Good morning. I hope everyone had time to recharge as we begin what is shaping up to be another busy COVID week.

Today under News Section I summarized an FDA alert that certain molecular tests may not detect new variants. IDSA updated their treatment guidelines with only minor changes.

Under Journal Reviews I reviewed an important pre-publication paper on IL-6 Receptor Antagonists. The NHS felt the trial was compelling enough to prompt a shift in guidance in the UK. The next article reports that the Pfizer vaccine should still be effective against the current variant: B.1.1.7. This is certainly good news. The next article is a very nice decision analytical model of multiple scenarios of proportions of asymptomatic individuals with COVID-19 and infectious periods, transmission from asymptomatic individuals estimated to account for more than half of all transmissions. The findings of this study suggest that the identification and isolation of persons with symptomatic COVID-19 alone will not control the ongoing spread of SARS-CoV-2. The last article looks at the incidence and secondary transmission of SARS-CoV-2 infections in schools. Bottom line, if accompanied by strict adherence to masking, distancing, and hand hygiene, in-person education did not result in substantial risk of SARS-CoV-2 spread within schools for children or staff.

I hope you have a good week

Ed

COVID-19 News

FDA Alert: Genetic Variants of SARS-CoV-2 May Lead to False Negative Results with Molecular Tests for Detection of SARS-CoV-2 - Letter to Clinical Laboratory Staff and Health Care Providers
January 8, 2021
Since molecular tests look for a specific sequence, it is possible for certain virus mutations to affect the performance of certain tests if the mutation is in a region of the genome targeted by the test. Tests that rely on the detection of multiple regions of the genome may be less impacted by genetic variation in the SARS-CoV2 genome than tests that rely on detection of only a single region. The B.1.1.7 variant carries many mutations, including a double deletion at positions 69 and 70 on the spike protein gene (S-gene), which is the mutation that appears to impact the pattern of detection when using the TaqPath COVID-19 Combo Kit and the Linea COVID-19 Assay Kit. All diagnostic tests may be subject to false negative results, and the risk of false negative results may increase when testing patients with genetic variants of SARS-CoV-2. Health care providers should always carefully consider diagnostic test results in the context of all available clinical, diagnostic, and epidemiological information.
Key take aways:

- Be aware that genetic variants of SARS-CoV-2 arise regularly, and false negative test results can occur.
- Be aware that tests that use multiple genetic targets to determine a final result are less likely to be impacted by increased prevalence of genetic variants.
- Consider negative results in combination with clinical observations, patient history, and epidemiological information.
- Consider repeat testing with a different test (with different genetic targets) if COVID-19 is still suspected after receiving a negative test result.

IDSA Updated Treatment Guidelines
January 8, 2021
This version includes new recommendations on the use of baricitinib and an updated literature review on hydroxychloroquine.

Among hospitalized patients with severe COVID-19 who cannot receive corticosteroids because of a contraindication, the IDSA guideline panel suggests use of baricitinib with remdesivir rather than remdesivir alone. (Conditional recommendation, Low certainty of evidence)
Below is the summary table.

		Setting and severity of illness			
		Ambulatory care: *mild-to-moderate disease*	***Hospitalized:*** *mild-to-moderate disease without need for suppl. oxygen*	***Hospitalized:*** *severe but non-critical disease (spO_2 <94% on room air)*	***Hospitalized:*** *critical disease (e.g., in ICU needing MV, or septic shock, ECMO)*
1	*Hydroxy-chloroquine (HCQ)**	NA	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯
2	*HCQ* + azithromycin*	NA	**Recommend against use** ⊕⊕◯◯	**Recommend against use** ⊕⊕◯◯	**Recommend against use** ⊕⊕◯◯
3	*Lopinavir + ritonavir*	NA	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯
4-6	*Corticosteroids*	NA	**Suggest against use** ⊕◯◯◯	**Suggest use** ⊕⊕⊕◯ R: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used.**	**Recommend use** ⊕⊕⊕◯ R: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used.**
7	*Tocilizumab*	NA	**Suggest against routine use** ⊕⊕◯◯	**Suggest against routine use** ⊕⊕◯◯	**Suggest against routine use** ⊕⊕◯◯
8	*Convalescent plasma*	NA	Recommended only in the context of a clinical trial (knowledge gap)	Recommended only in the context of a clinical trial (knowledge gap)	Recommended only in the context of a clinical trial (knowledge gap)
9-11	*Remdesivir*	NA	**Suggest against routine use** ⊕◯◯◯	**Suggest use** ⊕⊕◯◯ R: In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.	**Suggest use** ⊕⊕⊕◯ R: For consideration in contingency or crisis capacity settings (i.e., limited remdesivir supply): Remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.
12	*Famotidine*	NA	**Suggests against use except in a clinical trial** ⊕◯◯◯	**Suggests against use except in a clinical trial** ⊕◯◯◯	**Suggests against use except in a clinical trial** ⊕◯◯◯
13	*Bamlanivimab*	**Suggest against routine use** ⊕◯◯◯ R: In patients at increased risk*** bamlanivimab is a reasonable treatment option if, after informed decision-making, the patient puts a high value on the uncertain benefits and a low value on uncertain adverse	NA	NA	NA

Certainty of evidence

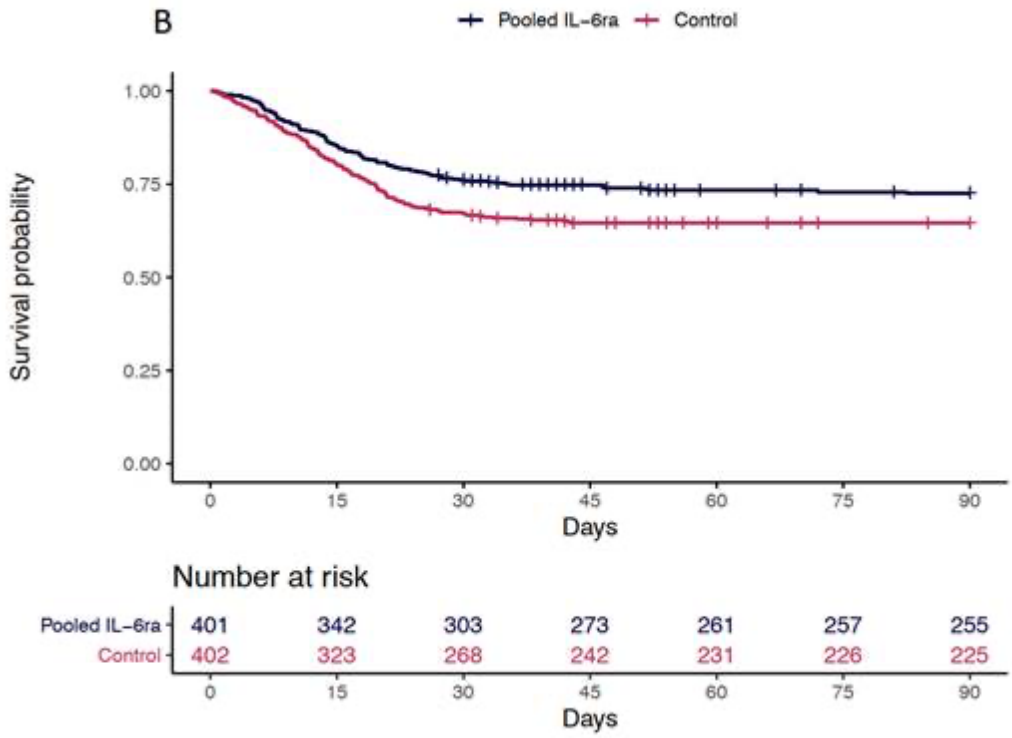
⊕⊕⊕⊕ high
⊕⊕⊕◯ moderate
⊕⊕◯◯ low
⊕◯◯◯ very low

Journal Review

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary Report

medRxiv published online January 7, 2021.
doi.org/10.1101/2021.01.07.21249390

The investigators evaluated tocilizumab and sarilumab in an ongoing international, multifactorial, adaptive platform trial. (REMAP-CAP-Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia). Adult patients with Covid-19, within 24 hours of commencing organ support in an intensive care unit, were randomized to receive either tocilizumab (8mg/kg) or sarilumab (400mg) or standard care (control). Corticosteroids were allowed as per recommended standard of care. Remdesivir use was recorded in 32.8% (265/807) of patients. The primary outcome was an ordinal scale combining in-hospital mortality (assigned -1) and days free of organ support to day 21. The trial uses a Bayesian statistical model with pre-defined triggers to declare superiority, efficacy, equivalence, or futility. 353 patients were assigned to tocilizumab, 48 to sarilumab and 402 to control. it is important to note in this trial, patients had to be enrolled within 24 hours after starting organ support. This may be an important factor to maximize effectiveness. Median organ support-free days were 10 (interquartile range [IQR] -1, 16), 11 (IQR 0, 16) and 0 (IQR -1, 15) for tocilizumab, sarilumab and control, respectively. Relative to control, median adjusted odds ratios were 1.64 (95% credible intervals [CrI] 1.25, 2.14) for tocilizumab and 1.76 (95%CrI 1.17, 2.91) for sarilumab, yielding >99.9% and 99.5% posterior probabilities of superiority compared with control. Hospital mortality was 28.0% (98/350) for tocilizumab, 22.2% (10/45) for sarilumab and 35.8% (142/397) for control. All secondary outcomes and analyses supported efficacy of either IL-6 receptor antagonists. The sensitivity analyses were consistent with the primary analysis. Of particular interest, the estimates of the treatment effect for patients treated either with tocilizumab or sarilumab and corticosteroids in combination were greater than for any intervention on its own suggesting benefit of using both IL6 receptor antagonists and corticosteroids together in this critically ill population. They saw beneficial effects of IL-6 inhibition across all CRP subgroups in this critically ill population. There were nine serious adverse events reported in the tocilizumab group including one secondary bacterial infection, five bleeds, two cardiac events and one deterioration in vision. There were 11 serious adverse events in the control group, four bleeds and seven thromboses: and no serious adverse events in the sarilumab group.



Comment: The investigators demonstrated that in critically ill patients with Covid-19 the IL-6 receptor antagonists, tocilizumab and sarilumab, are both effective compared with current standard of care, which included corticosteroids in the majority of patients (>80%). Benefit was consistent across primary and secondary outcomes, and across subgroups and secondary analyses. REMAP-CAP is a pragmatic, international design and results are likely more generalizable to the wider critically ill patient population with Covid-19. It uses an open-label design. The multifactorial design also allows multiple different interventions to be evaluated simultaneously, providing more efficient results and accounting for potential treatment-by-treatment interactions, however, this may have introduced confounders. Prior trials produced mixed results. Some believe the prompt administration of IL-6 receptor antagonists (within 24 hours of ICU admission) may be a key. The new study, which was posted to the preprint server medRxiv on Thursday, has not yet been vetted by experts for publication. But its findings were compelling enough to prompt a shift in guidance in the UK. This study is encouraging, but I think we need to understand why this data looks different from other studies before we start implementing this as standard of care.

Neutralization of N501Y Mutant SARS-CoV-2 by BNT162b2 Vaccine-Elicited Sera
medRxiv published online January 7, 2021
article provided by Josh Septimus
Rapidly spreading variants of SARS-CoV-2 have arisen in the United Kingdom and South Africa. These variants have multiple mutations in their S glycoproteins, which are key targets of virus neutralizing antibodies. These rapidly spreading variants share the spike N501Y substitution. This mutation is of particular concern because it is located in the viral receptor binding site for cell entry, increases binding to the ACE-2.

The investigators generated isogenic N501 and Y501 SARS-CoV-2. Neutralization of N501 and Y501 viruses by a 50% plaque reduction neutralization assay was used. Sera of 20 participants in a previously reported trial of the mRNA-based COVID-19 vaccine BNT162b2 (Pfizer) had equivalent neutralizing titers to the N501 and Y501 viruses.

Comment: This is certainly good news. A limitation of this study is that the Y501 virus does not include the full set of spike mutations found on the strains in the UK or South Africa. However, preserved neutralization of Y501 virus by BNT162b2-elicited human sera is consistent with preserved neutralization of a panel of 15 pseudoviruses bearing spikes with other mutations found in circulating SARS-CoV-2 strains. Because current vaccines provoke an immune response to the entire spike protein, it is hoped that effective protection will remain despite minor changes at antigenic sites. The evolution of SARS-CoV-2 necessitates continuous monitoring of the significance of changes for vaccine coverage. We must improve our genomic surveillance to rapidly detect that a future mutation in SARS-CoV-2 might necessitate a vaccine strain change. Such a vaccine update would be facilitated by the flexibility of mRNA-based vaccine technology. Moderna is also testing and I think it will also prove effective against the UK variant.

SARS-CoV-2 Transmission from People Without COVID-19 Symptoms
JAMA Netw Op published online January 7, 2021
doi:10.1001/jamanetworkopen.2020.35057
The investigators created a decision analytical model to assess the relative amount of transmission from presymptomatic, never symptomatic, and symptomatic individuals across a range of scenarios in which the proportion of transmission from people who never develop symptoms (i.e., remain asymptomatic) and the infectious period were varied according to published best estimates. For all estimates, data from a meta-analysis was used to set the incubation period at a median of 5 days. The infectious period duration was maintained at 10 days, and peak infectiousness was varied between 3 and 7 days (-2 and +2 days relative to the median incubation period. In addition, the baseline assumptions for the model were that peak infectiousness occurred at the median of symptom onset and that 30% of individuals with infection never develop symptoms and are 75% as infectious as those who do develop symptoms**.**

Combined, these baseline assumptions imply that persons with infection who never develop symptoms may account for approximately 24% of all transmission. In this base case, 59% of all transmission came from asymptomatic transmission, comprising 35% from presymptomatic individuals and 24% from individuals who never develop symptoms. Under a broad range of values for each of these assumptions, at least 50% of new SARS-CoV-2 infections was estimated to have originated from exposure to individuals with infection but without symptoms.

Comment: In this decision analytical model of multiple scenarios of proportions of asymptomatic individuals with COVID-19 and infectious periods, transmission from asymptomatic individuals was estimated to account for more than half of all transmissions. The findings of this study suggest that the identification and isolation of persons with symptomatic COVID-19 alone will not control the ongoing spread of SARS-CoV-2. This is not a surprise given what we have learned over the last 9 months. Effective control of spread will therefore require reducing the risk of transmission from people with infection who do not have symptoms. These findings emphasize the importance of NPIs such as wearing masks, hand hygiene, social distancing, and strategic testing of people who are not ill to slow the spread of COVID-19 until vaccination rates approach at least 70%.

Incidence and Secondary Transmission of SARS-CoV-2 Infections in Schools

Pediatrics published online January 2021
article provided by Dr Lindy McGee
DOI: 10.1542/peds.2020-048090

In an effort to mitigate the spread of SARS-CoV-2, North Carolina (NC) closed its K–12 public schools to in-person instruction on 03/14/2020. On 07/15/2020, NC's governor announced schools could open via remote learning or a "hybrid" model that combined in-person and remote instruction. In August 2020, 56 of 115 NC school districts joined the ABC Science Collaborative (ABCs) to implement public health measures to prevent SARS-CoV-2 transmission and share lessons learned. This meant districts were required to have universal masking for all ≥5 years of age (except the adapted curriculum, during meals, and when sufficiently distanced outside), implement 6-foot distancing, and wash hands ("3W's": wear a mask, wait 6 feet, wash hands), as well as perform daily symptom monitoring and temperature checks. This article describes secondary transmission of SARS-CoV-2 within participating NC school districts during the first 9 weeks of in-person instruction in the 2020–2021 academic school year.

From 08/15/2020–10/23/2020, 11 of 56 school districts participating in ABCs were open for in-person instruction for all 9 weeks of the first quarter and agreed to track incidence and secondary transmission of SARS-CoV-2. Local health department staff adjudicated secondary transmission. Superintendents met weekly with ABCs faculty to share lessons learned and develop prevention methods.

Over 9 weeks, 11 participating school districts had more than 90,000 students and staff attend school in-person; of these, there were 773 community-acquired SARS-CoV-2 infections documented by molecular testing. Through contact tracing, NC health department staff determined an additional 32 infections were acquired within schools. No instances of child-to-adult transmission of SARS-CoV-2 were reported within schools.

Comment: This study validated their hypothesis that in-person instruction, if accompanied by strict adherence to masking, distancing, and hand hygiene, did not result in substantial risk of SARS-CoV-2 spread within schools for children or staff. This and other articles reviewed in the Daily Briefing over the last few months indicate the science supports in person learning when effective safety strategies are in place.