Good day everyone

Today the first 2 articles focus on reinfection. To put into perceptive to date reinfection still appears to be very uncommon. The third review is the revised NIH Guidelines. The figure breaks down treatment options by stage of disease. There is an updated review on plasma as well. Also, in the revision is a review of COVID-19 and HIV. To round out todays offering there is a nice report on outcomes of newborns born to mothers with COVID-19. This study confirms other reports that show low rates of testing-based vertical or perinatal transmission and no clinical evidence for neonatal SARS-CoV-2 infection.

Have a wonderful day

Ed

Coronavirus Disease 2019 (COVID-19) Re-infection by a Phylogenetically Distinct Severe Acute Respiratory Syndrome Coronavirus 2 Strain Confirmed by Whole Genome Sequencing
Clin Infect Dis published online August 25, 2020
Genomic Evidence for Reinfection with SARS-CoV-2: A Case Study
Lancet Infect Dis published online October 12, 2020
In the first article comparative genome analysis was conducted to differentiate re-infection from persistent viral shedding. Laboratory results, including RT-PCR Ct values and serum SARS-CoV-2 IgG, were analyzed. The second episode of asymptomatic infection occurred 142 days after the first symptomatic episode in an apparently immunocompetent patient. During the second episode, there was evidence of acute infection including elevated C-reactive protein and SARS-CoV-2 IgG seroconversion. Viral genomes from first and second episodes belong to different clades/lineages. The virus genome from the first episode contained a stop codon at position 64 of ORF8, leading to a truncation of 58 amino acids. Another 23 nucleotide and 13 amino acid differences located in 9 different proteins, including positions of B and T cell epitopes, were found between viruses from the first and second episodes. Compared to viral genomes in GISAID, the first virus genome was phylogenetically closely related to strains collected in March/April 2020, while the second virus genome was closely related to strains collected in July/August 2020.

In the second paper a 25-year-old man who was a resident in the Nevada presented to health authorities on two occasions with symptoms of viral infection, once at a community testing event in April, 2020, and a second time to primary care then hospital at the end of May and beginning of June, 2020. Nasopharyngeal swabs were obtained from the patient at each presentation and twice during follow-up. Nucleic acid amplification testing was done to confirm SARS-CoV-2 infection. The investigators did next-generation sequencing of SARS-CoV-2 extracted from nasopharyngeal swabs. Sequence data were assessed by two different bioinformatic methodologies.

The patient had two positive tests for SARS-CoV-2, the first on April 18, 2020, and the second on June 5, 2020, separated by two negative tests done during follow-up in May 2020. Genomic analysis of SARS-CoV-2 showed genetically significant differences between each variant associated with each instance of infection. The second infection was symptomatically more severe than the first. The patient required ongoing oxygen support in hospital and reported symptoms that included myalgia, cough, and shortness of breath. CXR showed development of patchy, bilateral, interstitial opacities suggestive of viral or atypical pneumonia.

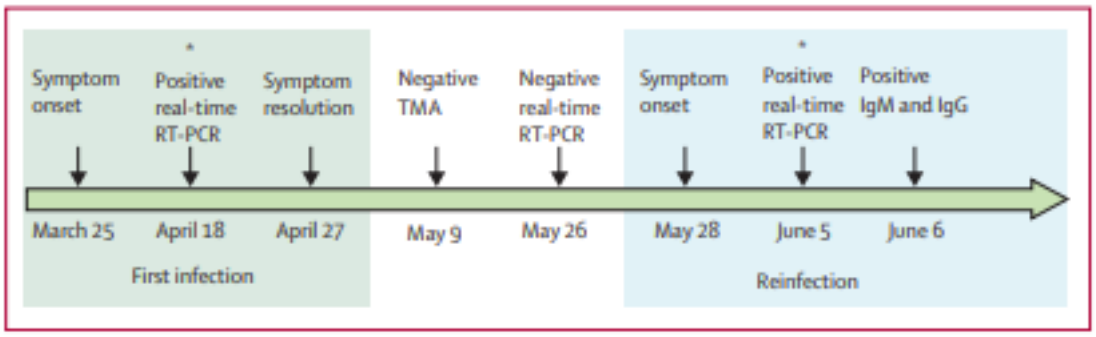


Figure 1: **Timeline of symptom onset, molecular diagnosis, and sequencing of specimens**
TMA=transcription-mediated amplification. *Sequenced specimens.

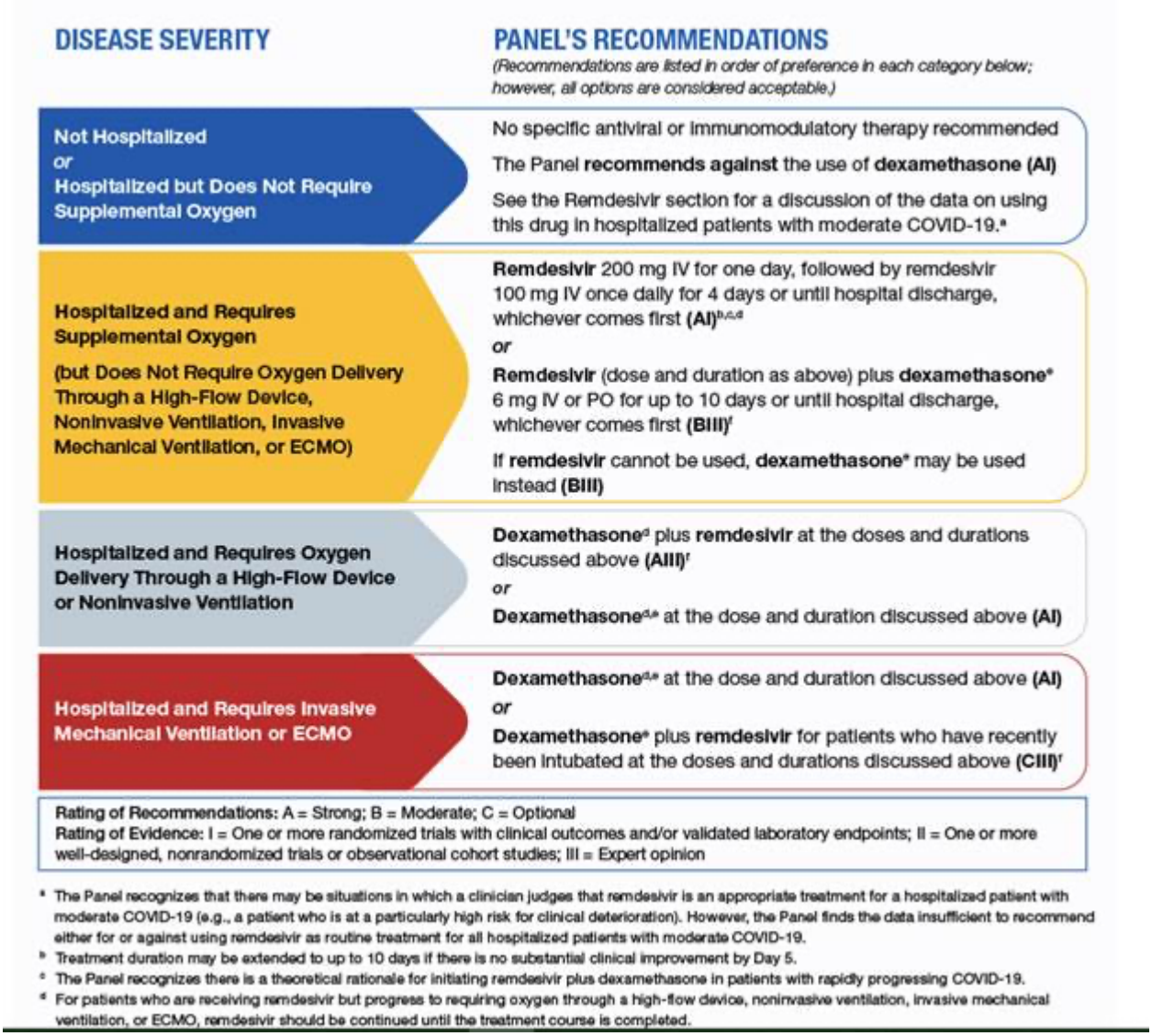
	Specimen A			Specimen B	
	April 18, 2020	May 9, 2020	May 26, 2020	June 5, 2020	June 6, 2020
Test methodology	Real-time RT-PCR	TMA	Real-time RT-PCR	Real-time RT-PCR	Immunoassay (IgG and IgM antibody detection)
Test result	Positive	Negative	Negative	Positive	Positive
Quantitative result	Ct 35·24	RLU 299	..	Ct 35·31	..

TMA=transcription-mediated amplification. Ct=cycle threshold. RLU=relative light units.

Table 1: **Summary of laboratory results**

Comment: These cases add to rapidly growing evidence of SARS-CoV-2 reinfection, in which viral genomic sequences were used to confirm infections by distinct isolates of SARS-CoV-2. What do reinfection cases mean for public health and vaccination efforts to control this pandemic? Does immunity protect an individual from disease on reinfection? The answer appears not necessarily. It is important to keep in mind that the reinfection cases in general are being picked up because of symptoms and may be biased towards detection of only symptomatic cases. Due to limited broad testing and surveillance, we really do not know how frequently reinfection occurs among individuals who recovered from their first infection. Asymptomatic reinfection cases can only be picked up by routine community testing and we may be underestimating the number of asymptomatic reinfections. Does infection by different viral strains mean we need a vaccine for each type? Does immunity prevent transmission? As more cases of reinfection are identified we need to study what correlates with protection and how long does immunity last. To put into perceptive to date reinfection still appears to be very uncommon. Since the first confirmed case of reinfection, reported in Hong Kong on Aug. 24, there have been only three published cases; reports of another 20 await scientific review.

NIH COVID-19 Treatment Updates October 9, 2020
Panel recommends strategies for managing patients with different severities of disease



<u>For Hospitalized Patients with COVID-19 Who Require Supplemental Oxygen but Who Do Not Require Delivery of Oxygen Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or Extracorporeal Membrane Oxygenation</u>

- Remdesivir 200 mg intravenously (IV) for 1 day, followed by remdesivir 100 mg IV for 4 days or until hospital discharge, whichever comes first (AI); *or*
- A combination of remdesivir (dose and duration as above) plus dexamethasone 6 mg IV or orally for up to 10 days or until hospital discharge (BIII); *or*
- If remdesivir cannot be used, dexamethasone may be used instead (BIII).

<u>For Hospitalized Patients with COVID-19 Who Require Delivery of Oxygen Through a High-Flow Device or Noninvasive Ventilation but Not Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation</u>

- A combination of dexamethasone plus remdesivir at the doses and durations discussed above (AIII); *or*
- Dexamethasone alone at the dose and duration discussed above (AI).

- Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in this group of patients, the Panel does not recommend using remdesivir alone.
- For patients who initially received remdesivir monotherapy and progressed to requiring high-flow oxygen supplementation or noninvasive ventilation, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.
- In ACTT-1, there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.09; 95% CI, 0.76–1.57) in the subgroup of participants who required high-flow oxygen or noninvasive ventilation at enrollment (n = 193). A post hoc analysis did not show a survival benefit at Day 29. [reviewed in Monday's Daily Briefing]

For Hospitalized Patients with COVID-19 Who Require Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation

- Dexamethasone at the dose and duration discussed above (AI); *or*
- Dexamethasone plus remdesivir for patients who have recently been intubated at the doses and durations discussed above (CIII).
- The reason that dexamethasone is prioritized over remdesivir monotherapy is because there is uncertainty regarding the clinical benefit of using remdesivir in this group. In ACTT-1, there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 0.98; 95% CI, 0.70–1.36) among participants who were on mechanical ventilation or ECMO at baseline (n = 285). In a post hoc analysis of deaths by Day 29, there was no evidence that remdesivir affected the mortality rate in this subgroup (HR 1.13; 95% CI, 0.67–1.89

Convalescent Plasma

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.
- Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis. [reviewed several weeks ago in the Daily Briefing]
- There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers of plasma from patients who have recovered from COVID-19 are highly variable. [and decline over time] Furthermore, hospitalized patients with COVID-19 may already have SARS-CoV-2 neutralizing antibody titers that are comparable to those of plasma donors, potentially limiting the benefit of convalescent plasma in this patient population. Several randomized, placebo-controlled trials of COVID-19 convalescent plasma are ongoing. [NIH and RECOVERY]

Special considerations in People with HIV

The Panel emphasizes that recommendations for the triage, management, and treatment of COVID-19 in people with HIV are the same as those for the general population. The Panel also recommends continuing antiretroviral therapy and prophylaxis for opportunistic infections whenever possible in people with HIV who develop COVID-19, including in those who require hospitalization (AIII). For people who present with COVID-19 and a new diagnosis of HIV, clinicians should consult an HIV specialist to determine the optimal time to initiate ART.

Outcomes of Neonates Born to Mothers with Severe Acute Respiratory Syndrome Coronavirus 2 Infection at a Large Medical Center in New York City

JAMA Pediatrics published online October 12, 2020

This is a cohort analysis of 101 neonates born to mothers with perinatal SARS-CoV-2 infections at a single institution. Only 2 (2.0%) infants had positive test results for SARS-CoV-2, but none had clinical evidence of COVID-19, despite most infants rooming-in with mothers and direct breastfeeding. Testing for SARS-CoV-2 was performed using Cobas (Roche Diagnostics) or Xpert Xpress (Cepheid) assays. Newborns were admitted to well-baby nurseries (WBNs) (82 infants) and neonatal intensive care units (NICUs) (19 infants) in 2 affiliate hospitals at a large academic medical center in New York, New York. Maternal severe/critical COVID-19 was associated with newborns born approximately 1 week earlier (median gestational age, 37.9 [IQR, 37.1-38.4] vs 39.1 [IQR, 38.3-40.2] weeks; *P* = .02) and at increased risk of requiring phototherapy (3 of 10 [30.0%] vs 6 of 91 [7.0%]; *P* = .04) compared with newborns of mothers with asymptomatic/mild COVID-19. Newborns from the WBNs roomed-in with their mothers, who were required to wear masks. Direct breastfeeding after appropriate hygiene was encouraged. Fifty-five infants were followed up in the first 2 weeks of life in a COVID-19 Newborn Follow-up Clinic, all remained healthy.

Comment: This study confirms other reports that show low rates of testing-based vertical or perinatal transmission and no clinical evidence for neonatal SARS-CoV-2 infection. These data are particularly reassuring given that we describe mothers with a range of clinical presentations. Contrasting a previous report, the small number of mothers with severe/critical COVID-19 in this cohort did not transmit SARS-CoV-2 to their newborns. (Am J Perinatol. 2020;37(8):861-865) Neonates born to mothers with severe/critical illness were born at an earlier gestational age, a shift that did not appear to be driven by the NICU population. Maternal severe/critical disease was also associated with overall higher incidence of hyperbilirubinemia requiring phototherapy in WBN newborns for unclear reasons. Lastly rooming in and breast feeding appear safe when appropriate precautions are taken. [confirms earlier reports]