Good morning. I hope everyone had a good holiday weekend.

Today under COVID-19 News HHS no longer recommends the Lilly monoclonal due to increase of certain mutants. Next is the NIH revision on the use of baricitinib based on a pre-publication article also reviewed under Journal Review. The last is a review of the long-awaited revision of summer camps. IDSA also published Friday updates guidance on rapid antigen testing to be reviewed in the next edition of Daily Briefing scheduled for Friday. Thank you, Cesar Arias, for providing me with the guidance.

Under Journal Review I start with the pre-publication article on baricitinib which influenced the NIH revision. The next three articles I put together to try and focus on immunosuppression by certain drugs and response to Covid-19 vaccines. Several weeks ago, I reviewed a nice outline on the questions around vaccination and immunosuppression.

Have a wonderful day – remember, the Daily Briefing will now be published Tuesday and Friday. Great topics in the queue.

Ed

HHS Recommendation
CDC has now identified P.1 and/or B.1.135 now exceeds 10% in Arizona, California, Florida, Indiana, Oregon, Washington, and Massachusetts. In vitro assays suggest the combination monoclonal antibody bamlanivimab with etesevimab (Lilly) is not active against either P.1 or B.1.135. Therefore, Regeneron is now preferred monoclonal.

Comment: IDSA a few months ago had already revised their recommendations to prefer Regeneron due to resistance against certain mutants. In Daily Briefing Friday, the FDA has just approved sotrovimab for EUA for a new monoclonal, which is active against these mutants.

NIH Covid-19 Treatment Update Baricitinib for the Treatment of Adults with COVID-19
Baricitinib is an oral Janus kinase (JAK) inhibitor that is selective for JAK1 and JAK2. It has been evaluated for the treatment of COVID-19 because it may prevent cellular immune activation and inflammation. On November 19, 2020, the FDA issued an Emergency Use Authorization (EUA) for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation. The ACTT-2 trial demonstrated that baricitinib improved time to recovery when given in combination with remdesivir to patients who require supplemental oxygen but not invasive mechanical ventilation. However, the major limitation of ACTT-2 was the inability to evaluate the effect of baricitinib in addition to corticosteroids. IDSA recommended baricitinib only if steroids could not be used.

A recent study, COV-BARRIER, included patients with COVID-19 who required supplemental oxygen at enrollment but not invasive mechanical ventilation. The trial reported an additional survival benefit of baricitinib when added to the standard of care of corticosteroids (with or without remdesivir). Reduction of disease progression did not achieve statistical significance. [medRxiv – see below] Based on the preliminary results (not yet peer-reviewed) from COV-BARRIER, the Panel has updated its recommendations on the use of baricitinib for the treatment of adults with COVID-19.

The panel recommends using either baricitinib (BIIa) **or** tocilizumab (BIIa) (listed alphabetically) in combination with dexamethasone alone or dexamethasone plus remdesivir for the treatment of COVID-

19 in hospitalized patients on high-flow oxygen or noninvasive ventilation who have evidence of clinical progression or increased markers of inflammation.

Among hospitalized patients with hypoxemia who require supplemental oxygen therapy, there is insufficient evidence to identify which patients would benefit from the addition of baricitinib or tocilizumab to dexamethasone (with or without remdesivir). Some Panel members would add either baricitinib ortocilizumab to patients who are exhibiting signs of systemic inflammation and rapidly increasing oxygen needs while on dexamethasone, but who do not yet require noninvasive ventilation or high-flow oxygen.

In the rare circumstance when corticosteroids cannot be used, the Panel recommends using baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized, nonintubated patients who require oxygen supplementation (BIIa).

There is insufficient evidence for the Panel to recommend either for or against the use of baricitinib in combination with dexamethasone for the treatment of COVID-19 in hospitalized patients who require invasive mechanical ventilation.

Comment: Based on the COV-BARRIER study, baricitinib may be an alternative to tocilizumab in patients on supplemental oxygen who have clinical progression or increased markers of inflammation.

CDC Guidance for Operating Youth Camps
May 28, 2021, highlights

- Everyone aged 12 years and older is recommended to be vaccinated against COVID-19 as soon as possible to keep from getting and spreading COVID-19.
- For camps where everyone is fully vaccinated prior to the start of camp, it is safe to return to full capacity, without masking, and without physical distancing except if required by federal, state, or local regulations.
- Although people who are fully vaccinated do not need to wear masks, camp programs should be supportive of campers or staff who choose to wear a mask.
- Campers should be assigned to cohorts that will remain together for the entire camp session without mixing, to the largest extent possible.
- While generally encouraging the unvaccinated to wear face masks, the CDC said campers should leave them off during outdoor activities like boating or swimming that could get masks wet.
    - Mask use indoors is strongly encouraged for people who are not fully vaccinated including children. No child under the age of 2 should wear a mask.
    - In general, people do not need to wear masks when outdoors. However, particularly in areas of substantial-to-high transmission, people who are not fully vaccinated are encouraged to wear a mask in crowded outdoor settings or during activities that involve sustained close contact with other people who are not fully vaccinated.
- Children who are not fully vaccinated do not need to wear masks or physically distance when in their group without others around.
- At day camps, campers within one of the small groups who are not fully vaccinated should try to keep a distance of 3 feet from each other. Campers from different groups should stay 6 feet apart.

- People who are fully vaccinated do not need to undergo routine COVID-19 screening testing. If a fully vaccinated person is exposed to someone with COVID-19, they do not need to be tested for COVID-19 unless they are experiencing COVID-19 symptoms.
- People who are fully vaccinated with no COVID-19-like symptoms do not need to quarantine or be restricted from camp following an exposure to someone with suspected or confirmed COVID-19, except where required by federal, state, or local laws.
- For overnight camps, individuals who are not fully vaccinated should consider routine screening testing to help identify cases of COVID-19 in asymptomatic or pre-symptomatic people, and prevent secondary transmission. People who are fully vaccinated with no COVID-19-like symptoms and no known exposure should be exempted from routine screening testing programs, if feasible.

Comment: Many of us who have been advising summer camps have been waiting for the CDC's updates. The updates will help, but local factors and vaccination rates will need to be considered in implementing these revisions. Testing and which test to use will need to be discussed locally based on availability of testing. IDSA has just released recommendations on rapid antigen testing to be reviewed in the next edition of the Briefing.

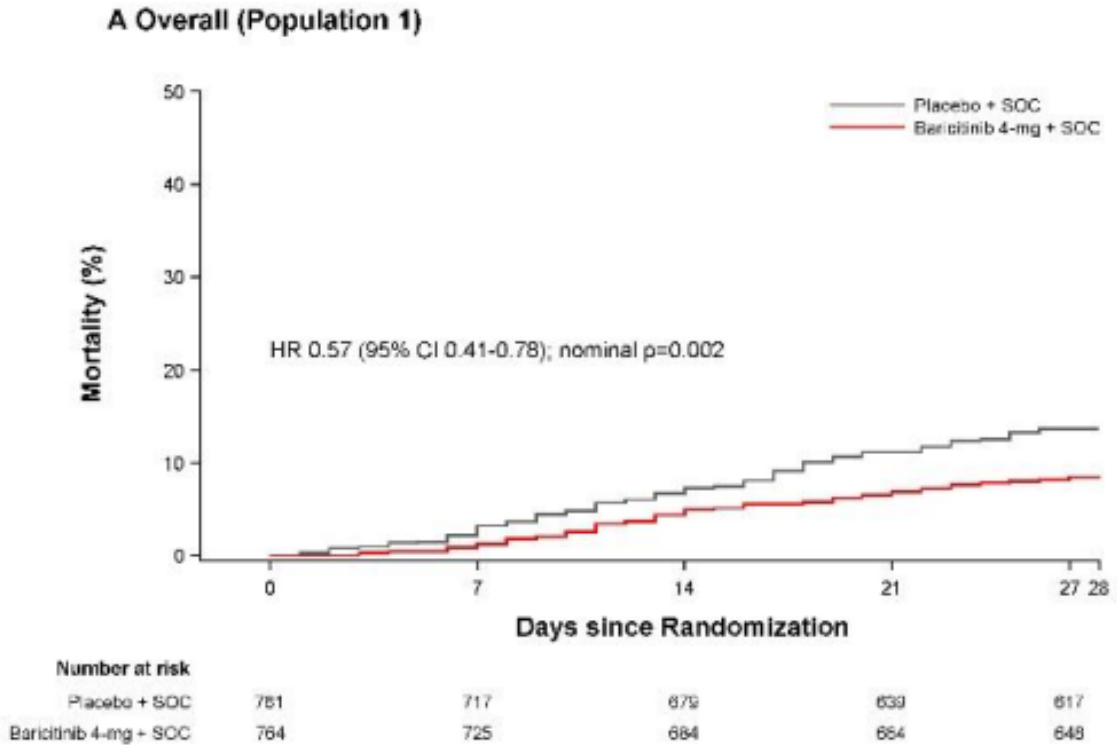
Journal Review

Baricitinib Plus Standard of Care for Hospitalized Adults with COVID-19
medRxiv published April 30, 2021
doi.org/10.1101/2021.04.30.21255934
The biochemical inhibitory effects of baricitinib on human associated kinases (AAK1, BIKE, and GAK) responsible for SARS-CoV-2 viral propagation has been confirmed. Baricitinib also reduced multiple cytokines and biomarkers implicated in COVID-19 pathophysiology. ACTT-2, a NIH-sponsored double-blind, randomized, placebo-controlled, phase 3 trial in hospitalized adults with COVID-19, found that baricitinib plus remdesivir was superior to remdesivir in reducing recovery time (p=0.03), with 28-day mortality reported (5.1% vs 7.8%, not statistically significant). [N Engl J Med 2021;384:795-807] The major limitation of ACTT-2 was the inability to evaluate the effect of baricitinib in addition to corticosteroids. IDSA recommended baricitinib only if steroids could not be used.

This is a phase 3, global, double-blind, randomized, placebo-controlled trial, involving 1525 hospitalized adults with COVID-19 receiving standard of care (SOC) randomly assigned (1:1) to once-daily baricitinib 4-mg (N=764) or placebo (N=761) for up to 14 days. [COV-BARRIER] SOC included systemic corticosteroids in ~79% of participants (dexamethasone ~90%). Participants were randomized 1:1 to placebo or baricitinib 4mg. Participants were stratified according to the following baseline factors: disease severity, age, region, and use of corticosteroids for COVID-19. Baricitinib or placebo was administered orally (or crushed for nasogastric tube) and given daily, for up to 14 days or until discharge from hospital, whichever occurred first. All participants received background SOC in keeping with local clinical practice for COVID-19 management, which could include corticosteroids, and/or antivirals. Dexamethasone use was permitted as described in the RECOVERY trial. Eligible participants were ≥18 years of age, hospitalized with laboratory confirmed SARS-CoV-2 infection, had evidence of pneumonia or active, symptomatic COVID-19, and had ≥1 elevated inflammatory marker (C reactive protein, D-dimer, lactate dehydrogenase, ferritin). Participants were excluded if requiring invasive mechanical ventilation at study entry, receiving immunosuppressants (high dose corticosteroids, biologics, T cell or B cell-targeted therapies, interferon, or JAK inhibitors), or received convalescent plasma or intravenous

immunoglobulin for COVID-19. The primary endpoint was the proportion who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28. A key secondary endpoint was all-cause mortality by day 28.

Overall, 27.8% of participants receiving baricitinib vs 30.5% receiving placebo progressed (primary endpoint, odds ratio 0.85, 95% CI 0.67-1.08; p=0.18). The 28-day all-cause mortality was 8.1% for baricitinib and 13.1% for placebo, corresponding to a 38.2% reduction in mortality (hazard ratio [HR] 0.57, 95% CI 0.41-0.78; nominal p=0.002); 1 additional death was prevented per 20 baricitinib-treated participants. Reduction in mortality was seen for all prespecified subgroups of baseline severity (most pronounced for participants on high-flow oxygen/non-invasive ventilation at baseline [17.5%, baricitinib vs 29.4%, placebo; HR 0.52, 95% CI 0.33-0.80; p=0.007]). The frequency of adverse events, serious adverse events, serious infections, and venous thromboembolic events was similar between groups.



Comment: While reduction of disease progression did not achieve statistical significance, treatment with baricitinib in addition to SOC (predominantly dexamethasone) significantly reduced mortality with a similar safety profile between groups of hospitalized COVID-19 participants. In comparison, dexamethasone in RECOVERY Trial showed a 10.9% relative reduction in mortality compared to SOC (22.9% vs 25.7%; age-adjusted rate ratio 0.83, 95% CI 0.75-0.93; p<.001). [N Engl J Med 2021;384:693-704] The evaluation of tocilizumab (anti-IL-6) in RECOVERY showed a 12.1% relative risk reduction in 28-day mortality (29% vs 33% SOC; HR 0.86, 95% CI 0.77-0.96; p=.007). [Lancet 2021; 397: 1637–45] In ACTT-2, the 28-day mortality for baricitinib plus remdesivir was 5.1% and 7.8% for remdesivir alone; however, the study was not powered to detect a mortality difference between the groups. In COV-BARRIER, baricitinib plus SOC showed a 38.2% relative reduction in mortality compared to SOC including

dexamethasone (8.1% vs 13.1%; HR 0.57, 95% CI 0.41-0.78; p=0.002). In comparison baricitinib shows the largest effect size on mortality for any COVID-19 treatment when compared to other randomized trials in hospitalized patients. Based on this prepublication study the NIH revised guidance reviewed under Covid-19 News. (See above)

Rituximab, but Not Other Antirheumatic Therapies, is Associated with Impaired Serological Response to SARS- CoV-2 Vaccination in Patients with Rheumatic Diseases
Ann Rheum Dis published online May 27, 2021 – see comment below
doi:10.1136/annrheumdis-2021-220604
Vaccination responsiveness was compared between patients receiving various antirheumatic medications. Primary outcome was the presence of a serological response to COVID-19 vaccination. Eighty-three subjects (93.26%) had received both doses of a COVID-19 vaccine at the time of immunoassay. Thirty patients (34%) were treated with rituximab. Thirty-five patients (39%) were taking more than one antirheumatic medication at time of assessment. A majority of the serologically negative results were among patients using rituximab (20/21). B-cell reconstitution was available for 11 patients and there was a significant difference among those with a positive serological response (N=7) compared with those with a negative response, (N=4) (p=0.026). Confirming B-cell reconstitution before vaccination may increase the likelihood of a positive serological response.

Methotrexate Hampers Immunogenicity to BNT162b2 mRNA COVID-19 Vaccine in Immune-Mediated Inflammatory Disease
Ann Rheum published online May 25, 2021 – see comment below
Doi:10.1136/annrheumdis-2021-220597
In two independent cohorts of IMID (immune-mediated inflammatory diseases) patients, methotrexate, a widely used immunomodulator for the treatment of several IMIDs, adversely affected humoral and cellular immune response to COVID-19 mRNA vaccines. Although healthy subjects (n=208) and IMID patients on biologic treatments (mostly on TNF blockers, n=37) demonstrate robust antibody responses (over 90%), those patients with IMID on background methotrexate (n=45) achieve an adequate response in only 62.2% of cases. Similarly, IMID patients do not demonstrate an increase in CD8+ T cell activation after vaccination. Although precise cut offs for immunogenicity that correlate with vaccine efficacy are yet to be established, our findings suggest that different strategies may need to be explored in patients with IMID taking methotrexate to increase the chances of immunization efficacy against SARS-CoV-2 as has been demonstrated for augmenting immunogenicity to other viral vaccines.

Evaluation of Seropositivity Following BNT162b2 Messenger RNA Vaccination for SARS-CoV-2 in Patients Undergoing Treatment for Cancer
JAMA Oncology published online May 28, 2021 – see comment below
doi:10.1001/jamaoncol.2021.2155
In this cohort study of patients with cancer who were receiving active systemic therapy, 90% of patients exhibited adequate antibody response to the BNT162b2 vaccine (Pfizer), although their antibody titers were significantly lower than those of healthy controls.

Comment: I put these 3 articles together for a reason. As our country begins to return to more “normal” existence, these articles and other articles reviewed in the Daily Briefing in the last month all remind us to be cautious when around people who have a weakened immune system even if fully vaccinated. We need guidance and testing to evaluate this population as we open society, so we keep our most vulnerable safe.