

COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
James Luby, M.D., and Robert Haley, M.D., editors

The Situation: U.S. Confirmed Cases Exceed 3.5 Million

In the world, as of July 17, 2020, 13,832,242 cases of COVID-19 have been confirmed, including 590,608 deaths. In the United States, there have been 3,576,430 cases, the most in the world followed in order by Brazil, India, Russia and Peru. In terms of cases, China is now twenty-third with 85,314 cases.¹ Deaths in the U.S. through July 17 have been estimated at 138,360.²

From March 10 through July 16, there have been 36,969 confirmed cases of Covid-19 reported from Dallas County with 485 confirmed deaths, 37% of these from long-term care facilities.³ Of hospitalized cases in Dallas County, more than two-thirds have been under 65 years of age, and about half have not had any high risk chronic health conditions. Diabetes mellitus has been seen in about one-third of all hospitalized patients. More men than women have died. As of 6/12/20, the age-adjusted rates of confirmed Covid-19 cases in non-hospitalized patients have been highest among Hispanics (667.4/100,000) with Asians (187.4/100,000), Blacks (136.4/100,000) and Whites (43.8/100,000) having lower incidence rates. Sixty percent of the cases have occurred in the Hispanic population. Specimens submitted for diagnosis of respiratory viruses show continuing positivity for SARS-CoV-2 with the latest result being 30%.³

References:

1. Covid-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 7/17/20)
2. Worldometer. Coronavirus update 7/17/20
3. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 7/16/20

Feature Article

Anti-Rheumatic Therapies for Covid-19 Infection

John J. Cush, MD, Rheumatology Division

Since the onset of the Covid-19 pandemic numerous anti-rheumatic therapies have been proposed as being potentially beneficial. The mechanistic effects of these agents, either presumed antiviral, anti-inflammatory and anti-thrombotic effects, may mitigate the damage seen with Covid-19 infection.

This review will examine the potential benefits and existing evidence for treating suspected or proven Covid-19 infection with antimalarials, inhibitors of interleukin-6 (IL-6) or interleukin-1 (IL-1), Janus kinase (JAK) inhibitors, TNF inhibitors or colchicine. There are many other anti-rheumatic and immunosuppressive therapies that are in clinical trials that will not be reviewed here including IVIG, rituximab, calcineurin inhibitors (sirolimus, etc.), apremilast, emapalumab (anti-IFN gamma), etc.

Antimalarials

In early March 2020, HCQ (HCQ) and chloroquine (CQ) were promulgated as potentially beneficial in Covid-19 patients because of their use with malaria and clinical trials treating other viral infections. However, HCQ and CQ have failed in other viral infections including influenza, dengue, chikungunya, Ebola and HIV. Nonetheless, the FDA green-lighted early studies of antimalarials by issuing an “emergency use authorization” for both CQ

and HCQ on March 31st. Contemporaneously Covid-19 treatment guidelines from the American College of Rheumatology (ACR) and NIH suggested that patients receiving chronic HCQ for a rheumatic condition should continue on HCQ and that if a patient had a presumed or proven Covid-19 this agent could be continued.

Between March and June 2020, there were numerous observational and cohort reports demonstrating either no evidence of a protective effect or poorer outcomes or more deaths when HCQ was used. Many of these poor and fatal outcomes could be attributed to only the sickest of patients being put on this speculative intervention. In fact, there were very few reports of HCQ or CQ cardiotoxicity or arrhythmias, including QT (QTc) prolongation or torsades de pointes. With mounting evidence of inappropriate HCQ used by the public, the FDA and Health Canada issued safety warnings against the routine or prophylactic use of anti-malarial agents in Covid-19, especially for those not hospitalized or participating in clinical trials. By mid-June 2020, growing equivocal or negative evidence resulted in: 1) FDA withdrawal of its “emergency use authorization”; 2) WHO suspending its large “SOLIDARITY” trial of HCQ in Covid-19; and 3) the NIH and numerous sponsors also suspending their HCQ trials.

More recently, a NEJM article showed that HCQ was ineffective at prophylaxis. When given to 812 Covid-19 exposed asymptomatic persons, it was not shown to reduce Covid-19 infections.¹ (See previous coverage of this topic in *C.A.N.* Vol. 1, No. 7, May 29, 2020.)

JAK Inhibition

Studies of Janus kinase (JAK) inhibitors in Covid-19 are showing that baricitinib inhibits viral endocytosis via inhibitory effects on AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK). Moreover, JAK inhibitors are known to substantially downregulate inflammation by blocking cytokine (e.g., IL-6 and interferon) signaling. Hence there may be a rationale for either the early (antiviral) or late (anti-inflammatory) use of baricitinib or other JAK inhibitors currently in clinical trials (tofacitinib, ruxolitinib, etc.). In a small group of 12 patients treated with baricitinib along with an antiviral for 2 weeks had more improvements in CRP levels, lymphopenia, ICU admissions and hospital discharges than those who did not receive baricitinib.²

Interleukin-6 Inhibition

IL-6 has been shown to be a key regulator of the “cytokine release syndrome” (CRS) seen with CART-cell therapy in acute leukemia. Such patients are at high risk for grade 3 and 4 CRS with fever, capillary leak, hypotension, and organ damage. When these patients were treated with intravenous tocilizumab (an IL-6 inhibitor) the vast majority showed substantial improvement.

Covid-19 patients are at morbid and mortal risk for the cytokine storm syndrome complication and IL-6 inhibition has been among the many agents under study for this complication and in severe Covid-19 pneumonia as well. Tocilizumab is currently approved for use in rheumatoid arthritis, juvenile arthritis, Still's disease, giant cell arteritis and CRS (with CAR-T cell therapy). The usual dose is 4 to 8 mg/kg given IV, but in extreme inflammation (e.g., Still's disease, CRS) most use either 8 to 12 mg/kg as a single dose that can be repeated in two weeks in those who are gravely ill. Common complications of IL-6 inhibitors would include a slight increase in serious infections, hepatic enzyme elevations, hyperlipidemia, neutropenia and a very low risk of GI perforation (0.26/100 patient-years exposure).

Most of the existing evidence is uncontrolled observational or cohort studies that have not been peer-reviewed. Nonetheless, thus far most of these trials have shown favorable outcomes when given to patients with severe Covid-19 infection. There are numerous trials ongoing on several different IL-6 inhibitors including tocilizumab, sarilumab and sirukumab, with most available evidence reported for tocilizumab. The uncontrolled clinical trials thus far have shown improvements in those receiving high doses sarilumab or tocilizumab. These trials were largely done in patients with Covid-19 pneumonia or more severe disease and impending respiratory failure. IL-6 inhibition reduced the need for mechanical ventilation and/or lowered death rates in these studies. Although IL-6 inhibition is given either to treat or prevent cytokine storm syndrome, there are no current results showing its efficacy in patients with severe Covid-19 infection and cytokine storm.³

Editorial Note: This is a rapidly developing field with new results almost daily. For example, the drug companies investigating sarilumab have just halted study of this medication at 400 and 800 mg dosages because of failure to reach primary and secondary end-points in patients receiving mechanical ventilation.

Interleukin-1 Inhibition

There are numerous IL-1 inhibitors in Covid-19 clinical trials, including the short-acting anakinra and the longer acting canakinumab. Anakinra has been used in 2 clinical studies. In one it was given as 100 mg twice a day subcutaneously (or 5 mg/kg twice a day intravenously) to 29 Covid-19 patients with non-ICU ARDS and elevated inflammatory markers (CRP or ferritin). Those on anakinra had better survival (90% vs. 56%; $p=0.009$) and better correction of CRP and respiratory function (72% vs 50%) compared to non-anakinra patients after 3 weeks of observation. Another retrospective series of 11 severe Covid-19 patients treated with anakinra showed that, if given within the first 36 hours, none of the 7 patients treated for 4 days or more required mechanical ventilation or died compared to 2 of 4 untreated patients did. Clinical trials of canakinumab are pending.⁴

Dexamethasone

While glucocorticoid use in Covid-19 patients is potentially life-saving, it may add to complications in severely ill patients. The NIH consensus guidelines on the treatment of Covid-19 recommended against the use of systemic corticosteroids in mechanically ventilated patients without evidence of acute respiratory distress syndrome (ARDS). And for those with ARDS, they did not recommend for or against their use. Last month, preliminary results of an open-label randomized trial were released before journal peer review by the RECOVERY (trial) Collaborative Group at Oxford showing that dexamethasone (DEX) was capable of reducing mortality rates by 30% in some patient groups. This trial was called a “major breakthrough” by some and viewed with skepticism by others. The study compared outcomes in 2104 Covid-19 patients randomized to dexamethasone with 4,321 patients given placebo. Overall the 28 day mortality rate was 21.6% with DEX and 24.6% with placebo and usual care ($p<0.001$). There were also fewer mechanical ventilations (5.2% vs 7.1%; $p=-.021$) and more hospital discharges at day 28 (64.6% vs. 61.1%; $p=0.002$). The apparent benefits were greater in more seriously ill groups.

Colchicine

Colchicine is currently used to treat gout, pseudogout, familial Mediterranean fever and pericarditis. It is thought to work by inhibition of microtubules, neutrophil chemotaxis and inflammasome activation via NALP3. The agent has been proposed as an early intervention and is under study by the Montreal Heart Institute (along with UCSF and NYU) in a 6000 patient trial. A recent *JAMA* report of the GRECCO study showed in an open-label clinical trial of 105 patients, those treated with colchicine had less clinical deterioration though without significant changes in biomarkers, such as high-sensitivity cardiac troponin and C-reactive protein.⁵

References:

1. Cush J. Hydroxychloroquine's world of confusion - what you need to know. *RheumNow.com* May 5, 2020 <https://buff.ly/3fxhYFR>
2. Boulware DR, et al A randomized trial of HCQ as postexposure prophylaxis for Covid-19. *N Engl J Med* 2020 Jun 3 PMID: 3249229
3. Richardson P, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 2020 Feb 15;395(10223):e30-e31
4. Cavalli G, et al. Interleukin-1 blockade with high-dose anakinra in patients with Covid-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020 Jun;2(6):e325-e331
5. Deftereos SG, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 Randomized Clinical Trial. *JAMA Netw Open* 2020;3(6):e2013136.

Pathogenesis

Masks Reduce Transmission and Severity of Covid-19 Infection

Support for the Effectiveness of Masking and for the Effect of Dose on Severity

A central question in control of the Covid-19 epidemic, absent a safe and effective vaccine, is the effectiveness of facial coverings in reducing the transmission rate and severity of transmitted infections. Numerous challenge studies in animal models since the 1930s have demonstrated that the risk of acquiring infection with influenza A virus and the severity of the resulting disease increase with the size of the infecting dose of virus, as reviewed by Paolo et al.¹ While SARS-CoV-2 might not behave the same as influenza A virus, recent epidemiologic evidence supporting the effectiveness of facial coverings in reducing Covid-19 spread suggests that it does (see review in *C.A.N.* June 19, 2020, Vol. 1, No. 10).

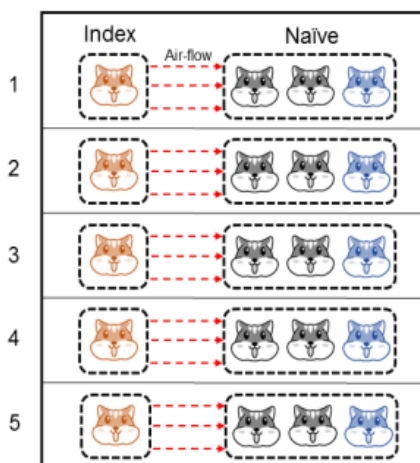
Enter a new laboratory study testing this principle in a hamster model by Chan et al. of the University of Hong Kong and Queen Mary Hospital, Hong Kong Special Administrative Region, China, presently in press at *Clinical Infectious Diseases*.² The investigators studied a well-established gold Syrian hamster SARS-CoV-2 model, placing hamsters in 2 cages separated by a polyvinyl chloride (PVC) air porous partition with unidirectional airflow. In the upwind cage they placed hamsters inoculated intranasally with SARS-CoV-2 virus and in the downwind cage, naïve hamsters.

In the first experiment, the control condition, with the cages separated only by the air porous PVC partition to prevent physical contact, they found at 2 days post inoculation (dpi) all of the inoculated hamsters developed clinical signs of Covid-19 infection and had virologic and histologic evidence of infection, and at 5 dpi 60% of the exposed naïve hamsters did likewise.

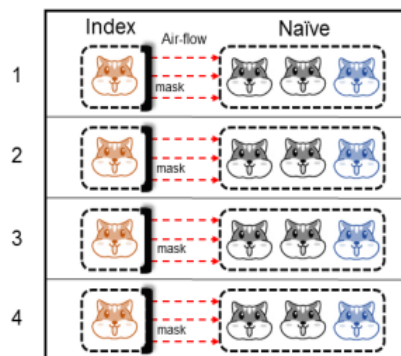
In the second experiment, a surgical mask was installed between the cages with the external side of the mask facing the naïve hamsters, simulating a mask being worn by the inoculated hamsters. At 5 dpi only 12.5% of the naïve hamsters became PCR positive for SARS-CoV-2 infection. At 7 dpi a quarter of the remaining hamsters had become PCR positive.

In the third experiment, the surgical mask was reversed with the external side of the mask facing the inoculated hamsters, simulating a mask being worn by the naïve hamsters. At 5 dpi only 37.5% of the naïve hamsters became PCR positive for SARS-CoV-2 infection. At 7 dpi a quarter of the remaining hamsters had become PCR positive.

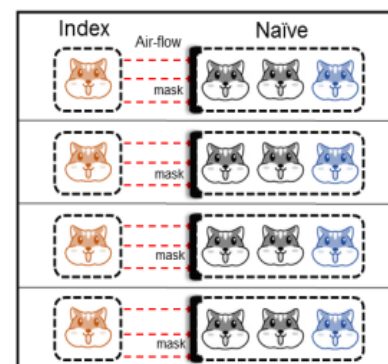
Experiment 1: no surgical mask partition



Experiment 2: surgical mask partition with the external surface facing exposed naïve hamsters



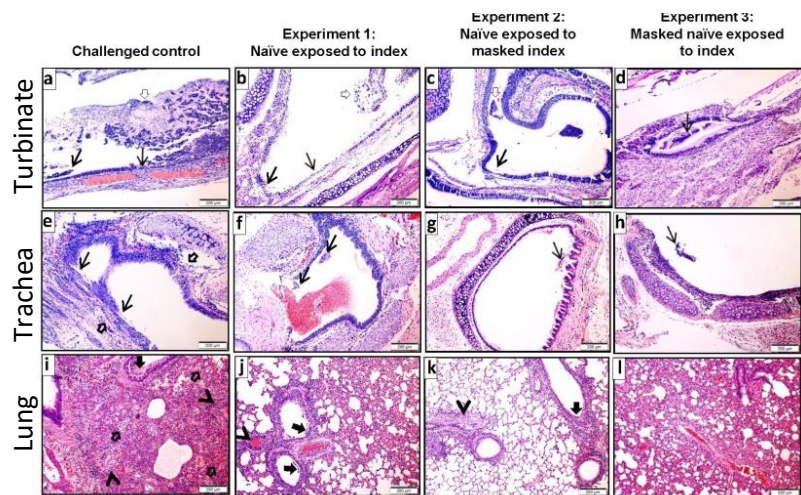
Experiment 3: surgical mask partition with the external surface facing challenged index hamsters



At the end of the experiment at 7 dpi all animals were sacrificed for study. From the control experiment, all of the inoculated hamsters had developed neutralizing antibody and 60% of the naïve hamsters had, indicating that the naïve hamsters had acquired antibody very early after exposure. In contrast, in the remaining experiments none of the naïve hamsters protected by the surgical mask had developed neutralizing

antibody, indicating that the infecting dose took longer to establish the systemic infection capable of stimulating an immunologic response.

Histologic examination of nasal turbinate, trachea and lung demonstrated severe pathological changes in the inoculated hamsters, moderate damage in the naïve hamsters from the control experiment, no damage in the naïve hamster exposed to the “masked” inoculated one in the second experiment, and mild effects in the “masked” naïve hamster in the third experiment.



Although this is only one study, it suggests that the dose effect characteristic of influenza A virus also applies to SARS-CoV-2 virus and that a surgical mask reduces the size of the viral inoculum sufficiently to prolong the establishment of infection in the recipient so that the immune system has time to control it more effectively.

References:

1. Paulo AC, Correia-Neves M, Domingos T, Murta AG, Pedrosa J. influenza infectious dose may explain the high mortality of the second and third waves of 1918–1919 influenza pandemic. *PLoS One*. 2010;5(7):e11655 doi:10.1371/journal.pone.0011655.
2. Chan JF-W, Yuan S, Zhang AJ, et al. Surgical mask partition reduces the risk of non-contact transmission in a golden Syrian hamster model for Coronavirus Disease 2019 (COVID-19). *Clin Infect Dis*. 2020 (in press) doi:10.1093/cid/ciaa644.

From the Editors

The editors thank Dr. Cush for his feature article on anti-rheumatic therapies in Covid-19 patients.

The aim of this weekly newsletter is to serve as a source of information for the UT Southwestern community which can lead to better understanding and control of a new disease (COVID-19) caused by the pandemic spread of an emerging viral pathogen (SARS-CoV-2). We welcome questions, comments, and suggestions for topics and authors.