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Medical Intelligence Report

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Topic: Update on COVID-19 Research

Potential Treatments for COVID-19

Convalescent Plasma

To date, there is preliminary evidence available on the effectiveness of convalescent plasma from observational studies and from partially completed randomized and controlled trials. Based on the available information, convalescent plasma may provide a benefit if it is administered early in the disease course and if it contains neutralizing antibodies against SARS-CoV-2 at sufficiently high levels (Sheridan, 2020). The results from these trials are still considered preliminary because the effectiveness has not been established compared to the outcome of individuals who did not receive the treatment, which is called a control group. At this time, the FDA characterizes the use of convalescent plasma as a treatment that may be effective for its intended use (FDA, 2020).

Additional information on the efficacy of convalescent plasma became available when the first randomized and controlled trial investigating the efficacy of convalescent plasma to treat COVID-19 was published as a preprint (Agarwal et al., 2020). The Phase 2 trial was performed in 39 hospitals across India and included 464 participants hospitalized and moderately ill from confirmed COVID-19 between April 22 and July 14.

Including the newly released trial from India, there have been seven trials investigating the use of convalescent plasma to treat COVID-19. Four of the trials included a control group, but all of the trials, except for the trial in India, were stopped early due to difficulty in recruiting enough participants. The first trial, from China, included 103 participants out of an expected 200, and there was no statistically significant reduction in time to clinical improvement during 28 days of observation of the participants. When the outcomes were analyzed based on the severity of symptoms, in participants with severe disease, 91% of those treated with convalescent plasma were found to have a clinical improvement within 28 days compared to 68% in the control group. The second trial published in July, from the Netherlands, was also stopped early because 79% of the participants were found to have already started producing their own antibodies, which would be expected to reduce the effect of the donated plasma. The researchers reported that there were no differences in mortality, length of hospital stay, or disease severity 15 days after treatment between those receiving plasma and control group. Another study, in Madrid, was stopped early due to an inability to enroll participants. There was not a statistically significant difference between the outcomes of the individuals who received plasma and those who did not.

There are two trials that used case-control design, one in Houston, Texas and one in New York City, New York. In a case-control study, the outcome from a particular event (or treatment) is investigated through evaluation of medical records of participants after resolution of the event. In the case of treatment for a disease, those that have received the experimental treatment are the "cases" investigated and a group of other individuals who did not receive the treatment are selected as "controls," hence a case-control trial (Lewallen and Courtright, 1998). The controls are typically chosen to be as similar as possible to the cases so that certain factors, such as age, sex, and time of hospitalization are the same. The differences in outcomes are then calculated.

Case-control studies may prove an association but they do not demonstrate causation.

The limits on case-control studies are due to the fact the treatment decisions are not randomized. The treatments that were used were based on the judgements of the physicians involved. Certain individuals may not have received a treatment because of their clinical symptoms not being thought to be a good match for the treatment. Other individuals may not have received the treatment because they were very sick, and the treating physicians did not feel that they would benefit. Biases such as this will affect the comparison and can lead to an apparent efficacy of a treatment when none exists. However, an association observed in a case-controlled study suggests that further study is warranted to more rigorously determine if the treatment causes a beneficial effect.

An interim data analysis of a case-control study in Houston that included 85 participants was released in August (Sheridan, 2020). The study organizers plan on enrolling 316 participants for the final analysis. The study involved treatment with convalescent plasma with a high amount of binding antibodies (but not necessarily neutralizing antibodies) within 72 hours of admission to the hospital. There was a statistically significant difference in the mortality of those who received plasma when the participant's records were evaluated the 28th day after treatment, 1.2% versus 7.0% respectively. When such a small number of participants are evaluated for the interim analysis, however, it is more likely that the final analysis will differ from the initial evaluation.

The study from New York included 39 participants with severe or life-threatening COVID-19. The medical records of the participants were evaluated for the information on the 14th day after treatment, and the researchers determined that oxygen requirements worsened in 18% of convalescent plasma recipients and in 28% of matched controls. The probability of survival was also higher for those receiving plasma.

The Mayo Clinic has also been recording the outcomes of people enrolled in the expanded use trial for convalescent plasma. As of a report in August, 35,322 people with (or at risk of) severe or life-threatening disease had received convalescent plasma. There was no comparator in this report. There is only the observed outcomes of those who were treated. Thirty days after treatment, the mortality rate was 22% for those who received convalescent plasma within three days of diagnosis compared to 27% for those who received it four or more days after diagnosis. While the magnitude of the difference is small, it is a statistically significant difference. There were also improvements in the mortality rate seven days after treatment when participants receiving different level of antibodies in the plasma were compared. Those who got plasma with

high levels of antibodies had a mortality rate of 9%, those with intermediate amounts had a mortality rate of 12%, and those with low levels had a mortality rate of 14%. The lack of a comparator group makes the efficacy difficult to determine, especially because many people with COVID-19 spontaneously recover even from severe disease. The positive effects observed in the Mayo Clinic trial are promising, but are not sufficient evidence to show the efficacy of convalescent plasma as a treatment for COVID-19.

The study from India included a control group who received best standard care to compare the outcome of those who received convalescent plasma in addition to the best standard (Agarwal et al., 2020).

Based on the results of the trial in India, convalescent plasma was not associated with reduction in mortality or a reduced risk of progression to severe COVID-19.

The amounts of antibodies in the plasma used was not determined in this study, and there was no limit on when in the course of the disease the plasma was given. At the time when the study was designed, the information on potential benefits of higher amounts of antibodies and earlier treatment was not available. Arturo Casadevall, chair of molecular microbiology and immunology at Johns Hopkins Bloomberg School of Public Health, mentioned while discussing the Indian trial, that new information from investigations of convalescent plasma are making randomized–controlled trials obsolete before they are even finished, and once the trial begins, it is not feasible to change the dosing or other details of the trial (Sheridan, 2020). In the case of the results from the Indian study, there is a possibility that changing the antibody levels or timing may have allowed for a detection of a beneficial outcome from the use of convalescent plasma, but it cannot be determined from the collected data.

The current conclusion offered by one of the authors of the trial in India was that the study answers definitively that the use of convalescent plasma without measurement of neutralizing antibodies in the donor plasma or the recipients does not reduce the risk of progression of severe disease or decrease mortality from COVID-19.

Safety Review of Effects of Remdesivir on Kidney Function

The European Medicines Agency sent out a report from their safety committee describing a safety review of remdesivir due to reports of serious kidney problems in some individuals after taking the drug (EMA, 2020). Effects on kidney function were observed during animal studies of the medication, and when remdesivir was provisionally approved for treatment of COVID-19, the European Medicines Agency highlighted that more information on effects in humans was required before full approval could be given. Officials on the safety committee stated that they had not yet been able to determine if the injury to patient's kidneys was due to remdesivir because it is known that COVID-19 can also cause kidney problems.

Remdesivir Shortages

The Guardian newspaper reported that a global shortage of remdesivir has led to rationing of the drug by the National Health Service in the United Kingdom (Boseley, 2020). Similar rationing occurred over the summer in the United States due to high demand for the drug in the South and Southwest regions of the country. In June, the United States bought all of the available doses for the following three month period. The Department of Health and Social Care in the United Kingdom issued a supply disruption note on September 29, and doctors were asked to temporarily prioritize patients to ensure those most likely to benefit can access it.

Access has been fluctuating in the United States and Europe, but nine companies were granted generic manufacturing licenses in Egypt, India, and Pakistan to increase production. However, the license agreement does not allow the companies to sell the remdesivir they make to high-income countries. Gilead has announced that they are ramping up their own production of remdesivir in order to meet the potential demand from October onwards.

Vaccine Updates

Moderna Vaccine in Older Adults

Researchers published the results of a Phase 1 trial that investigated the safety and dosing of the RNA-based vaccine being developed by Moderna in the *New England Journal of Medicine* (Anderson et al., 2020). The trial included 40 participants who were separated into two groups by age: those 56 to 70 years and those over 70 years. All participants received two doses of the vaccine 28 days apart, and two dose levels were administered for testing. The reported side effects after administration of the vaccine were mostly classified as mild to moderate in severity. Those most frequently reported were fatigue, chills, headache, muscle aches (or myalgia), and pain at the injection site. Side effects were more likely with the group getting the higher dose of vaccine and in participants who received their second immunization. The immune response to the vaccinations was found to increase rapidly after the first immunization, and measurements after the second shot showed that all of the participants had produced neutralizing antibodies. As might be expected, the group receiving the higher dose of vaccine produced a larger amount of antibodies. The response was reported to be “similar to those previously reported among vaccine recipients between the ages of 18 and 55 years and were above the median of a panel of controls who had donated convalescent serum.” There was also evidence that the vaccine activated a T-cell response.

> **Based on the data, the researchers conclude that use of the higher dose vaccine is safe for use in older individuals and is able to promote an immune response in antibody production and T-cell activation similar to that seen in younger individuals.**

Novamax

Novamax announced that they are preparing to begin a Phase 3 trial of their potential COVID-19 vaccine in the United Kingdom (Thomas and Zimmer, 2020). The vaccine candidate from

Novamax uses coronavirus proteins instead of RNA, as with the Moderna vaccine. Protein-based vaccines have been successfully used in the past while RNA based vaccines have not yet been approved to treat any diseases. It also has the advantage that it does not need specialized shipping conditions as required by the RNA-based vaccines.

However, the development and manufacture of protein-based vaccines takes longer, which is why Novamax is just starting Phase 3 trials while the other companies are soon expecting results from theirs. Researchers are interested in the results of Phase 3 trials because in the earlier safety trials (Phase 1 and 2) the participants were found to have a large immune response to the vaccine, and while it is difficult to make direct comparisons, the levels appeared to be higher than the response from other potential vaccines under study. The expansion of the number of people given the vaccine in the upcoming trial will help with a better understanding of the magnitude of the response and further the understanding of the safety profile.

Efficacy of Masks

A report in the journal *Scientific Reports* indicates that **surgical masks and unvented KN95 respirators, even without fit-testing, reduce the outward particle emission rates by 90% and 74% on average during speaking and coughing compared to not wearing a mask** (Asadi et al., 2020). The researchers also investigated the efficacy of non-medical grade cotton masks, but were unable to determine the particle emission rate because the masks themselves shed small cotton particles that interfered with the measurements.

There have been reports of KN95 masks that were imported from China that do not meet the standards for filtering particles (Rodriguez, 2020 and ECRI, 2020). **The difference in the name between KN95 and N95 is based on the organization that certifies the masks.** The efficacy of N95 masks is certified by the National Institute for Occupation Health and Safety (NIOSH), a part of the United States CDC, and certified masks filter more than 95% of airborne particles. However, testing has shown that between 60% and 70% of the respirator alternatives imported from China, which are called KN95, currently exhibit filtration performance significantly inferior to NIOSH-certified masks. Some of the imported masks were also fraudulently marked as certified by the NIOSH.

This could have negative effects on hospitals and other facilities where the masks are used to protect staff with a high risk of contact with individuals who have COVID-19 or other infectious diseases. The ECRI, an independent and non-profit group who performed the tests, also mentioned that often the manufacturer test reports were found to be falsified, and that the only way to determine if the masks function properly is to do independent testing for each manufacturer.

Viral Loads

Several trials have found that there is a correlation between the amount of virus in nasal secretions (also called viral load) and outcomes from COVID-19 (Service, 2020). Some researchers have begun advocating for use of the viral load as another component of the prognosis of people with SARS-CoV-2 infections. The viral load is already available from PCR-

based tests without adding steps to the test or costing more, and it is reported as the cycle threshold, or CT. The cycle threshold is a measure of how many rounds of replication are required for the viral RNA to be detected, and the lower the CT the more RNA that is present in the sample, corresponding to a higher viral load.

Higher viral loads have been associated with

- Increased infectivity
- Expansion of an outbreak when high viral loads present in large proportions of a population
- Increased risk of developing any symptoms
- Increased risk of developing severe symptoms

There are skeptics of the usefulness of the measurement of viral load because there are outliers in both directions. In one study, it was found that 40% of people with COVID-19 do not exhibit symptoms even though they have a similar amount of virus compared to patients who have symptoms. While proponents of the use of viral load acknowledge that the value is not always predictive, they indicate that when used with other patient characteristics it still can be useful for evaluating an individual's risk.

Two related studies were presented at the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Conference on Coronavirus Disease and suggest that the viral load associated with hospitalized cases has declined as the pandemic progressed, and the decline in viral load may explain the corresponding decline in the rate of admittance to the intensive care unit and a reduction in the number of deaths (Van Beusekom, 2020). Both studies were based on data observed from patient records, which means that they can only identify an association and not prove a cause and effect relationship. In one study from Wayne State University in Detroit, Michigan it was reported that 25.5% of viral loads were characterized as high, 48.7% were intermediate, and 25.5% were at low levels. Five weeks later, the proportions had changed, and 70% of the initial tests from participants had a low viral load. There was also a decrease in the death rate over the study that correlated with the reduction in viral loads. Overall, 45% of patients with high viral loads died, while 32% with intermediate loads and 14% with low loads died. In the sixth week of the study, there were no participants with high viral loads.

The reduction of viral loads was proposed to be an indication that the pandemic is becoming less severe as implementation of physical distancing and lockdowns may have helped to decrease the overall exposure to SARS-CoV-2.

The second study, conducted in Italy, also suggests that lockdowns used to reduce the spread of transmission have led to lower case numbers as well as a reduction in the viral load measured by PCR-based testing between March and May. There has also been a lower percentage of patients in the region that require intensive care and fewer people dying from COVID-19 as the pandemic has progressed. The percentage of individuals admitted to the intensive care unit declined from March to May with values of 6.7% in March, 1.1% in April, and 0.0% in May.

The authors conclude that "people were presumably exposed to a lower viral load, which has been previously associated to less severe clinical manifestations."

Changes in the Demographics of New Cases

Researchers from the CDC have reported that there has been an increase in the number of people between the ages of 18 and 22 years infected with SARS-CoV-2 between August 2 and September 5 (Salvatore et al., 2020). On a national level, the number of cases in this age group increased by 55%. By region, the increase was the largest in the Northeast (144%) and the Midwest (123%). The weekly incidence in the Northeast increased from 53 per 100,000 to 130 per 100,000 for persons aged 18 to 22 years during August to September. However, the weekly incidence in all other age groups in the region has remained steady at 53 per 100,000 since July 4.

The increases indicate that while individuals in this age range may be less at risk for severe symptoms, they have similar risks of infection compared to other adults.

Increased levels of transmission in a community mean that those who do have a high risk of severe symptoms are more likely to get COVID-19. There is also emerging evidence that even those with mild or no symptoms are at risk for long-term complications, including inflammation of the heart (myocardial inflammation).

It was estimated that 45% of the adults aged 18 to 22 years are enrolled in college or university in 2019. As might be expected from the age range, the reopening of universities and colleges are attributed to the increase in infection.

In a departure from previous time periods, the period from August to September included an increase in the proportion of white individuals (designated as non-Hispanic white) in this age group infected from 33.8% to 77.3%. This correlates to an increase of 149.7% in the weekly incidence among white persons aged 18 to 22 years during the time period, while incidence among persons of other racial and ethnic minority groups remained stable or declined.

Evaluation of clusters on a North Carolina university campus within two weeks of opening of the campus to students further emphasizes the risk of increased community transmission emanating from institutions of higher learning (Wilson et al., 2020). The name of the university was not reported in the study, but the administration had followed steps recommended by the CDC to reduce the risk of SARS-CoV-2 transmission on campus.

Mitigation strategies employed

- Staggered move-in appointments over a one week period
- Decreased classroom density to facilitate physical distancing
- Reduced maximum dining hall capacity and increasing takeout options

Students were also required to sign an "acknowledgment of community standards and university guidelines," which recommended daily symptom checks, use of masks in all indoor common spaces and classrooms, physical distancing of at least 6 feet in indoor and outdoor settings, and limitations on group gatherings consistent with local guidelines. The administration reported that about 95% of the returning students signed the acknowledgement, but the information on the adherence to these guidelines was not available. There was also no requirement for COVID-19 testing before return or quarantine before return or in the first week of arrival.

The dorms were filled at between 60% and 85% capacity with most students placed in rooms with one other roommate. It was estimated that approximately 29% of the returning students for the semester were living on campus. Students began to move into residence halls during the week of August 3, and classes began on August 10. The overall enrollment for the semester was 19,690 students.

By August 25, there were 670 laboratory-confirmed cases identified among students, faculty, and staff members of the university, and 96% of the people who tested positive were under the age of 22 years.

The median age of confirmed cases was 19 years, and 30% of those diagnosed with COVID-19 lived in on-campus housing. Between August 3 and 25, there were 18 reported clusters of five or more people with COVID-19 with the largest included 106 people in a university-affiliated apartment complex. Based on contract tracing, 30% of the confirmed cases were linked to one of the 18 clusters. As of August 25, none of the identified individuals with COVID-19 had been hospitalized or had died. Information on other potential complications was not available.

The rapid increase in cases within 2 weeks of opening campus suggests that student gatherings and congregate living settings, both on and off campus, likely contributed to the rapid spread of COVID-19 within the university community, and robust measures are needed to reduce transmission at institutes of higher education.

On August 19, the university transitioned classes back to an online format. Additionally, all students who were living in on-campus housing were required to return home unless they filed a hardship waiver. In 2019, 83% of the undergraduates at the school were North Carolina residents, suggesting that most of the returning students remained in the state upon returning home. Evaluation of the information on the Johns Hopkins Coronavirus Resource Center for the period between August 15 and August 25 shows an increase in the number of new cases reported, with a decrease that starts around August 25 (JHU, 2020).

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