

## COVID-19 DIGEST

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### *From the Cross-Campus Infectious Diseases COVID-19 Task Force*

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## EPIDEMIOLOGY

### LOCAL

Following a surge in reported infections and hospitalizations across the state throughout July, daily new cases and hospitalizations have been declining since mid-August. [California](#) now reports more cases than any other state with **726,182 confirmed COVID-19 cases** and **13,495 deaths**. The [positive test rate statewide](#) has also been decreasing since mid-August and was 4.9% over the last week. As of September 3, **9,696 positive cases** and **84 deaths** have been reported in [San Francisco](#) with an average of 75 new cases diagnosed per day over the last 7-days and a positive test rate of 2.5%. On August 28, California announced a [new color-coded system](#) to assess risk level by county to replace the previous watch list and Stage 1-4 approach to re-opening the economy. Under this system county risk level is classified from yellow (“minimal”) to purple (“widespread”) using rate of new cases and positive test rate from the previous 3 weeks. Most of the state is currently classified as purple, “widespread” risk and San Francisco is currently in the red, “substantial” risk level.

### NATIONAL

The [United States](#) continues as the undisputed global epicenter of the COVID-19 pandemic with over **6.1 million reported cases** of COVID-19 and more than **186,000 deaths**. Since late July the rate of new reported cases by day has decreased reaching a new plateau of approximately 42,000 cases per day the last week of August. Most of the [South and West](#), which saw rapid increases in cases and hospitalizations during June and July, are now reporting decreasing daily cases and hospitalizations, particularly the summer hotspots of Arizona, California, Texas, and Florida, with deaths plateauing or decreasing. However, many states in the mid-west, including Iowa, Kansas, Nebraska, and the Dakotas are reporting worrisome increases in new infections, positive test rates, and hospitalizations. [South Dakota](#) is currently experiencing the highest rate of new infections and positive tests nationally, with 348 per million population diagnosed daily and a 20% of tests that are positive. The annual [Sturgis Motorcycle Rally](#) was held in Sturgis, South Dakota from August 7-10 without social distancing measures or masks. To date [at least 260 cases in 11 states and 1 death](#) have been directly linked to the event. Many new cases across the country are also being tied to the re-opening of many [college and university campuses](#). Despite opening residence halls at significantly reduced capacity and less than 30% of total classroom seats taught in person the [University of North Carolina](#) switched to all-remote learning after just one week of classes after 4 outbreaks leading to 177 infections and 349 students in quarantine. The US is at increased risk of additional surges in COVID with the upcoming holidays, particularly in regions where public health measures are still not being recommended nor deployed 9 months into the pandemic.

### GLOBAL

[Worldwide](#) there are currently over **26.3 million** reported cases of COVID-19 and **over 869,000 deaths**. The United States, Brazil, and India contribute over 50% of cases to the global confirmed case burden and over 40% of deaths to the global death toll. Countries across Europe are seeing a [second wave of infections](#). Spain, one of the hardest hit countries in the spring, is now seeing case counts exceeding levels from March and April. Part of the increase in reported cases is due to a significant scale up in testing capacity, however the [percentage of positive tests](#) has also been steadily increasing since a nadir of <1% in mid-June to 9.7% at the end of August. Deaths have remained relatively low to date, unfortunately [hospitalizations are rising](#) quickly.

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## UP TO THE MINUTE DISPATCHES

### **SARS-CoV-2 re-infection has now been demonstrated**

This past week, the first confirmed case of a SARS-CoV-2 re-infection was [published](#). A 33-year-old man from Hong Kong was first infected in late March and then contracted the virus a second time approximately 4.5 months later after returning from Europe. The viral genomes were sequenced at both time points, identifying a difference of 24 nucleotides and placement of the genomes into two separate clades (groups). These results proved that the 2 strains were distinct and arose from independent infections. Notably, the patient was symptomatic during the first episode but asymptomatic subsequently, raising the possibility that the initial infection may have conferred at least partial immunity. During the second episode, the patient also seroconverted by SARS-CoV-2 IgG antibody testing, suggesting that he had either failed to generate an antibody response initially or that the response had waned. Following this publication, other reports of presumed SARS-CoV-2 re-infection have been released, including [2 cases from Europe](#) (an immunocompromised Dutch patient and a Belgian patient who had a mild initial episode of illness) and [a U.S. case from Nevada](#). Interestingly, in the Nevada case, the second episode of re-infection 48 days later was more clinically severe, as the patient needed to be hospitalized with pneumonia. **Conclusion:** These cases show that SARS-CoV-2 re-infection is possible, and that infection may not confer long-lasting immunity in some patients. Evidence to date suggest this is a rare event. More studies are needed to determine the incidence of re-infection in the population, the role of neutralizing antibody and other immune responses in re-infection, and what this means with respect to the durability of SARS-CoV-2 vaccines in development.

### **Remdesivir may be beneficial in COVID-19 patients without hypoxia**

Gilead-sponsored scientists published [results](#) of an open-label, randomized control trial to assess the safety and efficacy of remdesivir, given for 5 or 10 days, versus standard of care for treatment of patients with moderate COVID-19 (defined as infiltrates seen on chest x-ray, normal oxygenation). 584 patients were randomized to either 5 days of remdesivir (median 5 days received), 10 days of remdesivir (median 6 days received), or usual care. Primary endpoint was clinical status rating based on a 7-point ordinal scale (ranging from death to discharge) on day 11. They found that patients treated with 5 days of remdesivir had a higher odds of better clinical status at day 11 than those in the standard care group (OR 1.65, 95% CI, 1.09 to 2.48). There was no significant difference in clinical status between 10 days of remdesivir treatment and usual care. Both remdesivir treatment groups showed favorable comparison to standard care at Day 14 and 28. Mortality was very low in all groups. Limitations of the study included lack of blinding. In addition, spikes in discharges after completion of remdesivir courses suggest that providers may have kept patients hospitalized to finish treatment despite improvement, possibly de-emphasizing benefit. **Conclusion:** Remdesivir may have benefit in patients admitted to the hospital with COVID-19 who have lower respiratory tract infection but no hypoxia. A more permissive use of remdesivir in non-hypoxic patients with COVID-19 should be considered when there is ample supply. Further studies are needed to elucidate the ideal patient population for this treatment and to investigate the efficacy of outpatient administration of intravenous remdesivir, as most non-hypoxic patients will have a short or no hospital stay.

### **Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicenter prospective observational study**

Acute respiratory distress syndrome (ARDS) is the most common cause of death from COVID-19. Whether the pathophysiology of ARDS from COVID-19 is different from non-COVID-19 associated ARDS is unknown. A prospective, observational [study](#) of 301 patients with COVID-19 associated ARDS from Italy were compared to historical controls. Respiratory system compliance, ratio of partial pressure of arterial O<sub>2</sub>/fractional concentration of O<sub>2</sub> in inspired air, ventilatory ratio, and D-dimer were measured within 24 h of ICU admission. Lung CT scans were done when clinically indicated. Researchers found that the majority of COVID-19 ARDS patients had similar abnormalities in respiratory system compliance and arterial hypoxemia to non-COVID-19 patients. However, a subgroup of patients with both elevated D-dimer concentrations and a reduction in respiratory system compliance had a markedly elevated 28-day

mortality. There was also evidence of a significant increase in the pulmonary dead space in COVID-19 patients with elevated D-dimers, which correlated with CT angiogram evidence of pulmonary vascular occlusions. **Conclusion:** Many patients with COVID-19 associated ARDS have similar physiology to non-COVID-19 patients with ARDS, however high D-Dimer, high dead space, and pulmonary vascular occlusions were seen in some COVID-19 patients and associated with a poor outcome. Clinical trials, such as the NIH sponsored ACTIV-4, assessing the efficacy of anticoagulation strategies in patients with COVID-19 associated ARDS will help us better understand how to care for these patients.

### **The immune response to COVID-19 differs between the sexes**

Gender has been shown to have a significant impact on the outcome of infections and underlying differences in immune response for several viral infections, including Hepatitis A and C, HIV, and TB. Although age and underlying health conditions have been identified as risk factors for poor outcome in SARS-CoV-2 infection, men are almost twice as likely to die as women. To address whether there is gender-specific differences in the immune response, the authors reported a [study](#) that compared viral loads, SARS-CoV-2-specific antibody titers, plasma cytokines, and blood cell phenotyping in patients reporting as male and female who were hospitalized (non-ICU) for COVID-19 who had not received immunomodulatory therapies. The control population was uninfected male and female health care workers. For some of the analysis, the authors included additional COVID-19 patients with more severe disease (admitted to the ICU, received immunomodulatory therapy, or steroids). They found that male patients had higher plasma levels of innate immune cytokines such as IL-8 and IL-18 as well as more robust induction of non-classical monocytes. Female patients exhibited more robust T-cell activation. A poor T-cell response negatively correlated with patient's age and was associated with worse outcome in male but not female patients. Higher innate immune cytokines in female patients but not male patients were associated with worse disease progression. Limitations of the study are that it was observational, the number of patients was relatively low, the study group was heterogenous, and only a few differences between male and female patients were statistically different despite surveying a large number of parameters.

**Conclusion:** There appears to be key differences in the baseline immune capabilities in men and women during the early phase of SARS-CoV-2 infection and suggest a potential immunological basis for the different disease progression between sexes. Further studies are needed to better understand these results.

## **FAQ on convalescent plasma therapy with Dr. Annie Luetkemeyer and Dr. Sarah Doernberg**



**Dr. Annie Luetkemeyer**  
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### **1. What is convalescent plasma and is it useful in the treatment of viral infections?**

Plasma is the antibody rich part of blood that does not contain red blood cells. Convalescent plasma (CP) is plasma taken from individuals who have recovered from a specific infection, such as COVID-19. The concept behind treatment with CP is to provide passive immunity for treatment or prevention of infection. Doctors have administered CP for many indications over the past hundred years, including measles, mumps and polio. Most studies of this intervention have been small and lacked appropriate controls to draw definitive conclusions about

efficacy and safety. CP has been associated with a mortality benefit during the [2003 SARS outbreak](#) and with [acute Argentine hemorrhagic fever](#), with mixed data in [severe influenza](#). Early administration and plasma with higher antibody concentrations generally have been associated with better outcomes when CP is used.

## 2. Are there any published studies that support the efficacy of convalescent plasma in the treatment of COVID-19?

CP for treatment of COVID-19 is an area of intense interest. To date, there have been three RCTs, all terminated early and two not yet peer-reviewed, and multiple observational studies examining the role of CP. [Li and colleagues](#) performed an open-label randomized trial of high-titer CP versus usual care for patients with severe or life-threatening COVID-19. There was no difference in the primary outcome, time to clinical improvement within 28 days, though in the subgroup with less severe disease (not mechanically ventilated), there was a significant difference in clinical improvement with CP vs no plasma: 91.3% vs 68.2% (HR 2.15 [1.07-4.32]). [An open label Spanish RCT of hospitalized COVID patients](#) (n=81, stopped early due to end of local epidemic), reported CP associated with less progression to severe disease (0% vs 14%, P =0.03 in post hoc analysis and a non-significant trend towards improved mortality with CP. 50% of recipients has anti-COVID IgG and neutralizing antibodies at baseline. [In a pre-print](#), a Dutch RCT of 86 patients with early disease randomized to CP versus standard of care therapies was halted early by the safety monitoring committee after noting most participants already had neutralizing antibodies at the time of enrollment. No differences were found in clinical endpoints. Given challenges to full enrollment of these RCTs, a [data pooling effort](#) is underway to leverage data from these and ongoing RCTs.

Several observational studies suggest benefit, although these are subject to significant confounding. These include:

- A pre-print analysis of over 35,000 patients who received plasma through [the observational Mayo Clinic Expanded Access Program \(EAP\)](#) reported a modest 30 day mortality benefit if CP transfused within 3 days of COVID diagnosis vs after 3 days ( 21.6% vs 26.4%, p<0.01) and a lower relative risk of death (RR 0.77 [0.63 – 0.94]) if CP with an higher antibody level was used. Notably, the majority of CP administered through this program did not have high titers.
- An [observational case control series](#) of 316 Houston COVID patients demonstrated a significant reduction in mortality when CP was administered within 72 hours of admission and when higher titer plasma was used. However, neither study was a randomized control trial.

## 3. Are there any trials across the UCSF system (UCSF Health, ZSFG, SFVA) studying the efficacy of convalescent plasma or monoclonal antibodies for the treatment of COVID-19?

The [CAPRI study](#) is a randomized controlled trial evaluating CP administered to hospitalized COVID patients within 3 days of admission or within 14 days of symptom onset, actively enrolling at UCSF and ZSFG (PI's [Luetskemeyer & Hsue](#)).

Several studies are evaluating passive, monoclonal antibodies against SARS-CoV-2 as part of [the NIH-funded ACTIV initiative](#) in both outpatient and inpatient settings. [ACTIV-2](#) is an outpatient randomized controlled, adaptive platform trial currently evaluating a single infusion of monoclonal antibodies; the study is actively enrolling at ZSFG (Site PI [Luetskemeyer](#)). [ACTIV-3](#) is also an adaptive design RCT evaluating multiple different types of monoclonal antibodies in hospitalized COVID patients; the study is actively enrolling at UCSF Health (Site PI [Matthay](#)). Both studies are initially examining a Lilly monoclonal antibody.

## 4. Should we be giving convalescent plasma to patients regularly outside of a clinical trial?

Collectively, observational and randomized data indicate that CP is generally safe and suggest there is a signal towards clinical and mortality benefit in some populations. However, despite the enthusiasm for the potential role of CP as a COVID treatment, there are insufficient data to support regular use of CP outside of a clinical trial. This is consistent with the current [CP EUA guidance](#) and the NIH COVID [guidelines](#), which both state that CP is not yet standard of care therapy. Clinicians should prioritize enrollment of ongoing randomized trials, where available, to

definitively inform whether CP is beneficial for COVID patients and if so, in which populations. It is not clear to what degree the presence of anti-COVID antibodies in plasma recipients at the time of infusion may impact CP efficacy.

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**UCSF Hospital Epidemiology and Infection Prevention COVID-19 webpage:**

<https://infectioncontrol.ucsfmedicalcenter.org/ucsf-health-covid-19-resources>

**San Francisco DPH link:** <https://www.sfc-dcp.org/infectious-diseases-a-to-z/coronavirus-2019-novel-coronavirus/>

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