

# COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine  
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## The Situation: U.S. Confirmed Cases Exceed 5 Million

In the world as of August 14, 2020, 20,952,402 cases of Covid-19 and 760,213 deaths have been confirmed. In the United States, there have been 5,245,878 cases, the most in the world followed in order by Brazil, India, Russia and South Africa. China is now 32nd in the world with 89,192 cases. Deaths in the U.S. through August 14 have been estimated at 167,253.<sup>1</sup>

From March 10 through August 13, there have been 55,787 confirmed cases of Covid-19 reported from Dallas County with 785 deaths, about 27% of these from long-term facilities.<sup>2</sup> Of 6,685 hospitalized cases in Dallas County, 71% 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 54% of the hospitalized cases have occurred in the Hispanic population. As of 8/11, 785 deaths have been analyzed by race with 28% occurring in Whites (actual White population 29%), Hispanics 44% (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 8/7/20 being 19%.

### References:

1. Covid-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 8/14/20)
2. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 8/14/20

### Feature Article

## Pathology of the Respiratory Tract in COVID-19

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In common with most coronaviruses associated with human disease, including those associated with the Severe Acute Respiratory Distress (SARS) epidemic in 2002-2004 and the Middle East Respiratory Syndrome (MERS) that first appeared in 2012, the novel coronavirus associated with the COVID-19 pandemic (SARS-CoV-2) is most frequently associated with respiratory manifestations, ranging in severity from self-limited coughing, sore throat and nasal congestion to fulminant respiratory failure. While a growing body of evidence indicates that COVID-19 is a multisystem disease, acute lung injury continues to account for most of the morbidity and mortality associated with this infection, and most of the literature on the pathology of COVID-19 has focused, understandably, on changes occurring in the respiratory tract.

### Upper Respiratory Tract

The upper respiratory tract appears to be the initial site of SARS-CoV-2 infection in most patients. The ciliated columnar epithelial cells that line the upper respiratory tract express the ACE2 receptor, the principal receptor for SARS-CoV2. Postmortem studies have demonstrated persistence of virions in ciliated respiratory epithelium and adjacent extracellular space in the upper respiratory tract in patients dying of COVID-19, a distribution that has not been seen in other human coronaviruses.<sup>1</sup> Infection in cells of the upper respiratory

tract has been documented to persist for over two weeks after the onset of symptoms in COVID-19, and likely contributes to the notoriously contagious nature of this disease.<sup>1,2</sup>

## Lung

The most common morphological pattern documented in the lungs of patients dying with COVID-19 is that of **diffuse alveolar damage** (DAD),<sup>1,3-5</sup> with variably developed acute “exudative” features (interstitial and intra-alveolar edema, alveolar pneumocyte necrosis and hyaline membranes) and early-to-intermediate stage “proliferative” changes (injury to type I pneumocytes, type II pneumocyte proliferation, squamous metaplasia, macrophagic infiltration and interstitial myofibroblastic proliferation). Interstitial fibrosis has not been a prominent feature of SARS-CoV-2 –associated lung injury to date, although the long term sequelae of diffuse alveolar injury, particularly in older patients with COVID-19 infection have yet to be defined.<sup>6</sup>

DAD is a pattern of lung injury that reflects abnormal permeability of the pulmonary alveolar capillaries and alveolar epithelium, resulting in exudation of protein-rich fluid into the alveolar airspaces. It can be caused by a wide range of insults that damage the alveolar epithelium, alveolar capillaries or both. The pathogenesis of DAD in COVID-19 remains incompletely characterized, although autopsy studies have begun to provide us with some important clues. Ultrastructural and immunohistochemical studies have demonstrated SARS-CoV-2 virions and viral antigens in the cytoplasm of alveolar epithelial cells,<sup>1,4,5</sup> alveolar capillary endothelium<sup>1,7,8</sup> and some alveolar macrophages.<sup>1,9</sup> Viral antigens have been shown to be more readily detectable in areas of the lung less severely affected by DAD,<sup>5</sup> suggesting that viral infection of these target cells may be an early event in the development COVID-19 lung injury. The mechanism(s) whereby SARS-CoV-2 infection causes cell injury remain incompletely understood. Although a **direct cytopathic effect** on target cells has been suggested in some human coronavirus infections,<sup>10,11</sup> there is compelling evidence that dysregulation of the host immune response, culminating in the most severe cases in the development of a **cytokine release syndrome** (cytokine “storm”), plays a critical role in the development of the lung damage associated with COVID-19. Cytokine profiles documented in severe COVID-19 share many features with those reported in other cytokine release syndromes, including those associated with SARS and MERS.<sup>12</sup> Infection and activation of resident pulmonary macrophages and macrophages recruited to the lungs from extra-pulmonary sites has been suggested as an important event in the initiation and propagation of cytokine release syndromes in COVID-19 and other severe human coronavirus infections.<sup>13</sup> In this context it is of interest to note that aggregates of infected macrophages are an especially prominent feature of COVID-19-associated DAD.<sup>9</sup> The elevated levels of interleukin-6 and a host of other pro-inflammatory cytokines and chemokines that characterize the cytokine release syndrome cause apoptosis of both alveolar epithelium and capillary endothelium, resulting in abnormal permeability at the alveolar epithelial-capillary interface, massive fluid leakage and the clinical manifestations of diffuse alveolar injury. It is quite likely that the cytokine release syndrome also plays a role in the multiorgan failure documented in many patients dying with COVID-19.

## Pulmonary Vascular System

In addition to the exudative and proliferative lesions seen in COVID-19-associated DAD, striking pulmonary vascular abnormalities have been reported in many patients, including pulmonary arterial and arteriolar thrombosis and fibrin-platelet microthrombi within alveolar capillaries.<sup>3,4,8,14,15</sup> Pulmonary vascular abnormalities in COVID-19 appear to be much more common than in cases of DAD associated with other viral infections.<sup>4,8</sup> Like respiratory epithelial cells, endothelial cells express the ACE2 receptor and are another potential target for SARS-CoV-2 infection, an observation consistent with the demonstration of coronavirus particles within endothelial cells in COVID-19.<sup>7,8</sup> Local activation of the complement system has been suggested as one possible mediator of endothelial injury in this condition.<sup>15</sup> Endothelial injury provides a potential explanation for the thrombotic complications and laboratory evidence of coagulopathy seen in COVID-19. It is likely, in at least a subset of patients with COVID-19, that microvascular occlusion contributes to the hypoxemia seen in critically ill patients. In addition to promoting vascular occlusion, endothelial injury in COVID-19 is associated with additional vascular changes, including alterations in the expression of multiple angiogenesis-related genes and a special pattern of neovascularization termed intussusceptive (also termed “splitting”)

angiogenesis.<sup>8</sup> While various patterns of neovascularization have been documented in other forms of lung injury, intussusceptive angiogenesis appears to be more conspicuous in COVID-19 compared to H1N1 influenza.<sup>8</sup> The role of intussusceptive angiogenesis and other forms of neovascularization in the acute phases of COVID-19-associated lung injury, if any, remains uncertain. Microvascular remodeling plays a role in a number of repair processes, and it remains to be seen whether the intussusceptive angiogenesis associated with COVID-19 may prove to be a harbinger of chronic structural changes in the lungs in this disorder.

## Conclusion

In summary, the respiratory system appears to be the major site of organ damage in COVID-19, with acute lung injury manifested by DAD and variable degrees of thrombotic occlusion of pulmonary arterial and capillary channels accounting for most fatalities. Chronic sequelae of COVID-19 infection remain to be defined, although the alveolar wall injury and microvascular remodeling documented in fatal cases raise concern about the development of chronic lung disease in patients who survive the acute lung injury.

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**Epi Corner**

**Dallas Epidemic Continues Declining after Bar Closure and Masking**

Last week it became clear that the massive surge in Covid-19 cases from relaxing control measures in late May had peaked and was starting to decline, and this week the decline has continued so that the number of new

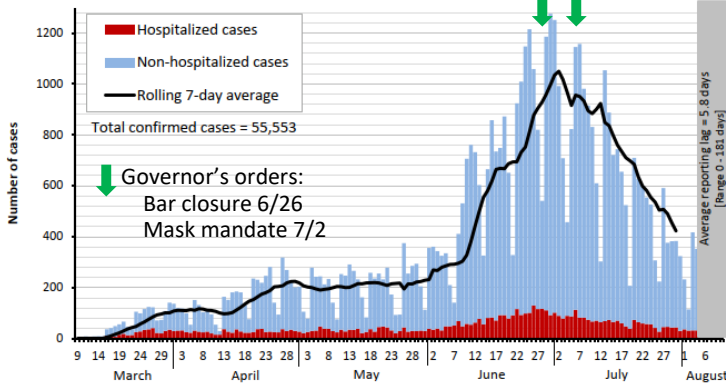
daily cases has dropped to one-third the number at the peak and is approaching the May plateau (Fig 1). The decline in hospital admissions for Covid-19 continues at the same rate as new cases (Fig 2), and ICU admissions continue to fall with the same lag as before (Fig 3). The number of deaths finally appears to have peaked after the expected lag and now should decline rapidly (Fig 4). These declines have occurred while the number of tests done has been increasing and the percentage of tests positive has been sharply declining (Fig 5). This suggests that the public health mitigations of distancing (bar closures) and apparent widespread compliance with masking are having a strong effect without a further massive increase in testing that many are saying is necessary to control the epidemic.

The same recent declines are occurring in Tarrant, Lubbock, and Travis counties, presumably also as a result of the governor’s bar and masking orders, but not yet in Harris County (see the trends by county at the state website).

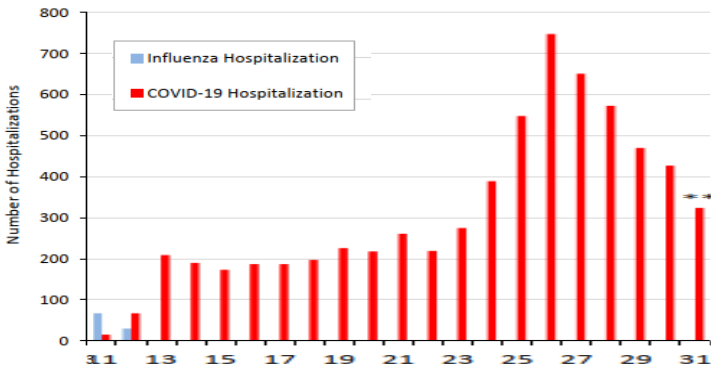
Still, the day-to-day volatility of new case counts has epidemiologists viewing the outlook with caution, concerned that renewed increases in mobility of the county’s population from the improving situation may trigger another resurgence.

The Dallas County graphs are published bi-weekly by the county health department at: <https://www.dallascounty.org/departments/dchhs/-2019-novel-coronavirus.php>

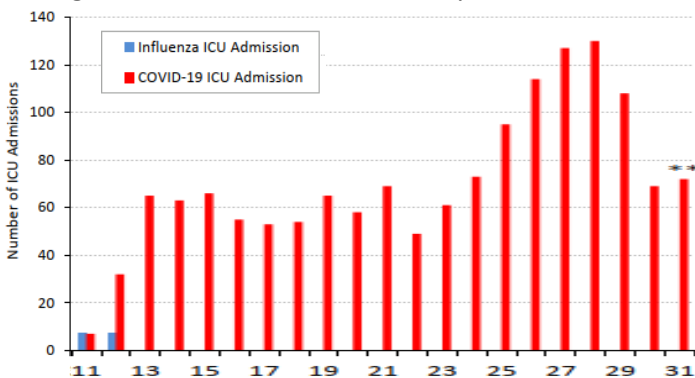
**Fig 1. Confirmed cases by day, Dallas Co.**



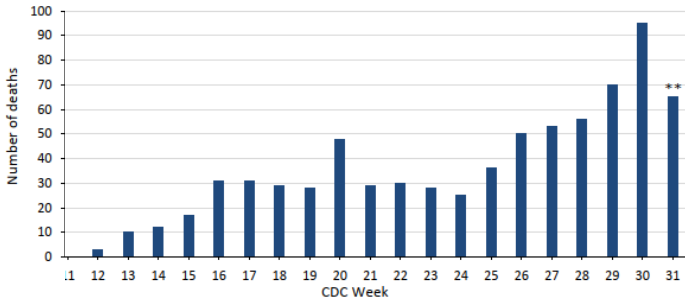
**Fig 2. Confirmed hospital admissions by week, Dallas Co.**



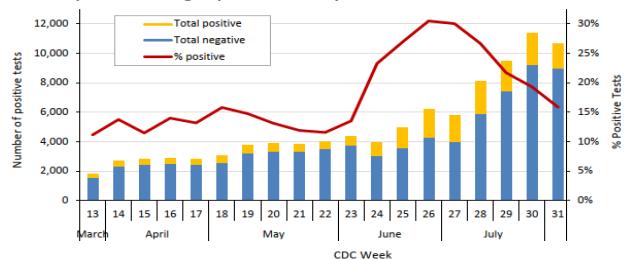
**Fig 3. Confirmed ICU admissions by week, Dallas Co.**



**Fig 4. Confirmed deaths by week, Dallas Co.**



**Fig 5. Total Covid-19 tests done and the percentage positive by week**



## **From the Editors**

The editors thank Dr. Burns for his feature article on the pulmonary pathology of Covid-19.

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.