

# 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. Cases Pass 6.6 Million

In the world as of September 18, 2020, 30,211,688 cases of Covid-19 and 946,710 deaths have been confirmed. In the United States, there have been 6,676,410, the most in the world followed in order by India, Brazil, Russia and Peru. China is now 40<sup>th</sup> in the world with a total of 90,297 cases. Deaths in the U.S. through September 18 have been estimated at 197,655.<sup>1</sup>

From March 10 through September 17, there have been 67,607 confirmed cases of Covid-19 reported from Dallas County with 986 deaths, about 25% of these from long-term facilities.<sup>2</sup> Of 7,406 hospitalized cases in Dallas County, 70% 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 53% of the hospitalized cases have occurred in the Hispanic population. As of 9/15, 979 deaths have been analyzed by race with 27% 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 9/5 being 10.8%, down from a peak value of 30.5% obtained during the week ending 7/4/20.

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### Feature Article

## COVID-19 in Children: Emergence of a New Mysterious Inflammatory Disease

**Zachary M. Most, MD and Jeffrey S. Kahn, MD, PhD, Division of Pediatric Infectious Diseases**

As the SARS-CoV-2 virus spread worldwide, one of the striking features of the COVID-19 pandemic was the relatively low burden of disease in the pediatric population. Early observations showed that children represented a smaller than expected proportion of positive cases and an even smaller proportion of hospitalized and fatal cases. As the COVID-19 pandemic evolved, it became quite clear that children were less prone to severe disease as compared to adults and often had mild or asymptomatic disease, although children can and do get infected, become ill and can spread the virus to other individuals. As an example, data collected by the Dallas County Department of Health and Human Services (<https://www.dallascounty.org/covid-19/>) revealed that children (individuals less than 18 years old) represented just 11% of confirmed COVID-19 cases and only 2% of the cumulative hospitalized confirmed COVID-19 cases (as of September 4, 2020). These data are consistent with public health data from across the United States. It seems that there are likely biological rather than epidemiological factors underpinning these initial observations, yet the immunological and or inflammatory mechanisms as to why children tend to be protected from severe respiratory disease remain elusive.

However, in late April 2020 reports emerged about an unusual febrile illness in children characterized by hyperinflammation and multi-organ involvement.<sup>1</sup> These initial reports described cardiogenic shock, myocardial

dysfunction and other features that were reminiscent of Kawasaki disease (KD), a known inflammatory syndrome of children (see *C.A.N.* V1, No. 4, May 8, 2020). KD, initially described by Tomisaku Kawasaki in the 1960s, is defined by clinical features including fever for at least 5 days and a combination of physical findings or history thereof that include changes in the lips, extremities and skin and the development of nonsuppurative unilateral cervical lymph node enlargement. The most concerning consequence of KD is coronary aneurysms that can result in thrombosis, myocardial infarction and death. While the underlying pathogenesis of KD is poorly understood, there is a proven treatment, specifically intravenous immune globulin and aspirin.

In early May 2020, several reports from New York City detailed children with a KD-like illness.<sup>2</sup> Some children, though not all, had evidence of acute SARS-CoV-2 infections (as defined as a respiratory specimen that tested positive by PCR), although many of these children had a history of contact with an individual with COVID-19 and some had serological evidence of prior SARS-CoV-2 infection. One curious aspect of the epidemiology of this new condition was that the peak of cases seemed to follow, by many weeks in some places, the peak of virus circulation, suggesting that this illness may be a post-infectious inflammatory syndrome.<sup>3</sup> On May 14, 2020, the Centers for Disease Control and Prevention (CDC) issued a Health Advisory (<https://emergency.cdc.gov/han/2020/han00432.asp>) that included a case definition for this new disease, now called **Multisystem Inflammatory Syndrome in Children (MIS-C)**. The emerging data indicate that MIS-C is a rare, but serious, complication of SARS-CoV-2 infection in children.

Several large studies have provided insights into MIS-C.<sup>3</sup> The majority of children with MIS-C have multiorgan involvement including the gastrointestinal tract, cardiovascular and hematological systems. All have biochemical evidence of inflammation since that is part of the case definition. The cardiac manifestations vary, although up to half of children required vasoactive or vasopressor support. While nearly half of children with MIS-C have KD-like features, relatively few had coronary aneurysms, although in some studies the rate has been as high as 20%. This finding along with demographic pattern suggest that MIS-C is distinct from, but shares features with, KD. In general, children with KD tend to be <5 years old; whereas, the median age of children with MIS-C is >8 years old. The KD attack rates are highest for children in Japan, China and other Asian countries (for reasons that are unknown), and yet there are few reports of MIS-C in these countries. Furthermore, African American and Hispanic children make up a disproportionate fraction of children with MIS-C, while these groups do not seem to be at greater risk for KD. Overall, the inflammatory responses observed in children with MIS-C are quite distinct from the cytokine storm associated with severe acute COVID-19 but share some features with the inflammatory profile in children with KD.<sup>4</sup> Defining the pathogenesis of MIS-C may provide further insights into the development of potential therapeutic strategies.

Due the rarity of this disease and the lack of randomized controlled trials, there is currently no high-quality evidence to support any therapeutics for MIS-C. Data from case series show rates of recovery around 98% regardless of intervention.<sup>3,5</sup> Supportive care is crucial in the management of MIS-C with nearly two-thirds of patients requiring ICU admission, two-fifths receiving vasoactive support, and one-sixth requiring intubation.<sup>5</sup> Pharmaceutical interventions have followed the paradigm of treatment for KD along with adjunctive treatments to address the hyperinflammatory state. Most patients have received intravenous immune globulin early in the course, and a second dose is sometimes given for refractory disease.<sup>5</sup> For severe disease with shock, high dose corticosteroids (compared to the low dose corticosteroids used for COVID-19 pulmonary disease) have a possible benefit and are frequently used.<sup>5</sup> Additional immunomodulatory agents have been used for patients with refractory shock and fevers including IL-1 inhibitors (anakinra) and IL-6 inhibitors (tocilizumab or siltuximab).<sup>3</sup> Whereas the potential benefit of these agents is yet to be demonstrated, at our institution we favor the use of anakinra due to its shorter half-life and more favorable side effect profile.

In addition to the disease seen in children, it is now recognized that many adults have cardiovascular complications of COVID-19 as well. A myocarditis-like presentation, features very similar to MIS-C, can occur in adults days to weeks after a primary infection and with or without pulmonary disease (see *C.A.N.* V1, No. 2, April 24, 2020). A few reports of cardiac biopsies and autopsies in these adult patients show a moderate lymphocytic infiltrate with no direct viral detection in cardiomyocytes. This suggests that this myocarditis-like presentation, like MIS-C, is a post-infectious phenomenon rather than direct viral infection of the involved tissue. Due to

these similarities, we hypothesize that multisystem inflammatory syndrome, or a similar disease, can occur in adults as well as in children.<sup>6</sup>

In conclusion, the emergence of MIS-C during the COVID-19 pandemic has led to a global shift in the perception of the effect of this virus on children. This disease is rare and most patients recover; however, there have been several deaths attributable to MIS-C, and at this point we do not know whether there will be long-term sequelae in the patients who have recovered. As the pandemic evolves, the pediatric community must continue to share data on patients with MIS-C and develop evidence-based treatment protocols.

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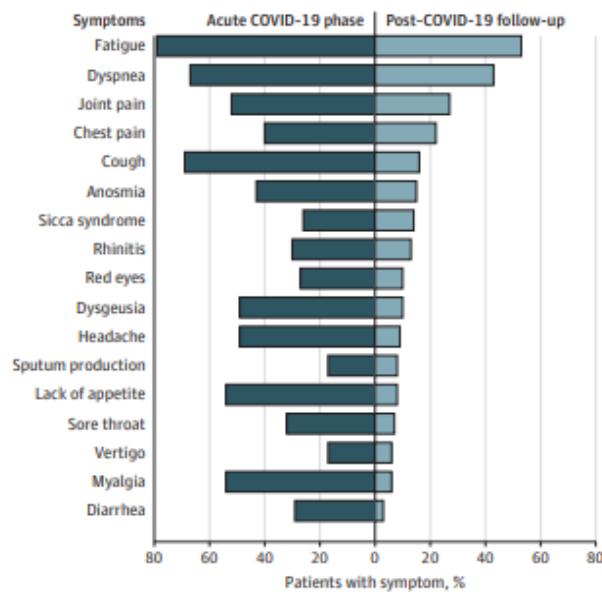
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## Clinical Advance

### Covid-19 Long Haulers

By analogy to the truck-driving situation, patients with long and protracted Covid-19 disease have been called “long haulers” as opposed to those presenting just with acute disease. In one of the first reports of these cases, Italian workers recently studied 143 patients in Rome, Italy.<sup>1</sup> The average age was 57 years, all had been hospitalized, and 21 of the patients had active cancer or an immune disorder. The mean hospitalization period was 14 days. Interstitial pneumonia had been found in 73% of patients, and they were assessed for persistent symptoms at an average of 60 days after illness onset. At the time of this latter evaluation, only 13% of patients were completely free of symptoms and 44% of patients said that their quality of life had worsened as compared to pre-illness. The most common persistent complaints were fatigue in 53%, dyspnea in 43%, joint pain in 27% and chest pain in 22%. None of the patients had fever. Loss of smell (anosmia) was seen in just over 40% of patients during acute Covid-19 but < 20% in the follow-up study. Loss of taste, total or partial, (dysgeusia) was observed in 50% of acute patients but less than 10% in follow-up patients. Anosmia and dysgeusia have been postulated to result from direct viral infection and inflammatory reactions in and around olfactory and gustatory epithelium. The results of the Italian study are depicted in the figure.

Figure. COVID-19-Related Symptoms



The figure shows percentages of patients presenting with specific coronavirus disease 2019 (COVID-19)-related symptoms during the acute phase of the disease (left) and at the time of the follow-up visit (right).

In another study of persistent symptoms sponsored by the Centers for Disease Control and Prevention (CDC), interviews were completed on 274 persons with positive pharyngeal RT-PCR tests from 14 academic Health Systems in 13 states.<sup>2</sup> The median age was 43 years and the interviews were conducted 14-21 days after the positive test date. The patients were not hospitalized and were seen as outpatients. The majority of persons, 65%, had returned to their original pre-illness state but 35% had not. Of symptoms that had not resolved at the interview and were evaluable, the most common were fatigue (35%), dyspnea (29%), cough (17%), and headache 15%. Only 4% had continuing fever. Both loss of taste and smell returned to normal at a median value of 8 days after the test. Older age, the presence of 3 or more chronic medical conditions, obesity and prior diagnosis of a psychiatric condition were associated with more than twofold odds of not having returned to usual health. A French study also described persistent symptoms in recovering Covid-19 patients.<sup>3</sup>

Important considerations for dealing with persistent symptomatology after the acute illness of Covid-19 are to be aware of how common it is and knowing its potential mechanism(s) to evaluate prognosis and possible therapy.<sup>5</sup> The frequency of symptoms differed only slightly between the two studies and might have been most influenced by the severity of the initial illness and the timing of the interviews. The Italian study focused on hospitalized cases, while the CDC study was performed on non-critical patients who were not hospitalized. Fever was seen in almost all acute illnesses in both studies but was not seen in the persistent patients in the Italian study and rarely in the CDC study. Fatigue occurred in 53% of the Italian study and in 35% of the CDC study (unresolved at interview time and estimated from the graphs presented). Dyspnea was more apparent in the Italian study with the more severely ill patients than the patients studied in the U.S. (43% vs 29%). The mechanism of persistent dyspnea might be active viral replication in lung and host immune responses with ongoing inflammatory changes producing x-ray abnormalities (ground glass opacities, new consolidation changes, or pulmonary fibrosis). The Chinese experience with SARS-2003 and their follow-up experience through 2018 might be applicable to Covid-19 in terms of prognosis; X-ray changes were found to be maximal during the first year after infection, but afterwards there were changes compatible with progressive resolution.<sup>4</sup> "Brain fog," persisting after this and other chronic disease, refers to a lack of mental clarity and impaired attention, concentration and memory for which no mechanism is known. With cardiac disease in Covid-19, we do not have a model of disease progression and patients will have to be followed over time to determine if heart failure will eventuate.<sup>5</sup>

The most common persistent complication seen in both studies was fatigue. This symptom can be chronic has been seen previously to follow other viral infections (Epstein-Barr virus, arboviral encephalitis, etc.). Its exact etiology is usually not ascertained. It has been associated with nervous system manifestations and can occur in outbreaks or epidemics. It has the tendency to fade with time, and generally has a good prognosis. Future studies will be necessary to delineate the way the patients in the present epidemic progress. At present, there is no scientifically established way to speed the resolution of symptoms in the long haulers syndrome.

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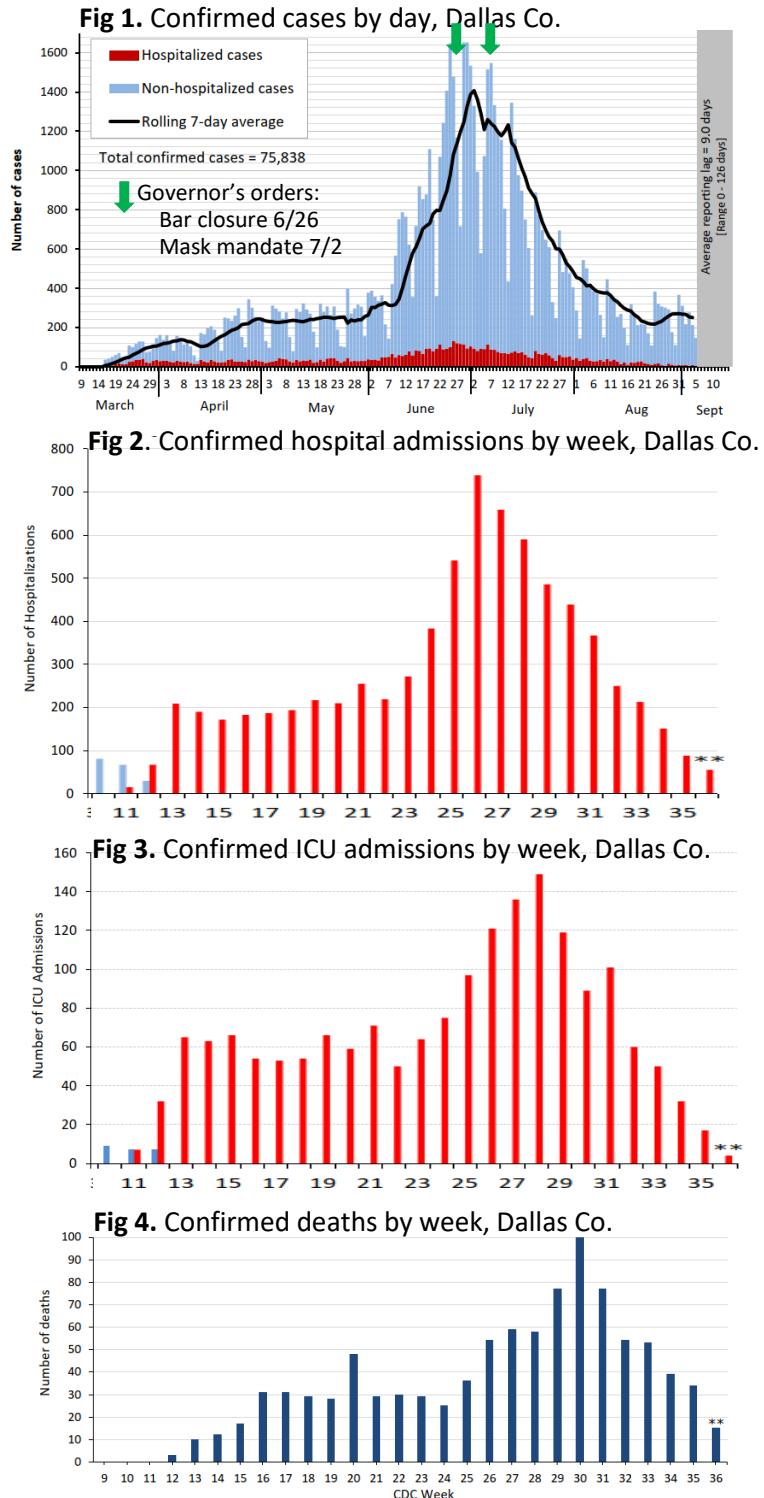
## Dallas Cases Plateau While Hospital and ICU Admissions and Deaths Continue Declining

The Covid-19 epidemic in Dallas County has reached an interesting stage. After a relentless decline since the zenith when the Governor issued executive orders closing bars and requiring masks statewide, in late August the incidence appeared to plateau at approximately 300 new cases per day (Fig. 1). At the same time, the number of new hospitalizations, ICU admissions and deaths have continued declining, albeit with the lags described in recent issues of the *Newsletter* (C.A.N. v. 1, p. 18, August 14) (Figs. 2 and 3). What is the possible explanation for this pattern?

Despite the great care taken by our County health department epidemiology staff in managing the data, there might still be some trend disruption by late reporting of a few cases. Under the likely assumption that the trends will persist as shown in the figures, however, a plausible explanation based on the known epidemiology is that masking and distancing, the main control measures, have been widely adopted by the groups at highest risk of severe illness—the elderly, those in nursing homes, patients with chronic diseases like diabetes, chronic renal disease, etc.—while younger people who enjoy far lower risk are starting to relax these measures.

The Texas Governor's orders for universal masking and closing bars appear to account for the dramatic drop in cases (Fig. 1). Recent opinion polls have shown that over 70% of the public say they usually or always wear masks when around other people. On the other hand, the loophole in the order allowing bars to open if >50% of their sales are in food has allowed many bars to reopen in recent weeks, and the resumption of in-person classes in some suburban public school districts and at the county's only university, Southern Methodist University, have clearly spawned a flurry of cases in young people.

Thus, the situation remains tenuous with a resurgence of severe cases possible if the young begin spreading their infections to their parents and grandparents. However, the initial surge at SMU appears to be declining, and schools are adapting. So stay tuned.



## From the Editors

The editors thank Drs. Most and Kahn for their feature article on the Covid-19-related inflammatory disease in children.

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.