there are lags for the intervention to take place</p> <p>3) no specific details on extent of certain targeted screening interventions like universal symptom survey, so individual strategies can not be evaluated</p> <p>4) ascertainment bias could account for initially high proportion of severe/critical cases seen initially. there were likely also many undetected cases earlier so asymptomatic cases could be infectious to others</p>
Main Results	After the initial outbreak of SARS-CoV-2, public health interventions including traffic restrictions, social distancing measures, home isolation, centralized quarantine and universal symptom survey were implemented in Wuhan, China and associated temporally with reduced secondary

	<p>transmission (including only RT-PCR confirmed cases) across all age groups/gender/geographic regions. A total of 32,583 cases were confirmed in Wuhan with most occurring from January 20-Feb 6, 2020. The impact of these interventions were studied from December 8, 2019 to March 8,2020 and a comparison between the rate of confirmed cases and key interventions divided into 5 periods were studied.</p> <p>The time until January 10,2020 was the 1st period with no specific intervention. The second period was from January 10,2020 to January 22,2020 with massive population movement and no strong intervention with a confirmed case rate per million of 45.9. The third period from January 23-February 1 was a period of city lockdown with suspended public transit, social distancing, and home quarantine with a peak case rate of 162.6. From Feb 2 until Feb 16, more centralized quarantine measures were instituted decreasing the rate to 77.9 and by the 5th period starting on February 17th, a community universal symptom survey was implemented with a case rate of 17.2. The effective reproductive number (<math>R_1</math>= mean number of secondary cases generated from a typical primary case) was calculated as a measure of transmission before and after transmission and the highest rates were found in urban districts. <math>R_1</math> increased in the second period with a peak of 3.8 and declined to below 1 starting Feb 6,2020 after a majority of interventions like distancing and quarantining took place. The proportion of severe cases decreased gradually over time, from 53.1% in the first period to 10.3% in the 5th period which could be attributed to these measures. In terms of distribution, the proportion of severe cases increased with age with the highest of 41.3% in those aged &gt; 80 years. Females were at lower risk of severe and critical disease than males (unadjusted proportion 20.6% vs 23.7%).</p>
Comments	<p>The Chinese government implemented multiple interventions within a limited time frame to contain the spread of SARS-CoV-2 and this study is an observational study to infer effectiveness of mitigation approaches like social distancing. While a causal inference is limiting, it seems these global approaches are highly effective and correlative with the decrease in <math>R_1</math>.</p>

### Am Soc of Infect Dis Guidelines for COVID-19 Patient Management

Article Title: Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infection

<https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>

Source: IDSA

Clinical Field: Infectious Disease

Article Type: International Document

Study Type: Other

Patient Group: COVID-19

Intervention: Guideline statement

Reviewer	Stefan Jovinge
Study Design	N/A
Study Design Concerns	N/A
Main Results	<ol style="list-style-type: none"> <li>1. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine in the context of a clinical trial. (Knowledge gap)</li> <li>2. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine plus azithromycin only in the context of a clinical trial. (Knowledge gap)</li> <li>3. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends the combination of lopinavir/ritonavir only in the context of a clinical trial. (Knowledge gap)</li> <li>4. Among patients who have been admitted to the hospital with COVID-19 pneumonia, the IDSA guideline panel suggests against the use of corticosteroids. (Conditional recommendation, very low certainty of evidence)</li> <li>5. Among patients who have been admitted to the hospital with ARDS due to COVID-19, the IDSA guideline panel recommends the use of corticosteroids in the context of a clinical trial. (Knowledge gap)</li> <li>6. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends tocilizumab only in the context of a clinical trial. (Knowledge gap)</li> <li>7. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma in the context of a clinical trial. (Knowledge gap)</li> </ol>
Comments	The use of new approaches (antiviral, biol agents incl convalescent plasma) in compassionate cases hasn't been addressed.

**Article Title: Compassionate Use of Remdesivir for Patients with Severe Covid-19**
<https://www.nejm.org/doi/full/10.1056/NEJMoa2007016>

Source: NEJM

Clinical Field: Infectious Disease

Article Type: Clinical Report

Study Type: Case Report

Patient Group: COVID-19 p[at with &lt;94% sat on ambient air

Intervention: Remdesivir

Reviewer	Kathrine A. Kelly-Schuette
Study Design	Major Concerns
Study Design Concerns	<p>Conflict of Interest: manuscript initially drafted by Gilead Science writer ( sponsor of the compassionate use program), data was collected and monitored by the sponsor</p> <p>Only 75% of patients received full 10-day course</p> <p>Small number of patients, no randomized control group.</p>
Main Results	<p>61 patients receiving at least one dose 8 patients had no post-treatment data or dosing error</p> <p>53 patients included in analysis, of which 30 (57%) were mechanically ventilated, 4(8%) on ECMO.</p> <p>36 patients (68%) improvement in oxygen support level, 17/30 (57%) were extubated, 3/4(75%) ECMO patients were alive at last follow-up</p> <p>25(47%) were discharged</p> <p>7(13%) died</p> <p>At 28 days follow-up: 84% had clinical improvement, this was more common in patients receiving non-invasive ventilation and younger patients.</p> <p>60% of patients had adverse events, only 23% were serious adverse events ( most common serious events were multiple organ dysfunction, septic shock, AKI, hypotension)</p>
Comments	Remdesivir: a nucleotide analogue that inhibits RNA polymerases



	<p>Compassionate Use: 10 day course; 200 mg day 1 then 100mg day2-10</p> <p>Limitations: No viral load data , non-uniformity in treatment, small sample size, short follow up, lack of randomized control group.</p> <p>Less patients died in the non-invasive ventilation group, however they might have improved without the treatment.</p> <p>With a single arm study no conclusions can be drawn about whether the patients improved due to disease course or treatment, although the reported improvement in ventilation status is impressive. This needs to be explored further.</p> <p>Mortality is lower than other studies looking at lopinavir-ritonavir (22%) and series from Wuhan, China (66% in mechanically ventilated patients)</p>
--	---

*The content of this newsletter is provided for informational purposes only and is not intended for direct diagnostic use or medical decision-making without review and oversight by a clinical professional. The information contained in this newsletter is offered on an AS-IS basis and Spectrum Health does not independently verify the validity or utility of any information contained in or made available through the newsletter. Such information is used and relied upon entirely at the user's own risk. Users are solely responsible for any liabilities arising from use or misuse of such information.*

*Neither Spectrum Health nor any of its officers, directors, employees, agents or affiliates make any representations or warranties of any kind, express or implied, with respect to the information provided in this newsletter nor to its use, and Spectrum Health hereby expressly disclaims all representations and warranties of any kind with regard to such information and use thereof, whether express or implied, including, without limitation, warranties of title, non-infringement and fitness for a particular purpose. Spectrum Health does not purport to own or have any rights in any material made available through links contained in the newsletter, and all such materials may be subject to their own terms of use. If you have questions about the information contained in or made available through this newsletter, please contact a health care professional. No physician-patient relationship is created by use of this newsletter.*