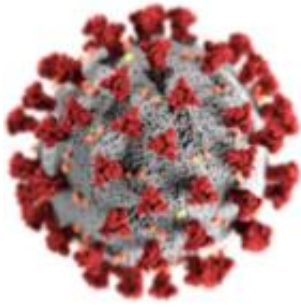




COVID-19 Action Newsletter

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

The Situation: U.S. Confirmed Cases Exceed 1.2 Million

In the world as of May 8, 2020, 3,303,296 confirmed cases of Covid-19, including 568,422 with onset in the past 7 days, and 270,279 deaths. In the United States, there have been 1,256,972 cases, the most in the world followed in order by Spain, Italy, the United Kingdom, Russia, France, Germany, Brazil, Turkey, Iran and China.¹ Deaths in the U.S. through May 1 have been estimated at 75,670.²

From March 10 through May 5 there have been 4,623 confirmed cases of Covid-19 reported from Dallas County with 121 confirmed deaths, 36% of these from long-term care facilities.³ Of the 971 hospitalized cases in Dallas County the majority have been over 60 years of age or older or have had at least one known risk condition. Diabetes mellitus was seen in about one-third of all hospitalized patients. More men than women have died. Of the first cases seen in Dallas County, the distribution of cases by race/ethnicity did not differ significantly from that of the Dallas population. Differences have been seen in other cities.

References:

1. Covid-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 5/8/20)
2. Worldometer. Coronavirus update 5/8/20
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Feature Article

Acute Respiratory Failure from Covid-19

Corey Kershaw, MD, Director of the Medical ICU and Respiratory Therapy at CUH

Since the appearance of SARS-CoV-2 in late 2019, the medical landscape has been deluged with experiential reports of the similarities and differences between the respiratory failure associated with typical pulmonary infections and that of Covid-19. In the absence of solid clinical trials evidence, clinicians around the world are struggling to find the correct therapeutic path for successful management of this ongoing problem. Challenges abound in differentiating fact to be widely applied from observations less applicable to most practices.

A seminal paper published in *The Lancet* in 1967 first described cases of refractory hypoxemia from a variety of unrelated causes.¹ Their commonality in physiology and radiographic appearance with infant respiratory distress syndrome led the authors to coin the term “adult respiratory distress syndrome.” Decades of research into what later became known as acute respiratory distress syndrome (ARDS) heralded the beginning of modern critical care medicine and taught us much about the triggers, pathophysiological changes, clinical findings, outcomes, and survival-extending interventions. These intervention, which are proving foundational to the management of the ARDS of Covid-19, are reviewed below.

ARDS is defined as refractory hypoxemia ($\text{PaO}_2/\text{FiO}_2 < 300$, severity further defined by the degree to which the ratio is reduced) despite application of positive end-expiratory pressure (PEEP) from the ventilator; bilateral airspace infiltrates on chest radiograph (CXR); and association with one of several well-known triggers.² The most common triggers are sepsis, pneumonia and aspiration. Absence of an identified trigger requires

exclusion of hydrostatic pulmonary edema, and the two entities can co-exist. The acute hypoxemic respiratory failure secondary to Covid-19 clearly meets the case definition of ARDS

Although there is no proven pharmacotherapy for ARDS, there are numerous interventions that are beneficial across the ARDS spectrum or that may benefit selected cases. The single most important intervention in managing ARDS is mechanical ventilation with delivery of low tidal volumes per ventilator breath, e.g., 6 mL/kg of ideal body weight.³ Other interventions of proven benefit include conservative management of fluids,⁴ the administration of PEEP (although the amount is individualized to each patient),⁵ and prone positioning for patients with especially severe hypoxemia.⁶ Other interventions of possible benefit in selected cases of severe ARDS, though of questionable value in broader application, are the use of early neuromuscular blockade to ensure ventilator synchrony and diminish oxygen consumption, the selective use of inhaled pulmonary vasodilators, and extracorporeal life support with ECMO. These interventions are fully deployed in the management of the severe hypoxemic respiratory failure of Covid-19 patients requiring management in the intensive care unit.

There is little question that Covid-19 has presented special management challenges. With the flood of well-intentioned email blasts, social media shares, lay news, non-peer-reviewed interviews and “articles” about individual experiences, the speed of our interconnected world has complicated these challenges. Early in the pandemic, communications from China and Europe reported that the hypoxemia of Covid-19 was relentless and irreversible once progression started and that patients could be severely hypoxemic but minimally symptomatic. The problem with these observations is they are just that: unverified observations. In the absence of quality peer-reviewed publications that confirm or explain these observations, we are having to use great caution in deciding to what extent we introduce them into our own practice.

For example, it has been our standard practice to use high-flow aerosolized nasal cannula (HFNC) for oxygen delivery with careful observation for patients with progressive respiratory failure. Recently other countries began recommending early intubation instead of HFNC on the basis of a small observational study from China in which 11 of 17 patients with ARDS failed HFNC.⁷ Since our recent experience has not shown this, we expect future larger studies will not sustain the concept of early intubation.

Likewise, controversy recently arose over a small study of 16 patients from Italy ostensibly showing two different types of Covid-19 ARDS based on differences in respiratory mechanics.⁸ Some of the patients had the expected poor lung compliance and high PEEP responsiveness usually associated with “typical” ARDS, whereas, the others had better compliance and were less responsive to higher applications of PEEP. The authors suggested that these may represent two distinct phenotypes of Covid-19 respiratory failure.⁹ This proposal has generated significant debate in the critical care community where ARDS has long been recognized as a heterogeneous condition with wide variation in responsiveness to PEEP and response not accurately predicted by the severity of hypoxemia.⁵

Other reports, however, appear more useful. One from China reported that most, but not all, of the patients with Covid-19-related ARDS placed in the prone position responded positively.¹⁰ This observation agrees with our own experience at CUH. Turning an intubated patient to the prone position, though not difficult, requires practice and experience by the nursing staff. Now, our nursing staff have become so proficient that we move to it much sooner than before the pandemic. We are also encouraging non-intubated patients to prone themselves to forestall intubation, both on the floor and in the ICU. Results have been inconsistent, but some patients have subjectively reported feeling less dyspneic.

Use of corticosteroids for ARDS has long been unproven, with no quality studies proving benefit from steroids in the direct treatment of non-Covid ARDS. In light of the varied presentation of Covid-19, some have suggested that some variants might respond to steroid therapy. But to date the lack of proven benefit in any subgroup as well as a concern for steroids’ potentially prolonging viral shedding and subsequent infectivity, corticosteroids are not recommended for Covid-19.

Interestingly, we have admitted numerous patients with various states of immunocompromise to the ICU with Covid-19, including solid organ transplants, stem cell transplants for hematogenous malignancies, chemotherapy-induced immunosuppression, and have noticed no difference from other patients in the likelihood of developing cytokine release syndrome and pulmonary toxicity. One of our sickest patients early on

was immunosuppressed from solid organ transplant, and the inflammatory markers were very high from presentation.

We are living in challenging times. Rarely in modern medicine has the discovery process played out so rapidly before our very eyes. There is no question that Covid-19 is unique in many ways. But, until we know more from proper clinical trials and research, we must stick with the fundamentals of ARDS management. Now is not the time to abandon two decades of care standards out of fear of the unknown until proven by well designed research.

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Breaking Clinical News

Rare Covid-Related Kawasaki-like Inflammatory Disease in Children

Typical Covid-19 illness with pneumonia and respiratory failure continues to be rare in children, but reporting in the *New York Times* on May 6 and 7, quoting Dr. Steven Kerner, former UT Southwestern pediatric intensivist and currently chief of pulmonary critical care at Columbia University and New York Presbyterian Children’s Hospital, and a letter from London pediatricians published online in *The Lancet* on May 6,¹ described a new, probably Covid-19-associated inflammatory syndrome initially being tagged “pediatric multisystem inflammatory syndrome.” Thus far the New York State Department of Health has received reports of 64 cases statewide, the *Lancet* article reported 8 cases in one London hospital and 20 in another, and additional cases have been reported from Britain, France, Switzerland, Spain and Italy, and from the states of Louisiana, Mississippi and California. First seen in Europe, all reports from the U.S. have come in only the past two weeks.

Though still rare, the illness has affected children ages 2-15 presenting with high fever, abdominal pain, rash, and shock, similar to the Kawasaki disease. Patients may have no history of Covid-19 illness but many in the U.S. have tested positive for the SARS-CoV-2 virus RNA or have IgG antibody for the virus.

It appears to be a diffuse inflammatory condition affecting multiple organs and blood vessels, often the coronary arteries. The complete syndrome includes high fever, abdominal pain, odynophagia, myalgia, rash, conjunctivitis, lymphadenopathy, non-bloody diarrhea, vomiting, myocarditis, peripheral edema, hypoxia, hypotension and warm, vasoplegic shock, refractory to volume resuscitation, but cough and shortness of breath

are notably absent. Most had no respiratory involvement, although a few have required nasal oxygen or mechanical ventilation. Some developed small pleural, pericardial and ascitic effusions. The illness may begin with only mild fever and fatigue but progress to the full syndrome, rarely ending with shock, dyspnea and cardiopulmonary arrest.

Treatment has included corticosteroids, Intravenous immune globulin, high-dose aspirin, antibiotics, nasal oxygen and rarely intubation. With ICU treatment as needed, the prognosis for full recovery appears good. Only one patient, a 14-year old boy in England, has died. Dr. Kernie's team is reportedly running genetic tests to try to identify a genetic predisposition.

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“Covid Toe”: A New Physical Sign of SARS-CoV-2 Infection

It has been recognized for some time that the sudden appearance of diminished or lost senses of smell (hyposmia or anosmia) or taste (hypogeusia or ageusia) occur commonly in Covid-19 and may be the only sign in otherwise asymptomatic patients. In the past week, however, dermatologists have begun reporting a rapidly growing number of adult patients presenting with painful red or purple lesions on one or more toes, the Achilles tendon or soles of the feet, quickly termed “Covid toe” (see photograph). They are identical to typical *chilblains* that a dermatologist might see in 4 or 5 patients a year, mostly in winter and in patients with a history of recurrent episodes. Suddenly they are being seen commonly in New York City and other epidemic communities, occurring mostly in children, teens and young adults, some with a history of a recent mild Covid illness or a positive SARS-CoV-2 test, suggesting an immunologic reaction to the viral infection. Lesions vary from a small patch 3-4 mm in diameter on one toe to full involvement of all 10 toes. Thus far federal officials have not added them to the list of Covid-19 symptoms, but some dermatologists now consider them an indication for Covid-19 testing. They appear to be a sign of a benign, usually asymptomatic, course of Covid-19 illness, probably indicating the reaction of a healthy immune system that is effectively rejecting the virus. They may be extremely painful during the day and itchy at night and may last for several weeks before resolving spontaneously. Symptomatic treatment has been with antihistamines, topical steroids and ice.



Typical example of “Covid toe” from the *New York Times*, May 5, 2020.

Website reviews

CDC Finally Out of the Shadows with Sequencing Leadership

<https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/spheres.html>

The U.S. Centers for Disease Control and Prevention (CDC), uncharacteristically in the background of leadership in the greatest pandemic of our lifetime, has emerged to lead a new national open genomics consortium for the Covid-19 response called **SPHERES (SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance)**. The effort will coordinate genomic sequencing facilities of federal, state, and local governments, academic institutions, corporations, and non-profit public health and research laboratories across the U.S. The goals are to monitor important changes in the virus as it continues to circulate; gain important insights to support contact tracing; provide crucial information to aid in identifying diagnostic and therapeutic targets; and advance public health research in the areas of transmission dynamics, host response, and evolution of the virus.

The effort will be led by *CDC's Advanced Molecular Detection (AMD) program*. Over the past 6 years, this program has quietly invested in federal, state and local public health laboratories to expand pathogen genomics and other advanced technologies for disease surveillance and outbreak response. The new effort will provide important federal coordination, support, data sharing, bioinformatics, consensus building and removal of barriers for all laboratories involved in the effort nationally and facilitate coordination with international efforts.

The website provides important information for laboratories including Real-Time PCR resources; Covid-19 laboratory advisories and alerts; new and archived messages from CDC's Laboratory Outreach Communication System (LOCS); and CDC's interim guidance for laboratories on collecting, handling and testing clinical specimens; laboratory biosafety guidelines; and laboratory biosafety FAQs.

Nextstrain: Real-Time Tracking of Pathogen Evolution

<https://nextstrain.org/>

Nextstrain is an open-source project to harness the scientific and public health potential of pathogen genome data. It provides a continually-updated view of publicly available data that one can view with powerful analytic and visualization tools. The goal is to aid epidemiological understanding of epidemic pathogens to improve outbreak response. Major divisions of the site include: Patterns of cladal spread of SARS-CoV-2 genomes from a global view and for regional views throughout the world (**Fig. 1**); similar cladal epidemiology of other internationally important pathogens including seasonal influenza, West Nile virus, Zika, West African Ebola, dengue, avian influenza, measles, mumps, enterovirus D68 and tuberculosis (not shown); and narrative storytelling of disease spread over time displayed alongside views of the cladal migration visualization, for example, the narrative story of "Twenty years of West Nile virus," tracing the spread from its origin in the Middle East to New York in 1999, across the U.S., and eventually to South America (**Fig. 2**).

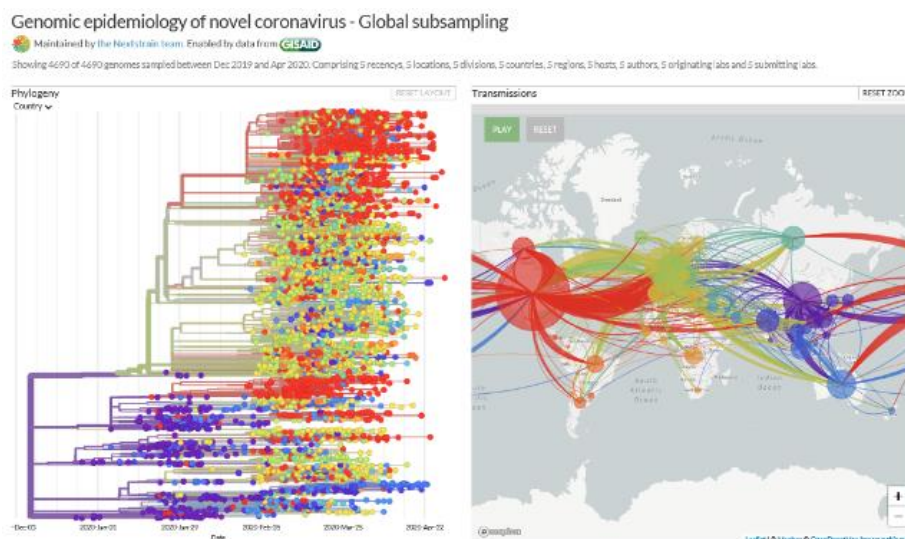


Fig. 1. (Left panel) Color code of the clades of SARS-CoV-2 virus, and (right panel) patterns of cladal spread of SARS-CoV-2 virus around the world, December 2019 through April 2020.



Fig. 2. Cladal spread of West Nile virus over time from the Middle East to North America and finally to South America, 1999 through April 2020.

Explanation of Genomic Spread for the Sophisticated Layperson

<https://www.nytimes.com/interactive/2020/04/30/science/coronavirus-mutations.html>

In its April 30 issue, the *New York Times* published a lucid explanation of genomic spread, entitled “How Coronavirus Mutates and Spreads” by Jonathan Corum, the *Times*’ graphics editor, and Carl Zimmer, the *Times*’ science columnist.

From the Editors

The editors thank Dr. Corey Kershaw for contributing his feature article and Dr. Trish Perl for suggesting CDC’s *Spheres* website and the *Nextstrain* website.

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.