Good morning and TGIF

I have taken up the issue of "cytokine storm" in the pathogenesis of severe SARS-CoV-2. The first 3 articles propose alternative hypothesis and suggest a central role for bradykinin in the inflammation and increased vascular permeability observed in severe SARS-CoV-2 infections. Not covered in this issue but proposed by others that respiratory failure may be associated with a type 2 immune response associated with IL-13 production. [this virus is fascinating!] The article in Nat Comm attempts to look at differences between patients hospitalized with SARS-CoV-2 infection versus influenza. There are some regional differences, but in the end, I am not sure this article provides actionable information that will help if we have co-circulation of SARS-CoV-2 and influenza this season. The next segment covers recent interest in monoclonals. As stated, 2 companies have now applied for EUA. These products I believe have enormous potential and will be a bridge before effective and widespread immunizations are in place. The last entry is a copy of the "Great Barrington Declaration". I would be interested in your opinion on the statement. Some prominent public health officials and physicians have signed this declaration.

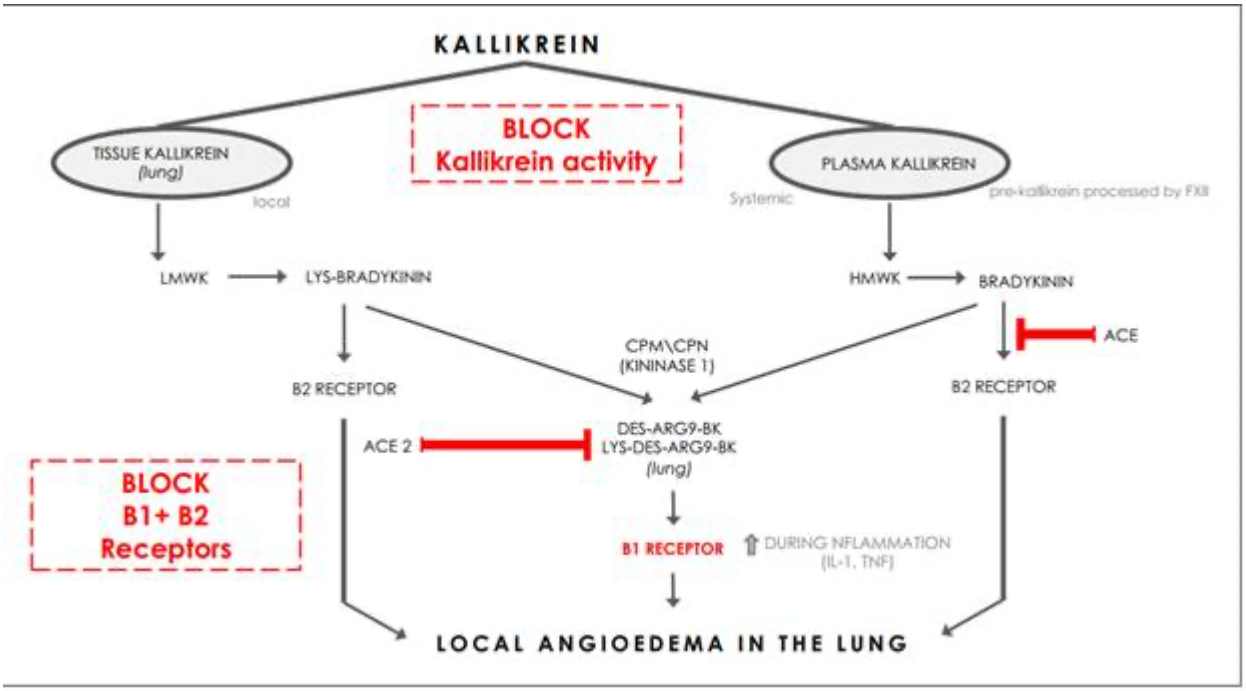
Have a safe and relaxing weekend - your feedback is always welcomed.

Ed

Introduction Is a "Cytokine Storm" Relevant to COVID-19
JAMA Intern Med published online June 30, 2020
Cytokine storm is used to explain the hyperactive immune response characterized by the release of IFN, interleukins, TNF, and other mediators. These mediators are part of the normal innate-immune response which helps with clearance of microorganisms. Cytokine storm suggests that levels of cytokines are injurious to host cells. Distinguishing between appropriate response and over responses can be difficult to define. Although actual levels may suggest severity of response, they do not necessarily correlate with pathogenesis. Early publications on SARS-CoV-2 infections reported increased cytokine levels, however, in most cases they were lower compared to previous reports of other patient with ARDS. IL-6 is felt to be a key mediator in the acute inflammation and has been associated with cytokine storm. Several articles have documented the median values of IL-6 are lower than the median values in typical ARDS due to other etiologies. In fact, the studies show the median IL-6 levels in patients the hyperinflammatory phenotype of ARDS are 10-200-fold higher than levels in patients with severe SARS-CoV-2 infections. Publications reviewed in Daily Briefing over the last 3 months document postmortem finding in SARS-CoV-2 ARDS of severe vascular injury, including microthrombi that are almost 10 times more prevalent in postmortem studies of patients with influenza ARDS. Taken together, based on current science, in fact SARS-CoV-2 is actually characterized by lower levels of cytokines. Therefore, current knowledge is insufficient to make valid conclusions. However, IL-6 levels ≥80 pg/ml are associated with increased risk of respiratory failure and death. [J Allergy Clin Immunol 2020; 146:128-136] Another explanation suggests bradykinin may play a central role in the inflammation and increased vascular permeability seen in SARS-CoV-2 pneumonia. The 2 articles below discuss the role of bradykinin.

Kallikrein-Kinin Blockade in Patients with COVID-19 to Prevent Acute Respiratory Distress Syndrome
eLife published April 27, 2020
The authors propose that pulmonary edema may be due to a local vascular problem because of activation of bradykinin 1 receptor (B1R) and B2R on endothelial cells in the lungs. SARS-CoV-2 enters the cell via ACE2 that next to its role in RAS (renin angiotensin system) is needed to inactivate des-Arg9

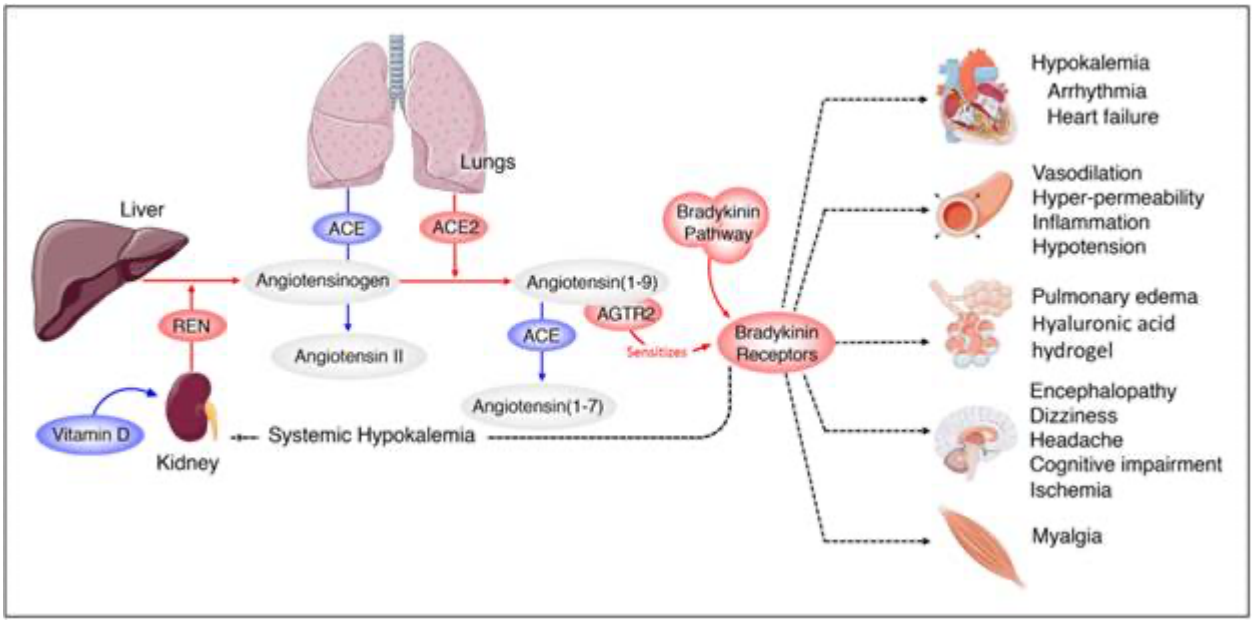
bradykinin, the potent ligand of the B1R. Without ACE2 acting as a guardian to inactivate the ligands of B1R, the lung environment is prone for local vascular leakage leading to angioedema. Here, the authors hypothesize that a kinin-dependent local lung angioedema via B1R and eventually B2R is an important feature of COVID-19. They propose that blocking the B2R and inhibiting plasma kallikrein activity might have an ameliorating effect on early disease caused by COVID-19 and might prevent acute respiratory distress syndrome (ARDS). See next article.



A Mechanistic Model and Therapeutic Interventions for COVID-19 Involving a RAS-Mediated Bradykinin Storm

eLife published July 7, 2020

The entry point for the virus is ACE2, which is a component of the counteracting hypotensive axis of RAS (renin angiotensin system). Bradykinin is a potent part of the vasopressor system that induces hypotension and vasodilation and is degraded by ACE and enhanced by the angiotensin1-9 produced by ACE2. Here, the investigators performed a new analysis on gene expression data from cells in bronchoalveolar lavage fluid (BALF) from COVID-19 patients that were used to sequence the virus. Comparison with BALF from controls identifies a critical imbalance in RAS represented by decreased expression of ACE in combination with increases in ACE2, renin, angiotensin, key RAS receptors, kinogen and many kallikrein enzymes that activate it, and both bradykinin receptors. This very atypical pattern of the RAS is predicted to elevate bradykinin levels in multiple tissues and systems that will likely cause increases in vascular dilation, vascular permeability, and hypotension. These bradykinin-driven outcomes explain many of the symptoms being observed in COVID-19.



Comment: The authors comment that SARS-CoV-2 uses ACE2 like a "Trojan Horse" to sneak into the cells of the patients. Their analysis found that SARS-CoV-2 caused the levels of ACE in the lung cells to decrease, while levels of ACE2 increased. This led to increased levels of bradykinin which led to increases in vascular dilation and vascular permeability. They call this "Bradykinin Storm". This proof of concept needs more study to see if this is clinically relevant. If so, then this may lead to treatments such as drugs like icatibant (a BKB2R antagonist) or lanadelumab (plasma kallikrein inhibitor).

Deep Phenotyping of 34,128 Adult Patients Hospitalised with COVID-19 in an International Network Study

Nat Comm published online October 6, 2020

This study explored the demographics, medical conditions, and medication use of more than 34,000 hospitalized COVID-19 patients in the United States, Spain, and South Korea, comparing these characteristics with those of 84,585 patients hospitalized with influenza from 2009 to 2019. Because COVID-19 and the flu both cause respiratory disease that can vary in severity and symptoms, flu has been identified as a possible model for identifying COVID-19 risk factors.

Patients hospitalized with COVID-19 were more likely to be older (between 60 to 75 years) and male in the United States and Spain, and more often younger and female in South Korea. COVID-19 patients were also likely to have comorbidities such as high blood pressure (37% to 70% in the US; 30% to 46% in Spain; 24% in South Korea). Use of medications acting on the renin-angiotensin system 30 days before COVID-19 hospitalization was common among all geographic areas (18% to 39% in the US, 27% in Spain, 14% in Korea).

COVID-19 patients tended to be younger, with a higher proportion of men than flu patients. Flu patients had higher rates of respiratory disease, cardiovascular disease, and dementia than COVID-19 patients, as well as higher use of corticosteroids and alpha-blocker medications.

Comments: Individuals hospitalized with COVID-19 appear to be more likely younger and male, and in the United States and Spain, to have fewer comorbidities than those hospitalized with influenza in previous years. Indeed, those hospitalized with COVID-19 were consistently seen to be less likely to have

COPD, cardiovascular disease, and dementia than those hospitalized with influenza in recent years. The study was based on routinely collected data and so, as always, data quality issues must be considered. Medical conditions may have been underestimated as they were based on the presence of administrative codes. This is an extensive review but may not be actionable given the overlap and regional differences.

Monoclonals

Data from a new interim analysis of the BLAZE-1 clinical trial showed that combination therapy with two of Lilly's SARS-CoV-2 neutralizing antibodies reduced viral load, symptoms and COVID-related hospitalization and ER visits. The randomized, double-blind, placebo-controlled Phase 2 study evaluated LY-CoV555 and LY-CoV016, which bind complementary regions of the SARS-CoV-2 spike protein, for the treatment of symptomatic COVID-19 in the outpatient setting. The combination cohort enrolled recently diagnosed patients with mild-to-moderate COVID-19, who were assigned to 2800 mg of each antibody (n=112) or placebo (n=156).

The combination therapy significantly reduced viral load at day 11 ($p=0.011$), meeting the primary endpoint of the study. Most patients, including those receiving placebo, demonstrated near complete viral clearance by day 11. Further, combination treatment reduced viral levels at day 3 ($p=0.016$) and day 7 ($p<0.001$)—earlier time points during the course of infection when higher viral loads are typically seen. Combination therapy also significantly reduced the time-weighted average change from baseline from day 1 to 11. An exploratory analysis showed that the proportion of patients with persistent high viral load at day 7 for combination therapy was lower (3.0 percent) versus placebo (20.8 percent), corresponding to a nominal p value of $p<0.0001$ without multiplicity adjustment. No emergent putative resistance variants have been observed thus far in patients treated with combination therapy.

Combination therapy also met prespecified clinical endpoints, including the time-weighted average change from baseline in total symptom score from day 1 to 11 ($p=0.009$). The improvement in symptoms was observed as early as three days after dosing and was similar in magnitude and timing to improvements previously seen with LY-CoV555 monotherapy. The rate of COVID-related hospitalization and ER visits was lower for patients treated with combination therapy (0.9 percent) versus placebo (5.8 percent), a relative risk reduction of 84.5 percent ($p=0.049$). This was also similar to observations for LY-CoV555 monotherapy. Combination therapy has been generally well tolerated with no drug-related serious adverse events. In LY-CoV555 monotherapy studies there have been isolated drug-related infusion reactions or hypersensitivity that were generally mild (two reported as serious infusion reactions, all patients recovered). Treatment emergent adverse events were comparable to placebo for both LY-CoV555 monotherapy and combination therapy.

The BLAZE-1 clinical trial continues to enroll a confirmatory cohort of higher-risk patients who have been recently diagnosed with mild-to-moderate COVID-19, testing the ability of the antibody combination to reduce the number of patients with persistent high viral load and reduce COVID-related hospitalizations.

Comment: Regeneron is another monoclonal-two-antibody combination that was given to President Trump. Regeneron in initial trials has reduced viral levels and improved symptoms in non-hospitalized patients with mild-to-moderate COVID-19. Both monoclonals are being evaluated by the FDA for EUA. The Daily Briefing believes monoclonals will replace plasma and be the bridge until we have a vaccine and/or develop herd immunity. We await peer reviewed publications of these trials.

The Great Barrington Declaration

As infectious disease epidemiologists and public health scientists we have grave concerns about the damaging physical and mental health impacts of the prevailing COVID-19 policies and recommend an approach we call Focused Protection.

Coming from both the left and right, and around the world, we have devoted our careers to protecting people. Current lockdown policies are producing devastating effects on short and long-term public health. The results (to name a few) include lower childhood vaccination rates, worsening cardiovascular disease outcomes, fewer cancer screenings and deteriorating mental health – leading to greater excess mortality in years to come, with the working class and younger members of society carrying the heaviest burden. Keeping students out of school is a grave injustice.

Keeping these measures in place until a vaccine is available will cause irreparable damage, with the underprivileged disproportionately harmed.

Fortunately, our understanding of the virus is growing. We know that vulnerability to death from COVID-19 is more than a thousand-fold higher in the old and infirm than the young. Indeed, for children, COVID-19 is less dangerous than many other harms, including influenza.

As immunity builds in the population, the risk of infection to all – including the vulnerable – falls. We know that all populations will eventually reach herd immunity – i.e. the point at which the rate of new infections is stable – and that this can be assisted by (but is not dependent upon) a vaccine. Our goal should therefore be to minimize mortality and social harm until we reach herd immunity.

The most compassionate approach that balances the risks and benefits of reaching herd immunity, is to allow those who are at minimal risk of death to live their lives normally to build up immunity to the virus through natural infection, while better protecting those who are at highest risk. We call this Focused Protection.

Adopting measures to protect the vulnerable should be the central aim of public health responses to COVID-19. By way of example, nursing homes should use staff with acquired immunity and perform frequent PCR testing of other staff and all visitors. Staff rotation should be minimized. Retired people living at home should have groceries and other essentials delivered to their home. When possible, they should meet family members outside rather than inside. A comprehensive and detailed list of measures, including approaches to multi-generational households, can be implemented, and is well within the scope and capability of public health professionals.

Those who are not vulnerable should immediately be allowed to resume life as normal. Simple hygiene measures, such as hand washing and staying home when sick should be practiced by everyone to reduce the herd immunity threshold. Schools and universities should be open for in-person teaching. Extracurricular activities, such as sports, should be resumed. Young low-risk adults should work normally, rather than from home. Restaurants and other businesses should open. Arts, music, sport and other cultural activities should resume. People who are more at risk may participate if they wish, while society as a whole enjoys the protection conferred upon the vulnerable by those who have built up herd immunity.

Comment: Currently, almost 5000 medical and public health professionals have signed this declaration. Over 9000 physicians and almost 130,000 public have also signed this declaration. I copy this for all of you in case you had not seen this and also to get your opinion concerning the recommendations.