Good morning. A heads up, The Daily Briefing will not be published Monday in honor of Memorial Day. Since Covid-19 activity has slowed down, the Daily Briefing will be published twice a week on Tuesday and Friday. Special editions may be published based on new science which maybe more time sensitive.

Today I start with the VaST (Vaccine Safety Technical) from last week on myocarditis following mRNA vaccines. The second report is the exciting news on the preliminary data on the efficacy of the Moderna vaccine in children 12-17.

Under Journal Review I have tried to select a diverse group of articles. First is the use of tocilizumab in moderate Covid-19 patients with high CRPs. The next article looks at a model on aerosolized SARS-CoV-2 in an electrocautery plume. The third article compares two rapid molecular assays for the detection of SARS-CoV-2. The last article is a CDC update on SARS-CoV-2 vaccine breakthroughs.

Have a wonderful day

Ed

COVID-19 News

COVID-19 VaST Work Group Technical Report – May 17, 2021
The VaST session on May 17, 2021, included several presentations on myocarditis following mRNA vaccines, from the Department of Defense (DoD), the Vaccine Adverse Event Reporting System (VAERS), and Vaccine Safety Datalink (VSD). There were also brief updates from the Veteran's Administration (VA) and the Clinical Immunization Safety Assessment (CISA) groups about their plans for future investigation of myocarditis.

VaST (Vaccine Safety Technical) concluded that there are relatively few reports of myocarditis to date and that these cases seem to occur:

- predominantly in adolescents and young adults,
- more often in males than females,
- more often following dose 2 than dose 1, and
- typically, within 4 days after vaccination.

Most cases appear to be mild, and follow-up of cases is ongoing.

Comment: The American Heart Association/American Stroke Association has issued a statement noting that the benefits of COVID-19 vaccination "enormously outweigh" the rare, possible risk of heart-related complications, including myocarditis.

Moderna and Vaccine Efficacy in Adolescents
In this trial, more than 3700 children were enrolled. No cases of Covid-19 were observed in subjects who received two doses. They calculated vaccine efficacy of 93% among seronegative patients 14 days after the first dose. Antibody levels among the adolescents were similar to adults.

The most common side effects were mild to moderate with the most common being pain at injection site. More side effects were seen after the second dose including HA, fatigue, myalgias, and chills.

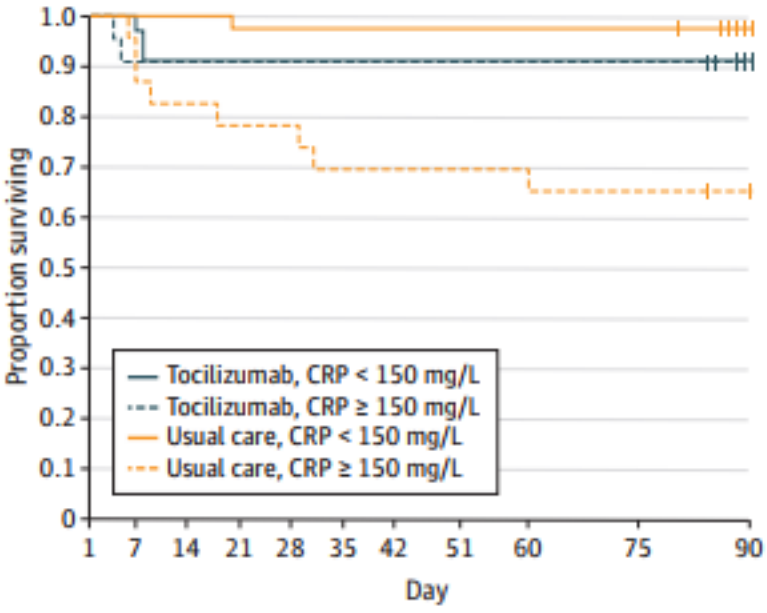
Comment: This is remarkably similar to Pfizer's results. Moderna will apply to FDA in the next few weeks for EUA.

Journal Review

Effectiveness of Tocilizumab in Patients Hospitalized with COVID-19: A Follow-Up of the CORIMUNO-TOCI-1 Randomized Clinical Trial
JAMA Intern Med published online May 24, 2021
doi:10.1001/jamainternmed.2021.2209
These investigators had previously published a trial of tocilizumab in hospitalized patients who were receiving oxygen (rate, ≥3 L/min) but did not require high-flow or mechanical ventilation. [JAMA Intern Med. 2021;181(1):32-40] The study met its primary composite end point, which was the proportion of patients who required noninvasive ventilation or intubation or who died at day 14 but found no survival difference at day 28. In this follow-up study, they extended follow-up to 90 days and examined whether survival varied with baseline CRP levels.

By day 90, death had occurred in 7 of 63 (11%) and 11 of 67 patients (18%) in the tocilizumab and usual care arms, respectively (adjusted hazard ratio [HR], 0.64; 95% CI, 0.25- 1.65). When outcomes were analyzed according to CRP levels, we found a statistical interaction between CRP levels and the primary composite end point at day 14 and survival at day 90, with a benefit of tocilizumab in patients if their CRP levels were greater than 15.0 mg/dL [to convert to mg/L, multiply by 10], but not if CRP levels were 15.0 mg/dL or less. In patients with CRP levels greater than 15.0 mg/dL, the chance of achieving the primary end point (the percentage of patients who received noninvasive or invasive ventilation or those who died) was 18% and 57% in the tocilizumab and usual care groups, respectively (HR, 0.18;95% CI, 0.06-0.59. Likewise, day-90 mortality was 9% and 35% in the tocilizumab and usual care groups, respectively (HR, 0.18; 95% CI, 0.04-0.89).

Overall survival stratified by CRP level

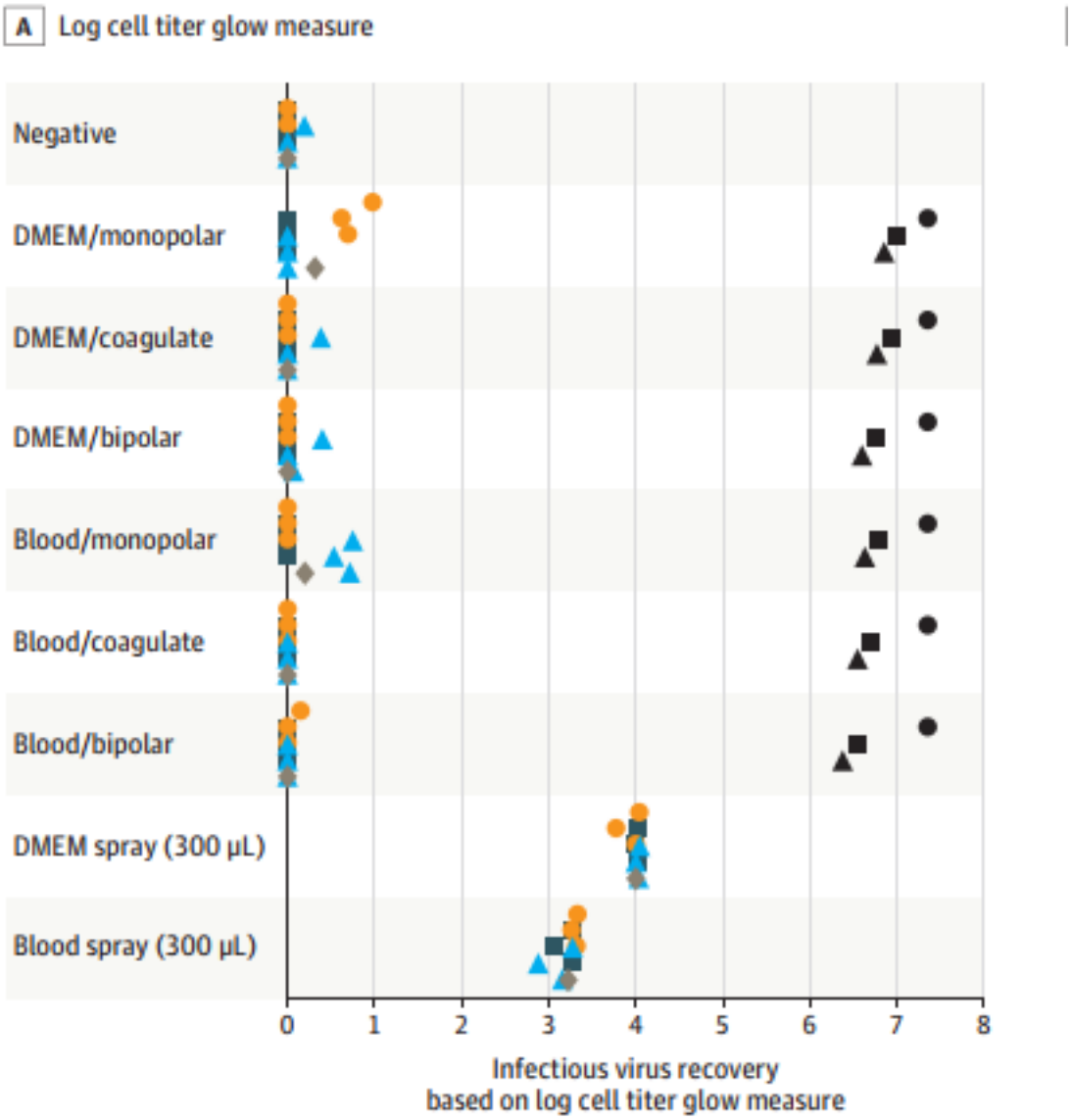


Comment: This follow-up analysis suggests that tocilizumab may be considered for treating patients presenting with moderate-to-severe COVID-19-associated pneumonia with high CRP levels. The sample size, however, was small and analysis had wide confidence intervals. Lastly this trial targeted a narrow segment of the COVID-19 patient population (patients with a WHO Cognitive Performance Scale score of 5 exactly and requiring at least 3 L/min of oxygen). Nonetheless this study suggests tocilizumab may have a role in patients presenting with less severe COVID-19 with high CRP.

Assessing the Risk of SARS-CoV-2 Transmission via Surgical Electrocautery Plume
JAMA Surg published online May 21, 2021
doi:10.1001/jamasurg.2021.2591
Direct transmission to surgical staff from aerosolized virus in an electrocautery plume (as has been observed with other viruses) has been raised as a safety concern. Cautery performed in areas of high potential viral load (e.g., the nasopharynx, oropharynx, lung parenchyma) could pose a risk to those in the operating room.

Electrocautery at 25W was applied using 3 different methods (monopolar cut, monopolar coagulate, and bipolar electrocautery for 1 minute on raw chicken breast with an added 4 mL of Dulbecco modified eagle medium (DMEM) or a DMEM: blood mixture containing 1 × 105.7 median tissue culture infectious dose (TCID50) per mL of SARS-CoV-2, similar to the viral load in pulmonary sputum of a patient with symptoms. An estimated volume of 1.7 ± 0.3 mL, 1.5 ± 0.1 mL, and 1.0 ± 0.2mL of liquid was vaporized during the monopolar cut, monopolar coagulate, and bipolar electrocautery, respectively, and collected using a Western AirScan air sampler at 60 L per minute. The gelatin filters were solubilized in phosphate-buffered saline and added in undiluted and 1:10 serial dilutions to VeroE6 cells to determine the TCID50 value of the vaporized virus following electrocautery.

Using a cell titer glow measurement for replicating virus, they observed no virus recovered from any electrocautery performed. However, collected aerosolized blood or media containing SARS-CoV-2 (approximately 0.3 mL) resulted in a recovery at least 3 or 4 base 10 logs higher than electrocautery or the negative control. The maximal theoretical recovery of SARS-CoV-2 on the gelatin filter was approximately 1 × 106.2 units (or 1 × 109.2 viral cytopathic effect units, from the cell titer glow measurement). Viral RNA was readily detected in the control aerosols of both fluids in the absence of cautery. The lack of SARS-CoV-2 was also confirmed by the lack of viral RNA on quantitative real-time polymerase chain reaction with undiluted vapor collected on the filter.



Comment: In this study, SARS-CoV-2 was not detectable in the aerosol cautery plume generated from electrocautery under any of the conditions studied despite the high viral titers used. By mimicking surgery on a patient with a high SARS-CoV-2 load, there was a minimum of a 9-log reduction of viral RNA with any of the electrocautery methods. This suggests that electrocautery smoke is an unlikely source of SARS-CoV-2 transmission for health care workers. This study is limited by the in vitro nature of the experiment and not collecting cautery plumes from actual airway surgery in patients with active SARS-CoV-2.

Diagnostic Accuracy of the Cepheid Xpert Xpress and the Abbott ID NOW Assay for Rapid Detection of SARS-CoV-2: A Systematic Review and Meta-Analysis
J Med Virology published online April 29, 2021
DOI: 10.1002/jmv.26994

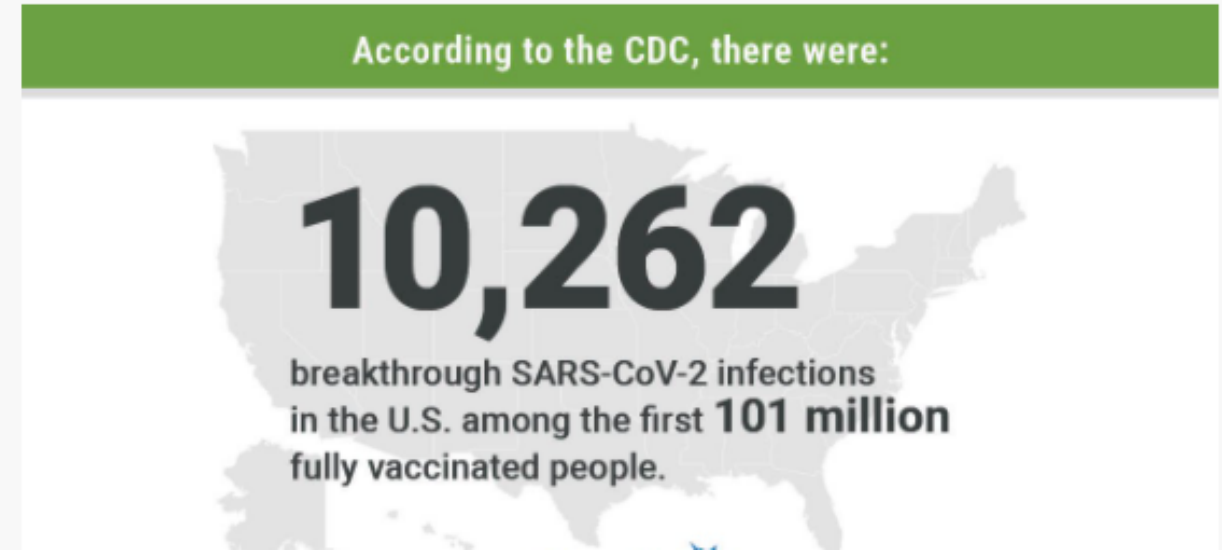
The authors investigated the diagnostic accuracy of the Xpert Xpress and the ID NOW assays for rapid detection of SARS-CoV-2 using a systemic review and meta-analysis approach. A systematic literature search was performed using PubMed, Embase, and the Cochrane COVID-19 Study Register. The sensitivity and specificity of these tests for detecting viruses in patients with suspected SARS-CoV-2 infection were pooled.

They used commercial and laboratory-developed PCR as reference standards. The authors identified 11 studies involving 1734 subjects for the Xpert Xpress assay and 10 studies involving 1778 subjects for the ID NOW assay. The pooled sensitivity and specificity of the Xpert Xpress assay for detection of SARS-CoV-2 were 0.99 (95% confidence interval [CI], 0.97 to 0.99) and 0.97 (95% CI, 0.95 to 0.98), respectively. The pooled sensitivity and specificity of the ID NOW assay were 0.79 (95% CI, 0.69 to 0.86) and 1.00 (95% CI, 0.98 to 1.00), respectively. The Xpert Xpress assay showed excellent diagnostic accuracy for rapid detection of SARS-CoV-2.

Comment: Ideal performance of tests for SARS-CoV-2 detection is judged by accuracy and turnaround time. The two NAATs evaluated in the present study were used for rapid diagnosis of SARS-CoV-2 infection: the Xpert Xpress assay, which provides results within 45 min, and the ID NOW assay, which delivers results in approximately 5-13 min. False-negative results could have serious consequences, especially in vulnerable elderly patients. Also, false-positive results could have a negative impact by delaying management of the causative disease or causing unnecessary isolation. A possible explanation for the low sensitivity of the ID NOW assay is the difference in sensitivity related to viral load. A recent study compared the Xpert Xpress assay and the ID NOW assay with the Roche Cobas SARS-CoV-2 assay for samples with low, medium, and high SARS-CoV-2 viral concentrations. [J Clin Microbiol. 2020;58(8):e00772-20] The two tests showed 100% positive agreement for medium and high viral concentrations, defined as Ct value <30. However, for low viral concentrations defined as Ct value >30, positive agreement for the Xpert Xpress assay was 97.1%, whereas it was 34.3% for the ID NOW assay. They could not assess publication bias as no reliable methods exist to investigate this in diagnostic test accuracy studies. They used various types of commercial or laboratory-based RT-PCRs for reference comparisons in SARS-CoV-2 diagnosis, which can introduce bias due to diagnostic differences.

Cepheid has developed the Xpert Xpress SARS-CoV-2/Flu/RSV test, which is a rapid, multiplexed real-time RT-PCR test intended for the simultaneous qualitative detection and differentiation of SARS-CoV-2, influenza A, influenza B, and respiratory syncytial virus (RSV) viral RNA in either nasopharyngeal swab, nasal swab or nasal wash/aspirate specimens collected from individuals suspected of respiratory viral infection. Assays like this may prove very valuable next fall and winter if we have a more “normal” respiratory viral season with co-circulation of RSV, influenza, and SARS-CoV-2.

COVID-19 Vaccine Breakthrough Infections Reported to CDC — United States, January 1-April 30, 2021
MMWR May 25, 2021
A total of 10,262 SARS-CoV-2 vaccine breakthrough infections were reported from January 1 through April 30 in 46 US states and territories. 27%, were asymptomatic. Two percent, or 160 people, with breakthrough infections died. A total of 995 people were hospitalized, including 289 hospitalized for asymptomatic infection or for reasons unrelated to COVID-19. Sequence data were available from 555 (5%) reported cases, 356 (64%) of which were identified as SARS-CoV-2 variants of concern, including B.1.1.7 (199; 56%), B.1.429 (88; 25%), B.1.427 (28; 8%), P.1 (28; 8%), and B.1.351 (13; 4%). Many breakthrough cases (63%) occurred in women. The median age of people in the study was 58 years (interquartile range, 40-74 years).



Comment: As of April 30, 2021, approximately 101 million persons in the United States had been fully vaccinated against COVID-19. However, vaccine breakthrough infections occur in only a small fraction of all vaccinated persons and account for a small percentage of all COVID-19 cases. [<.01] The number of COVID-19 cases, hospitalizations, and deaths that will be prevented among vaccinated persons will far exceed the number of vaccine breakthrough cases. Many persons with vaccine breakthrough infections, especially those who are asymptomatic or who experience mild illness, might not seek testing. Breakthrough infections are expected since no vaccine is 100% effective. Because the reporting of breakthrough cases was voluntary, it is likely that the numbers are an underestimate.