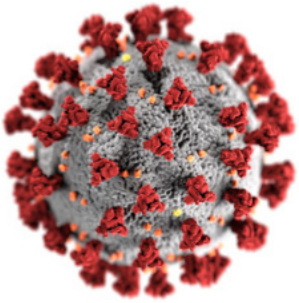

COVID-19 Action Newsletter

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

The Situation: Confirmed U.S. Deaths Pass 231,000

In the world as of November 2, 2020, 46,632,558 cases and 1,201,927 deaths have been confirmed. In the United States, there have been 9,209,165 cases, the most in the world followed in order by India, Brazil, Russia and France. China is now 56th in the world with 91,403 cases. Deaths in the U.S. through November 2 have been estimated at 231,003.[1]

From March 10 through November 1, there have been 97,398 confirmed cases of Covid-19 reported from Dallas County with 1,117 deaths, about 24% of these from long-term care facilities.[2] Seventy percent of hospitalized cases in Dallas County have been under 65 years of age. Diabetes mellitus has been seen in about one-third of all hospitalized patients. More men than women have died, and 52% of the hospitalized cases have occurred in the Hispanic population. As of 10/30, 1,114 deaths have been analyzed by race with 25% occurring in Whites (actual White population 29%), Hispanics 46% (population 41%), Blacks 24% (population 24%), and Asians 3% (population 7%). Specimens submitted for diagnosis of respiratory viruses show continuing positivity for SARS-CoV-2 with the latest result on 10/24 being 15.4%, down from a peak value of 30.5% obtained during the week ending 7/4/20. Influenza A and B antigen tests in specimens from the respiratory tract from 8/1 through 10/24 have been negative.

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2. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 10/30/20

Feature Article

Rehabilitation of Covid-19 "Long Haulers"

Surendra Barshikar, MD, Medical Director of UT Southwestern and Parkland PMR Clinics, Department of Physical Medicine & Rehabilitation

Covid-19 which is caused by SARS-CoV-2 and first diagnosed in China in late 2019 continues to affect the world's population including the United States which has reported over 9 million cases. Currently, Texas has had over 920,000 cases, leading the US. It is now understood that Covid-19 is not just a pulmonary disease. It affects multiple systems and unfortunately, in many patients these effects persist.

Acutely, the disease may present with cough, shortness of breath, hypoxemia and eventually respiratory failure. Other systems affected are cardiac with heart failure, arrhythmias, shock and myocardial infarction; central nervous with confusion, altered consciousness, stroke, smell and taste abnormalities, headaches and dizziness; gastrointestinal with diarrhea, liver and pancreatic damage; psychological with anxiety, depression and post-traumatic stress symptoms; and even a skin rash and ocular findings.[1]

While 80% of patients develop mild to moderate symptoms, about 20% are seriously ill and may require hospitalization. For those admitted to intensive care units, ICU stays of 3 weeks or more are common. Even for those with moderate illness who stay quarantined at home, significant weight loss, weakness, cardiopulmonary

deconditioning, and fatigue may result. It is well-known that prolonged bedrest can result in decreased muscle mass and strength, which further impacts recovery of patients and prolongs hospitalization.

Numerous preliminary medical reports have now established that symptoms of Covid-19 can be prolonged and can last months after initial acute illness. These patients are now being termed the "Long Haulers." One such online survey study done by Indiana University School of Medicine reported that the top 5 chronic symptoms are fatigue, muscle or body aches, shortness of breath or difficulty breathing, difficulty in concentration, and inability to exercise or be active. Another study published in *JAMA* reported that about 87% of patients report persistent symptoms.[2] Unfortunately, at present there is little explanation, or treatment for such symptoms. Only symptomatic management is recommended.

Rehabilitation of persons after Covid-19 needs to be highly individualized and based on the particular symptoms present. There have been no specific studies or recommendations for rehab for these long haulers or post-acute cases. The coordinated international taskforce for European Respiratory Society and American Thoracic Society came up with consensus guidelines which recommend comprehensive assessment of rehabilitation needs, physical and psychological, and multidisciplinary rehabilitation focusing on musculoskeletal, cardiopulmonary, and psychological functional restoration.[3] The goals of an outpatient-based Covid-19 rehabilitation program are preventing further debility, reconditioning, improving respiratory function and mental health, returning to normal ADL function and mobility, and a gradual return to work/school or to other social roles.

Wade lays down the framework of rehabilitation and recommendations made for the Royal College of Physicians.[4] He lists rehabilitation intervention in five main categories including general exercise that increases cardio-respiratory work, repeated practice of functional activities, psycho-social therapies, education with emphasis on self-management, and a set of specific actions tailored to patients' priorities, needs and goals. As with acute care and management of Covid-19, rehabilitation recommendations and outcomes have not been well studied at this time. To date, one study randomized 72 patients to 6 weeks of pulmonary rehabilitation after acute Covid-19 illness and found substantial improvements in pulmonary function compared with the control group,[5] but outcomes for long term sequalae have not been studied. Individual outcomes after rehabilitation are promising, but conclusions await published studies. Fortunately, the primary symptoms experienced by these patients are common in other disorders where they are often effectively managed by a multi-disciplinary rehabilitation team.

The Department of Physical Medicine and Rehabilitation (PMR) at UT Southwestern, after evaluation of hospitalized patients and early reports from Europe, realized that patients benefited from a comprehensive approach to recovery. To respond to the need in the DFW Metroplex for patients to return quickly back to their pre-Covid status, we have developed a multi-disciplinary outpatient program called "COVID Recover." It is an individualized outpatient program for patients that were hospitalized or home-isolated while recovering from Covid-19. The program starts with a detailed history and physical examination conducted by a physiatrist (PMR physician), followed by referral to appropriate therapists depending on the main complaints.

Our physical therapy program targets aerobic endurance, balance, and respiratory improvement. Cognitive complaints are both evaluated by rehabilitation psychology and speech therapists followed by an individualized cognitive recovery program. For persons experiencing stress and psychological symptoms, in addition to individual counseling, we designed 4-week group therapy sessions focusing on brain and mental health, physical activity, sleep, fatigue, community activities with Covid-19 recovery, and wellness. Patients can be treated in person on our main campus in Dallas or in Frisco, or evaluation and treatments can be delivered by video visits. Referrals can be made internally in EPIC or by faxing us at 214-645-2558 or calling 214-645-2080.

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Clinical Advance

Evidence that Recent Endemic CoV Infection May Make Covid-19 Less Severe

Endemic coronaviruses (CoV-OC43, CoV-229E, CoV-NL63, and CoV-HKU1) are common circulating viruses that can cause the common cold and occasionally pneumonia. They usually do not produce cross-reacting antibody sufficient to elicit a falsely positive serological test against SARS-CoV-2. They may, however, produce T-cell responses which may explain the reactivity of T-cells of some persons to peptide antigens derived from SARS-CoV-2 without serological evidence of exposure to that virus.

Investigators from Boston University School of Medicine recently completed a study that will soon appear in the *Journal of Clinical investigation* demonstrating an effect of exposure to endemic CoV on the clinical severity of Covid-19.[1] They studied adults with respiratory illnesses with positive RT-PCR tests to endemic coronaviruses encountered in their hospital system from May 18, 2015, to March 11, 2020, using a comprehensive respiratory PCR panel, and compared patients with positive tests (eCoV+, 875 patients) and negative tests (eCoV-, 15,053 patients). They obtained the results of SARS-CoV-2 PCR tests performed between March 12 and June 12 and studied the differences in clinical outcomes of Covid-19 illnesses between the eCov+ and eCov- groups (Table).

SARS-Cov-2 infection and Covid-19 outcomes in patients with and without a documented endemic coronavirus exposure.

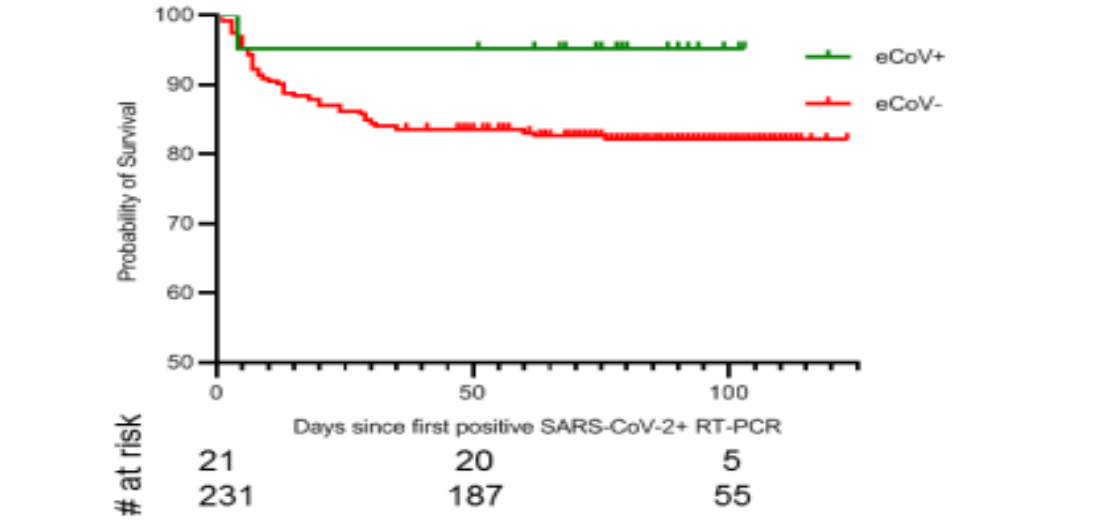
	eCoV- (n = 15,053)	eCoV+ (n = 875)	OR (95% CI) eCoV+/eCoV-	Adjusted OR (95% CI)
SARS-CoV-2 tested, no. (% of total)	1,679 (11.2)	133 (15.2)	1.4 (1.2 – 1.7)	1.4 (1.2 – 1.7)[b]
SARS-CoV-2+, no. (% of tested)	437 (26.0)	33 (24.8)	0.9 (0.6 – 1.4)	
Hospitalized, no. (% of SARS-CoV-2+)	231 (52.9)	21 (63.6)	1.6 (0.8 – 3.2)	
Intensive care unit, no. (% of hospitalized)	65 (28.1)	1 (4.8)	0.1 (0.0 – 0.7)	0.1 (0.1 – 0.9)[c]
Mechanical ventilation, no. (% of hospitalized)	38 (16.4)	0 (0)	0.0 (0.0 – 1.0)	

Abbreviations include eCoV: endemic coronavirus; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: coronavirus disease-19; OR: odds ratio; CI: confidence interval
[a] Data are expressed as number (%) and odds ratio was calculated using Fisher's exact test.
[b] OR after adjusting for race/ethnicity, chronic obstructive pulmonary disease, HIV, number of co-morbidities, and level of clinical care using multivariate logistic regression.
[c] OR after adjusting for age, gender, body mass index, and diabetes mellitus using penalized logistic regression.

The results showed that more eCoV+ patients were tested for Covid-19 infection (15.2% vs. 11.2%). Both groups had the same frequency of positive tests (24.8% in eCoV+ vs. 26.0% in eCoV-) and were hospitalized at approximately the same frequency (63.6% vs. 52.9%). Importantly, the eCoV+ patients were hospitalized in the ICU less often than the eCoV- patients (4.8% vs. 28.1%) for an odds ratio of 0.1 (0.0 – 0.7) and underwent

mechanical ventilation less often (0% vs. 16.4%). The percentage of hospitalized patients that eventually died was lower in the eCoV+ group than the eCoV- group (4.8% vs. 17.7%). The unadjusted hazard ratio (0.3, 95% CI 0.1-0.7, Figure) was statistically significant by the log-rank nonparametric test, while after adjustment for age, gender, BMI and diabetes by Cox regression analysis, the hazard ratio remained the same, but the confidence interval widened to encompass 1.0 (0.3, 95% CI 0.0-2.0).

Mortality among patients with and without documented endemic coronavirus. The tick marks denote right censoring after July 14, 2020.



The authors concluded that recent clinically significant endemic CoV infection was associated with less severe Covid-19 and extended to a mortality benefit.

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Epi Corner

Re-infection with SARS-CoV-19 Occurs, but Rarely

Investigations in the 1960s with the endemic coronaviruses CoV-0C43 and CoV-229E established that reinfections with endemic coronaviruses could occur. In one study, five adults had serial blood samples drawn between 1963 and 1970, and 5 seroconversions (fourfold rises in antibody titer) occurred in persons with preceding stable positive antibody levels, e.g., OC43 in one person with titers of 10, 10, 10, 10, 10, =>160, =>160.[1,2] No seroconversions occurred in persons with high antibody levels (=>1:80). There is little data on clinical severity of illness in persons with primary infection vs re-infection in these studies. The studies are limited by not considering the effect of other recently discovered coronaviruses like CoV-NL63 and CoV-HKU1.

Re-infection has been debated with regard to SARS-CoV-2, and criteria have been established to document this phenomenon and establish its clinical significance. To increase our understanding of re-infection, studies must address the following: 1) the genetic sequence of the initial virus isolate (isolate 1) has to be compared with the virus implicated in the second episode (isolate 2) to exclude persistence of the initial virus or its reactivation, 2) the time interval between the initial viral isolation and the second episode should be specified, 3) the antibody status of the patient should be determined, and 4) the patient's overall state of immunosuppression should be ascertained.[3]

Characterization of the virus isolates is the most important part of the investigation. Isolate 1 has to be identified and potentially quantified. The virus must be in high quantity, viable and able to be sequenced to compare it to the second isolate. Its quantity may be estimated by the cycle threshold (Ct) of the RT-PCR. Isolate 2 should also be in high quantity, replication competent and able to be grown in tissue culture.

In South Korea, investigators simplified the re-infection determination by assuming that isolate 2 was recently acquired if it was isolated in high enough titer to be grown. By this approach, they were able to exclude 285 instances of potential re-infection in which isolate 2 was not grown.

Both isolates need to be sequenced for verification. Coronaviruses are thought to mutate 2 nucleotides per month. If the second isolate is grown 3 months after the first, it should have (2 isolates x 3 months =) 6 nucleotide differences from the first if it is the same virus. Being in a different clade or having a difference in more than the expected number of nucleotides between specimens favors an introduction of a new virus and re-infection. Documented or highly suspected re-infections usually are associated with a ≥90-day interval between the 2 isolations; an interval of 45-89 days is less commonly encountered. Antibody findings and clinical status should be available to tell whether the re-infection indicates problems in the patient's immune status.

Two cases documenting reinfection are instructive. The first case, considered to be the initial documentation of re-infection in the world, is that of a 33 year old man from Hong Kong who had consistent symptoms of Covid-19 and a positive pharyngeal PCR test on March 26, 2020. He was hospitalized and had 2 PCR-negative tests before discharge on April 15. On August 15, he had a positive PCR test on return to Hong Kong after traveling from Spain through England. The test was done for public health purposes. Analysis by sequencing showed that the 2 isolates of virus, taken 142 days apart, were from different clades than were occurring in areas of the world in which he had been travelling.[4]

The second case, the first to be reported in the U.S., involved a 25 year old man from Nevada who had SARS-CoV-19 isolated twice. The first was isolated on April 18 and the second on June 4, a 48-day interval separated by two negative tests. IgG and IgM antibody were present in serum from June 6. Sequencing of the two viral isolates showed that the second had more nucleotide mutations than the rate expected from random changes (2 isolates x 2 months), effectively ruling out persistence of the original isolate. The second clinical illness was more severe than the first.[5]

At least 8 cases of re-infection with SARS-CoV-2 have been documented. They support the following tentative conclusions. The second isolates have generally been obtained 90 or more days after the first.[6] Infrequently, cases have been documented 45-89 days after isolation of the first virus. The cases have occurred in widely separated regions of the world, viz., Belgium, Ecuador, Austria, Netherlands, Nevada, Hong Kong, and India. Reinfection can occur in antibody-positive persons. The second illness may be more severe than the first. Screening for re-infection may be facilitated by the fact that the second virus isolate is usually at high titer, is replication competent, and usually can be grown in tissue culture. To date, although re-infection can be demonstrated, it is rare and its clinical and epidemiologic significance are yet to be determined. As the epidemic persists, immunity to first infections declines, and vaccines become available, issues around re-infection should increase in number and complexity.

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From the Editors

The editors thank Dr. Barshikar for his feature article on rehabilitation of 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.