



Articles about Covid 19, Reviewed April 13-17 By MS Covid Literature Review Task Force

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Name of Article	Journal, Date	Category of Study	Question it asks	Results in Brief	Clinical Implications, Limitations
April 13					
Respiratory virus shedding in exhaled breath and efficacy of face masks link	Nature Medicine 3APR2020	RCT	What is the importance of respiratory droplet and aerosol routes of transmission in several respiratory viruses including COVID19? Are surgical face masks efficacious in reducing transmission of COVID19?	Non-significant (p=0.07) reduction in covid19 respiratory droplets by wearing a mask, and significant reduction p=0.02) in covid 19 aerosols with mask.	Limitations: small n, different people in the with and without masks groups (could have dif viral load). Non-blinded
Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China NR	JAMA Neurology, 10 Apr 2020	Retrospective, observational case series	What are the neurologic manifestations of COVID-19? Do the neurologic symptoms differ in patients with moderate or severe COVID?	Of a subset of patients hospitalized in Wuhan, China, 36.4% had neurological symptoms. The most common neurological symptoms were general CNS symptoms (dizziness, headache, impaired consciousness), but skeletal muscle damage, loss of taste and smell, and acute cerebrovascular event were also observed. Patients classified as having severe disease were more likely to display neurological	Small sample size (n=214), patient population limited to 3 hospitals in Wuhan. Data taken from hospital records, so more subtle symptoms were likely missed. Patients were not tracked longitudinally to determine the effect of their neurological manifestations on their outcome.

				symptoms when compared to those with moderate disease (p=0.02): acute cerebrovascular diseases (5.7% vs 0.8%), impaired consciousness (14.8% vs 2.4%), and skeletal muscle injury (19.3% vs 4.8%).	
Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy MCG	JAMA, 06 April 2020	Retrospective Case Series	What are the treatments used for patients with coronavirus in ICUs? What are the health demographics of the COVID-19 patients in ICUS? What is the ICU length of stay for patients and what is the mortality in the ICU?	The median age was 63 (56-70) years; 1304 of the patients were male (82%); 1043 patients had past medical history data available and 709 of them had at least 1 comorbidity and 509 had hypertension; Only 1300 had available respiratory data, and 1287 of that group required respiratory support with 1150 receiving mechanical ventilation and 137 receiving noninvasive ventilation. The median PEEP level was 14 (IQR 12-16) and the median was not significantly different between younger patients (age less than or equal to 63 years) and older patients (age greater than or equal to 64 years); 1581 patients had ICU data on 03/25/2020 and 902 of those were still in the ICU, 256 had been discharged and 405 had died in the ICU. Older patients (n = 786; age greater than or equal to 64 years) had a higher mortality than younger patients (n = 795, age less than or equal to 63 years) (36% vs 15%; difference 21% [95% CI, 17-26%]; p <.001)	Retrospective observational study – therefore limited in data collection and full data analysis (some large amount of data missing for certain categories); intensive care being provided to patients outside of the ICU hospitals and floors designated in the study; short follow up with patients therefore long term morbidity/mortality not assessed
Factors associated with hospitalization and critical illness among 4,103	Medrxiv, 11 April 2020 (Pre-proof)	Cross-sectional	What are factors associated with hospitalization and critical illness in Covid-	Strongest hospitalization risks were age ≥75 years, age 65-74, BMI>40, and heart failure. Strongest critical illness risks were admission oxygen saturation <88%, d-	Limitations: Non-peer reviewed, one site in one geographic area, admission laboratory protocol was only established two weeks into the pandemic, resulting in

patients with COVID-19 disease in New York City UA			19 positive patients in the NYU Langone Health system?	dimer>2500, ferritin >2500, and C-reactive protein (CRP) >200. In the decision tree for admission, the most important features were age >65 and obesity; for critical illness, the most important was SpO2<88, followed by procalcitonin >0.5, troponin <0.1 (protective), age >64 and CRP>200	missing lab data for earlier patients, no inflammatory markers for non-hospitalized patients. Implications: Give an idea of the potential risk factors clinicians might consider when determining trajectory of Covid-19 patients
Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study XF	BMJ 2020 26 March 2020	Retrospective case series	What are the clinical characteristics of patients who died of COVID-19 infection.	This study gives general outlines of COVID-19 risk factors which contribute to fatality. Risk factors for moderate to severe patients include advanced age (>60), male sex, comorbidities especially hypertension and cardiovascular disease. It is notable that the time from onset of symptoms to hospital admission was longer in deceased patients, which highlights the need to develop community awareness about prompt seeking of medical care and earlier referral to the intensive care unit for high risk populations. Leukocytosis and elevated procalcitonin were shown in most deceased COVID-19 patients, indicating the likelihood in developing secondary bacterial infection.	Implications: The research results are important information for healthcare professionals to determine population with risk factors, in order to give special care. Limitations: Patient data is collected in one hospital in Wuhan, China. Most of patients are transferred from other sites when their symptoms progressed to moderate to severe, so the data is biased and might not represent the general patient characteristics.
April 14					
Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-	Cell Peer-reviewed Pre-proof (not yet published)	RCT (Basic science)	Can human recombinant soluble ACE2 inhibit SARS-CoV-2 infection <i>in-vitro</i> and in	ACE2 is the receptor by which SARS-CoV-2 enters the cell, and SARS-CoV-2 decreases ACE2 expression after infection. <i>In vitro</i> , administration of hrsACE2 significantly decreased viral infection of Vero-E6 cells (African green monkey cell line) in a dose-	Implications: This early work in cell culture and in human-derived organoids suggests that clinical grade human recombinant soluble ACE2 may disrupt SARS-CoV-2's entry into cells by serving as a decoy receptor.

<p>grade soluble human ACE2</p> <p>Link</p> <p>NR</p>			<p>human-derived organoids?</p>	<p>dependent manner. The authors used induced pluripotent stem cells to produce human capillary and human kidney organoids. Application of hrsACE2 with SARS-CoV-2 significantly inhibited viral infection of both capillary and kidney organoids. Notably, mouse ACE2 was not sufficient to inhibit viral infection.</p>	<p>Limitations:</p> <p>The experimental design only administers hrsACE2 in a mixture with SARS-CoV-2 (co-administration); this means it is only simulating efficacy of hrsACE2 in early stages of infection by inhibiting viral entry. The authors never infect cells and then later administer hrsACE2, so this study does not fully test ACE2 as a therapeutic in late-stage COVID-19.</p> <p>The study does not use lung or heart organoids, the 2 organs that appear to be most commonly affected in severe COVID-19.</p> <p>Cell culture and organoids do not fully recapitulate the complexity of the human body.</p>
<p>Incidence of thrombotic complications in critically ill ICU patients with COVID-19</p> <p>Link</p> <p>UA</p>	<p>Thrombosis Research, 10 April 2020</p>	<p>Prospective cohort</p>	<p>What is the incidence of thrombotic complications in COVID-19 patients admitted to the ICU?</p>	<p>The cumulative incidence of thrombotic complication (defined as symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial emboli) was 31% (95% CI 20-41), of which CTPA and/or ultrasonography confirmed VTE in 27% (95% CI 17-37%) and arterial thrombotic events in 3.7% (95%CI 0-8.2%). PE was the most frequent thrombotic complication (n= 25, 81%).</p>	<p>Limitations: each of the three Dutch hospitals in the study varied regarding their standard procedures for thromboprophylaxis. Furthermore, VTE is difficult to recognize in intubated patients, for whom the threshold for diagnostic testing is high due to isolation precautions. However, this could mean that the incidence of thrombotic complications could be higher in reality.</p> <p>Implications: these findings reinforce the recommendation to strictly apply pharmacological thrombosis</p>

					prophylaxis in all COVID-19 patients admitted to the ICU
Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection link MCG	BMJ, April 2, 2020	Retrospective case study	What GI symptoms are seen in SARS-CoV-2 positive patients? Can the virus be found in feces or GI secretions?	58 out of the 95 patients had GI symptoms during their hospital stay with 11 of the 58 had GI symptoms upon admission and then 47 developed symptoms during their hospital stay. Diarrhea was the most common symptom for those who presented with GI symptoms and those who developed symptoms during their stay. 22 stool samples from 42 patients with GI symptoms were positive for SARS-CoV-2. In two severe patients, virus was found in esophagus, stomach, duodenum and rectum specimens. And in four non-severe patients, only one sample from the duodenum was positive. There were 11 patients who did not present with CT findings indicative of pneumonia but only GI symptoms. Overall, there was no significant difference between outcomes.	Implications: It is possible that COVID-19 patients will present with only GI symptoms. The GI symptoms do not seem to alter the course of the disease or outcomes. Limitations: This was a small study, looking at 95 patients in one medical center and only 58 showed symptoms. Additionally, the authors mention that the GI symptoms patients developed during their hospital stay could have been side effects from different medications including antibiotics. So it is difficult to say if the symptoms are related to the virus or not.
Pharmacologic treatments for coronavirus 2019 (COVID-19) - a review XF	JAMA. Published online April 13, 2020	Literature review	Have any medical therapies been definitively shown to improve outcomes in a patient with COVID-19?	Remdesivir is a promising potential therapy for COVID-19 due to its broad-spectrum, potent in vitro activity against several nCoVs, including SARS-CoV-2 with EC ₅₀ and EC ₉₀ values of 0.77 μM and 1.76 μM, respectively. Notably, remdesivir is not currently FDA-approved and must be obtained via compassionate use (only for children <18 years and pregnant women), expanded access, or enrollment in a clinical trial.	Implications: This literature review performed research on all the COVID-19 research using English-language published through March 25, 2020. The search resulted in 1315 total articles. Due to the lack of RCTs, the authors also included case reports, case series, and review articles. Limitations: most published clinical research are non-randomized trials, case reports, and data are collected

			<p>No high-quality evidence exists for the efficacy of chloroquine/hydroxychloroquine in the tx of coronavirus, even though they show some evidence in viral clearance. Relatively well tolerated, safe in pregnancy woman.</p> <p>The current data suggest a limited role for lopinavir/ritonavir (anti-HIV agents) in COVID-19 treatment.</p> <p>In vitro activity of Ribavirin against COVID-19 was limited and required high concentrations or combination therapy to inhibit viral replication. Effective formulations include only intravenous or enteral administration. Substantial severe dose-dependent hematologic toxicity.</p> <p>Umifenovir, a S protein/ACE2 inhibitor shows some promising data of lower mortality rates (0% [0/36] vs 16% [5/31]) and higher discharge rates in the observational study.</p> <p>Favipiravir demonstrated broad activity against other RNA viruses. In vitro, EC₅₀ of favipiravir against SARS-CoV-2 was 61.88 µM/L in Vero E6 cells. However, favipiravir is currently available in Japan for the treatment of influenza, but not available in the United States for clinical use.</p>	<p>outside of US. Further RCT is needed to provide more evidence of different treatment options to COVID-19.</p> <p>Both CDC and WHO announced that “there is no current evidence to recommend any specific anti-COVID-19 treatment for patients with confirmed COVID-19”, and “prompt implementation of recommended infection prevention and control measures and supportive management of complications.”</p>
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<p>Estimates of the severity of coronavirus disease 2019: a model-based analysis Link</p> <p>CS</p>	<p>Lancet 3/30/2020</p>	<p>Retrospective case study</p>	<p>How long is the disease course? What is the true death rate in COVID patients in China?</p>	<p>Time of onset to death 17.8 days (95% CI 16.9-19.2). Time of onset to hospital discharge 24.7 days (95% CI 22.9-28.1). Adjusted for censoring and under-ascertainment, case fatality ratio estimated at 1.38%(1.23-1.53) with dramatically increased ratios when stratified by age: 6.4%(5.7-7.2) in those >60yo; 13.4%(11.2-15.9) in those >80yo.</p>	<p>Limitations: Extrinsic validity is a concern because the patient population was strictly from China. Although the authors attempted to control for censorship and underreporting, these factors still are present. Likely, there are more cases than reported which would ultimately drive the death rate down especially among younger patients (asymptomatic carriers, etc). However, the authors question how it would affect DR for older patients since they are more likely to be symptomatic and be tested and contribute to confirmed cases.</p> <p>Implications: Useful in judging length of hospital stays/advising patient monitoring based on time course. Reinforces wide reports of COVID being more severe and fatal in older populations.</p>
<p>April 15</p>					

<p>Temporal dynamics in viral shedding and transmissibility of COVID-19 Link</p> <p>CS</p>	<p>Nature 4/15/2020</p>	<p>Basic Science</p>	<p>When do COVID patients become infective? How does infectivity change over disease course?</p>	<p>Based on throat swabs and viral loads, infectivity calculated to begin 2.3 days (0.8-3.0) before symptom onset. Peak infectiousness calculated to be 0.7 days (-0.2-2.0) before symptom onset. Viral shedding decreased monotonically after symptom onset and is detectable for a median length of 20 days (as high as 37 days in patients who survive). Based on viral load, they suggest infectivity declines sharply after 8 days post symptom onset. Sex, cases severity, and age do not appear to be factors related to infectivity.</p>	<p>Limitations: Determination of onset of first symptoms relied on patient recall. Authors discuss patients likely had delayed recognition of their symptoms, meaning estimates of presymptomatic transmission are likely inflated. Additionally, viral loads came from patients who were treated based on current Chinese protocols. Therefore, medications could affect the shedding pattern and may not be generalizable to asymptomatic carriers and those who do not seek treatment.</p> <p>Implications: These data are most likely to have the biggest impact after the first case spike in the spring subsides and public health measures shift from mitigation back to containment. Understanding when a patient is infective is crucial for setting quarantine timelines and contact tracing. These findings also highlight how crucial physical distancing is since the authors suggest patients are most infective before they even know they are sick.</p>
<p>Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma</p>	<p>JAMA 3/27/20</p>	<p>Case series</p>	<p>Is convalescent plasma beneficial in treating severe COVID-19?</p>	<p>5 patients in Wuhan, China received plasma from donors who had recovered from COVID-19. All 5 patients displayed increased Ct value (correlated with decreased viral load) to the undetectable range by 12 days post-transfusion, decreased SOFA scores, increased PAO2/FiO2 and decreased body</p>	<p>Implications: This study provides a first look into convalescent plasma as a treatment for COVID-19. The decreased viral load, decreased SOFA scores and increased lung function are encouraging.</p>

<p>Link</p> <p>NR</p>				<p>temperature. All 5 patients displayed decreased CRP and procalcitonin, and 4 had decreased IL-6. As of March 25th, 3 of the patients had been extubated and discharged, while 2 were stable but still receiving mechanical ventilation. One patient, who was on ECMO at time of transfusion, removed from ECMO 5 days post-transfusion.</p>	<p>Limitations: This is an n=5 study with no controls, so it cannot truly assess whether convalescent plasma was responsible for patient recovery. Also, only one of the patients tested had any identifiable pre-existing conditions, so the sample likely does not accurately reflect the population with severe COVID-19 infection. (May have been cherry picked as those most likely to recover.)</p>
<p>Compassionate Use of Remdesivir for Patients with Severe Covid-19</p>	<p>The New England Journal of Medicine 10 April 2020</p>	<p>Prospective cohort</p>		<p>“During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support” required. By 28 days of follow-up, 84% (95% CI 70 to 99) had clinical improvement.</p> <p>All 12 patients on ambient air or low-flow o2 improved clinically. Improvement was observed in 5 of 7 patients (71%) who were receiving noninvasive oxygen support (NIPPV or high-flow supplemental oxygen). “It is notable that 17 of 30 patients (57%) who were receiving invasive mechanical ventilation were extubated, and 3 of 4 patients (75%) receiving ECMO stopped receiving it; all were alive at last follow-up.”</p>	<p>Limitations: No adjustments made for multiple comparisons in tests (multiplicity effect). Did not standardize when in the duration of illness the patients were started on remdesivir. Other limitations include small sample size and no randomized control group.</p> <p>the 13% mortality observed in this remdesivir cohort study is actually relatively low given reported mortality rates of up to 22% in hospitalized patients in China. This mortality rate is also smaller than the mortality in many other COVID19 studies, including an RCT of lopinavir.</p> <p>An RCT is needed to assess efficacy and safety; however, the results of this cohort study suggest Remdesivir may be useful in treating patients with COVID19 at all stages of disease.</p>

April 16	<p><i>Science Translational Medicine</i> 06 Apr 2020</p>	<p>Basic science: in-vitro assays and in-vivo mice models</p>	<p>What is NHC's antiviral activity against multiple emerging strains of coronavirus (CoV with dif mutations)? What is the mechanism of action? And was is NCH's efficacy in mouse models of CoV?</p>	<p>NHC is potently antiviral against two genetically distinct emerging CoV. In a clinical isolate of SARS-CoV2 (2019-nCoV/USA-WA1/2020), NHC had a maximum effective concentration IC50 of 0.3 μM and no observed cytotoxicity (50% cytotoxic concentration, CC50, >10 μM). It inhibited virus production and viral RNA genomes (IC50 of 0.08 μM and 0.09 μM, respectively). In human airway epithelial (HAE) cell cultures SARS-CoV-2, MERS-CoV and SARS-CoV there was a dose dependent reduction in virus production without cytotoxicity. Previously found resistance to remdesivir was by mutations in by RdRp residues F480L and V557L. These 2 mutations were still sensitive to NHC. In assays in HAE with three zoonotic Bat-CoV: SHC014, HKU3, and HKU5, NHC diminished virus and RNA in all three Bat-CoVs. High-fidelity sequence analysis demonstrated increased mutations in MERS-CoV RNA after NHC treatment of primary HAE cell cultures. In mice treated with EIDD-2801 (NHC pro-drug) there was a significant decrease in pulmonary hemorrhage, body weight loss, and SARS-CoV lung titer. There was a prophylactic effect by treating 2 hours pre-infection. It was also effective at decreasing pulmonary hemorrhage up to 24 hours post-infection. viral loads were decreased at 12,</p>	<p>NHC is effective against remdesivir (RDV)-resistant virus and multiple distinct zoonotic CoV. Because NHC was effective in CoVs with over 20% variation in RdRp, "if another SARS- or MERS-like virus were to spillover into humans in the future, they would likely be susceptible to the antiviral activity of NHC."</p>
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[An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice](#)

Science Translational Medicine 06 Apr 2020

Basic science: in-vitro assays and in-vivo mice models

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				24, and 48 hours. Blindly evaluated hematoxylin and eosin-stained lung tissue showed treatment initiated up to +12 hours significantly reduced ALI (acute lung injury)	
<p>A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19</p> <p>Link</p> <p>CS</p>	<p><i>NEJM; March 18, 2020</i></p>	RCT	Does Lopinavir-Ritonavir treatment shorten clinical course, reduce mortality, and/or decrease viral load in COVID-19 patients?	<p>Time to clinical improvement was 16 days for both treatment and control groups. Hazard ratio for clinical improvement was 1.31 (95% CI 0.95-1.8). The 28 day mortality ARR for the treatment group was 5.8% (95% CI, 17.3 to -5.7). No significant difference in viral load at days 5, 10, 14, 21, and 28 after randomization.</p>	<p>Implications: This study suggests no clinical benefit for lopinavir-ritonavir therapy in severe COVID-19 illness.</p> <p>Limitations: Trial was no blinded, no placebo therapy given to standard care alone patients. Additionally, mortality rate for the study was 22.1% which is much higher than the mortality rate of hospitalized COVID-19 cases reported elsewhere of 11%-14.5%. This suggests patients in this trial were more ill than the generalized population of hospitalized patients. This means further trials would be needed to determine efficacy of lopinavir-ritonavir treatment in mild COVID cases.</p>
<p>Assessment of N95 respirator decontamination and re-use for SARS-CoV-2</p> <p>Link</p> <p>NR</p>	<p><i>MedRxiv, April 15, 2020</i></p> <p><i>Not yet peer-reviewed</i></p>	Experimental	Can N95 masks be decontaminated without compromising mask integrity? What method is best?	<p>NIH study compared ethanol spray, UV, heat and vaporized hydrogen peroxide (VHP) in ability to decontaminate N95 masks and mask effectiveness after multiple cleanings. VHP appears most practical: decontamination of SARS-CoV-2 in 10 minutes and masks retained sufficient integrity for 3 uses. Ethanol spray rapidly decontaminated, but compromised mask quality too much for reuse. UV and heat required longer treatment length to</p>	<p>Implications: This study suggests that use of vaporized hydrogen peroxide could be a method for hospitals to reuse N95 masks in the current PPE shortage.</p> <p>Limitations: Study is not peer-reviewed. Laboratory conditions may not reflect those in the hospital.</p>

				sufficiently decontaminate, and maintained mask integrity for 3 treatments, suggesting maximum of 2 uses.	
Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations Link UA	<i>Lancet</i> <i>April 6, 2020</i>	Review	What are the challenges that ICUs might face during this pandemic and how can they navigate these issues?	This well written review covers a variety of subjects including respiratory management, pharmaceutical interventions and infection control. They also mention surge options that include the addition of beds to a pre-existing ICU, provision of intensive care outside ICUs, and centralization of intensive care in designated ICUs, while considering critical care triage and rationing of resources should surge efforts be insufficient	Implications: This review gives insight to the challenges that ICUs have and will experience during this pandemic. It also outlines some basic strategies that can be utilized so that healthcare systems are not overwhelmed. Limitations: The issues faced by ICUs across the country differ in many ways and there are few solutions that can be broadly applied to every institution.