PINNACLECARE

Medical Intelligence Report

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Topic: Update on COVID-19 Research

CDC Changes Definition of Close Contact

There has been an update to the definition that the CDC provided for close contact with someone who has COVID-19 (CDC_Appendix A, 2020). This change may affect how people interact with each other and change recommendations for social distancing. Previously, close contact leading to a high-risk encounter was defined as being within six feet of a person for 15 consecutive minutes or more.

> **The new recommendations state that a close contact is someone who was within six feet of an infected person for a cumulative total of 15 minutes or more, and individual exposures are totaled over a 24hour period.**

What this means is that the 15 minutes of close contact do not have to be continuous, and several short, repeated exposures over 24hours have a similar risk of transmission to one combined exposure.

The change is reported to be based on a report from the CDC describing the infection of a correctional officer in Vermont (Sun, 2020). In the report, researchers describe that the officer was supervising six asymptomatic inmates who were awaiting the results of COVID-19 tests (Pringle, 2020). All six were found to be positive, but video surveillance from the facility showed that the officer did not meet the previous definition of close contact of being within 6 feet of infectious persons for more than 15 consecutive minutes. The officer did have multiple brief exposures to all six over the day. The inmates wore microfiber cloth masks during most interactions with the correctional officer that occurred outside a cell. During several encounters in a cell doorway or in the recreation room, inmates were not wearing masks. During all interactions, the correctional officer wore a microfiber cloth mask, gown, and eye protection (goggles). He also wore gloves during most interactions. Based on the contact tracing, the researchers concluded that at least one of the asymptomatic inmates transmitted SARS-CoV-2 during these brief encounters.

Treatments and Vaccines under Development

Remdesivir

The WHO released their interim results from the RECOVERY clinical trial to investigate re-purposed antiviral drugs: remdesivir, hydroxychloroquine, lopinavir (fixed-dose combination with ritonavir) and interferon-β1a (Pan, 2020). The trial took place in 405 hospitals in 30 countries and involved 11,266 adult participants, and 2,750 received remdesivir, 954 hydroxychloroquine, 1,411 lopinavir, 651 interferon plus lopinavir, 1,412 only interferon, and 4,088 no study drug, which was used as the control.

None of the study drugs definitely reduced mortality (in either unventilated participants or any other subgroup of participants), reduced the need for initiating ventilation, or shortened the duration of time in the hospital.

These results **do not agree with the previously published clinical trial for remdesivir** that reported a moderately reduced time to recovery (the ACTT-1 trial). There was also no difference observed in the RECOVERY trial in either the time until ventilation was needed or the time until discharge when compared to those who did not receive an experimental treatment.

There have been four previous trials of remdesivir: SOLIDARITY, ACTT-1, and two smaller trials. When the researchers from the WHO consortium performed a combined analysis of the data on the mortality rate from the four previous trials, they found no evidence that remdesivir can prevent a substantial fraction of all deaths from COVID-19 based on the level of effect observed in the trials. There is a correlation that suggests that remdesivir may prevent a small fraction of deaths, but there is the same statistical probability of the medication preventing no deaths.

The other medications in the RECOVERY trial have previously been shown to have no effect on the outcome of SARS-CoV-2 infection, and this study is in agreement with previous results. The RECOVERY trial is continuing with sections investigating the effect of medications that reduce the immune response and monoclonal antibodies that target SARS-CoV-2.

The ACTT-1 clinical trial investigating the effect of remdesivir also published their final results, which follows up their previous publication of the interim results (Beigel, 2020). The trial was a double-blind, randomized, placebo-controlled study of intravenous remdesivir in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. It included 1,062 patients with 541 assigned to remdesivir and 521 to placebo. The final analysis of the trial data had the same results as the previously reported interim analysis, indicating that participants who had received remdesivir had a median recovery time of 10 days compared to a median recovery time of 15 days for the group that received the placebo.

Based on this final version of the study results, as well as the other three trials mentioned above, the FDA announced that it has approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization (FDA, 2020).

This is the first drug to be approved for the treatment of COVID-19.

This approval replaces the Emergency Use Authorization (EUA) previously granted to remdesivir for this population. There are other patient groups who were in the EUA that are still covered under the temporary approval.

The FDA stated in the announcement of the approval that

> "Under the Federal Food, Drug, and Cosmetic Act, approval of a new drug product requires substantial evidence of effectiveness and a demonstration of safety for the drug's intended use(s). In considering approval of a drug, the FDA conducts a benefit-risk assessment based on rigorous scientific standards to ensure that the product's benefits outweigh its risks for the intended population. This is different from the standard used in the issuance of an EUA."

Vaccines

The first participant has received a dose of a COVID-19 vaccine that is administered orally in a tablet form (Vaxart, 2020). The vaccine, called VXA-CoV2-1, is an adenoviral vector-based vaccine which delivers a portion of the SARS-CoV-2 genetic code to cells in the body. The Phase 1 trial is enrolling 48 healthy volunteers, and enrollment is expected to be completed by early November.

Immune Response after Infection

A study investigating the immune response after infection with COVID-19 evaluated the blood samples of 343 participants who had previously had COVID-19 (Iyer, 2020). The researchers report that 93% of the people in the study had been hospitalized for treatment, suggesting they should have robust responses to the virus. The participants' samples were compared to samples that had been stored previous to the start of the pandemic. The researchers report that antibodies targeted to the receptor binding domain are excellent markers of previous and recent infection, that differential isotype measurements can help distinguish between recent and older infections, and that IgG responses persist over the first few months after infection and are highly correlated with neutralizing antibodies.

Even though the immune response for some individuals seems strong and lasting, there have been several confirmed cases of people being re-infected with SARS-CoV-2. In a report from India, COVID-19 was detected in two healthcare workers who were being tested as part of a routine surveillance program (Gupta, 2020). The workers were 28-years-old and 25-years-old and initially tested positive for COVID-19 on May 5 and May 17 with PCR-based testing. Both were asymptomatic, but were isolated at the hospital based on established protocol. Retesting showed negative tests on May 13 and May 27, respectively. One of the workers then tested positive again on August 21, and the other tested positive on September 5. Both were again negative six and 14 days after the initial test. During the second infection, both workers also remained asymptomatic. The samples from the tests were genetically sequenced, and in both cases, the second infection was a different genetic variant, indicating that the second positive test was not a lingering infection from the first episode.

> **Based on their results, the authors suggest that asymptomatic reinfection may be occurring more frequently than has been reported as most asymptomatic individuals would not be tested**.

Excess Deaths during the Pandemic

Researchers have published a study of an updated analysis on the number of excess deaths during the COVID-19 pandemic up to August 1 (Woolf, 2020). Excess deaths are the gap between observed and expected deaths over a time period based on historical data. In previous analyses that examined the time period from March through April, COVID-19 was listed in 65% of the excess deaths. COVID-19 deaths included those in which COVID-19 was cited as an underlying or contributing cause. The cause of the excess deaths not attributed to COVID-19 are expected to result from unrecognized infection with SARS-CoV-2 or deaths among uninfected patients resulting in disruptions produced by the pandemic. Deaths from non-COVID-19 causes (e.g. Alzheimer disease, diabetes, heart disease) also increased sharply in the 5 states with the most COVID-19 deaths.

The number of deaths in the United States is typically consistent every year, but between March 1 and August 1 there was a 20% increase over the expected number of deaths based on historical data. The 10 states with the highest per capita rate of excess deaths were New York, New Jersey, Massachusetts, Louisiana, Arizona, Mississippi, Maryland, Delaware, Rhode Island, and Michigan. Three states with the highest death rates (New Jersey, New York, and Massachusetts) accounted for 30% of United States excess deaths but had the shortest epidemic, which was less than 10 weeks. During the expanded time period in the second study, 67% of the excess deaths were attributed to COVID-19. The mortality rate for heart disease increased between March 21 and April 11, and there were two periods where the mortality rate for Alzheimer disease or dementia increased, from March 21 to April 11 and from June 6 to July 25.

In the second study where additional information was added, a similar proportion of excess deaths were attributed to COVID-19, and increases in deaths from heart disease and Alzheimer disease or dementia were correlated to peaks in COVID-19 outbreaks in the Northeast (March through April) and the South and Southwest (June to July).

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