Update on SARS-CoV-2 / COVID-19: Medication Interactions

March 18th, 2020

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To our patients,

Given the speed at which the situation on the ground is evolving, we will be issuing more frequent, less-heavily redacted updates that will address our most salient new information and as importantly, find the signal-in-the-noise on the numerous reports/rumors/conjecture circulating on social media and "in-the-know" circles.

When we have time on our side, we have the luxury of scrutinizing sourcing, rigor, type, and level of evidence--and ideally at least some preliminary clinical trial data. Unfortunately, our customarily stringent process is too sluggish and cumbersome to be of practical use in the current scenario. That said, please be cautioned that our analyses here are based on very imperfect information.

In the past few days we had multiple inbound comms, all unpublished, citing that European ICU doctors were noticing many of the younger critically ill patients had been taking NSAIDs like ibuprofen. That's it, no other context. We can't "unsee" the information, and so now we have to integrate this fragment into our mental framework and either (a) ignore it or (b) translate it into guidance. This one happens to be reasonably straightforward and yet two physicians of sound mind could interpret the exact same data in polar opposite ways:

> Physician #1: "This data is unreliable. Speculation and rumors are only going to increase from here and we can't make medical decisions based on viral tweets. Ibuprofen is a safe and effective antipyretic, let's not make hasty decisions until we get some more data."
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> Physician #2: "NSAIDs like ibuprofen can have unpredictable effects on the immune system. The evidence looks shaky but we are in a crisis where otherwise healthy young adults are getting bizarre presentations of Acute Respiratory Distress Syndrome (ARDS) and critical illness. We have alternative antipyretics like tylenol. For the most part, let's stay away from the ibuprofen until we get some more data."

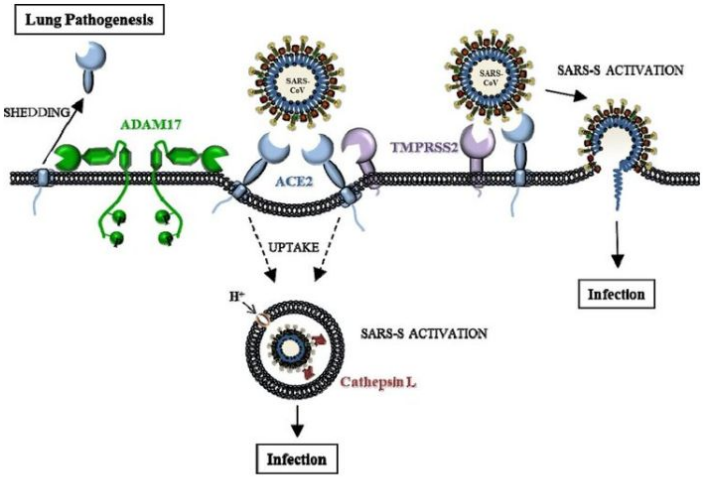
We think the latter approach is the lower risk approach of the two, and are recommending our patients for the moment to use tylenol as needed for high fevers/pain relief unless there is a specific reason to use another antipyretic. Just keep in mind that as these off-handed reports multiply in number, we will almost certainly encounter some data that is patently "fake news."

With this in mind, we will turn our attention to the other, more impactful question circulating among the medical community: the relationship between the virus, which uses the human ACE2 Receptor to enter human cells and begin replication, and the potential benefit/harm of very common blood pressure medications that affect the behavior and amount of ACE2 receptor in various tissues (one of them, lisinopril, is the 3rd most commonly prescribed medication in the country).

(If you want a scientist-level discussion of this topic, the *Nephrology Journal Club* has an even-keeled analysis here: The Coronavirus Conundrum: ACE2 and Hypertension | 14 March 2020).

Background (please keep this in mind also as we discuss potential drug targets and mechanisms the future)

- The coronavirus is coated in an S (spike) protein that is used to attach to ACE2 receptors on host cells.
- Another protein called a protease, TMPRSS2, cleaves the Spike protein allows the virus to enter the cell.



- *From Heurich et al Journal of Virology January 2014*
- The virus will replicate, destroy the host cell, and go for the next nearest cell with an ACE2 receptor - potentially anywhere in the body.
- It's important to note, then, the tissues that have the highest density of ACE2 receptors, as some of the devastation we see from the virus is wrought on these organs specifically.
- The most relevant ACE receptor-rich cells are the critical surfactant-producing "type 2 pneumocytes." If enough of these cells go down, the alveoli in the lungs can't maintain surface tension and will collapse - which is precisely the respiratory distress syndrome that we see in the sickest COVID19 patients.
- There are also ACE2 Receptors in the intestine, and importantly, in the heart muscle. Indeed, some of the first studies out of Wuhan province suggested that some of the patients who perished had cardiac muscle damage in the late stage of the illness, showing "dual peaks"--with high mortality around day 7-10 from lung complications, and around day 14 from fulminant myocarditis/cardiac events.

Where do the ACE inhibitors and ARBs come into play?

They reduce ACE receptors in the short-term (desirable, with respect to SARS-CoV-2), but may increase them in heart after a few weeks (not desirable, with respect to SARS-CoV-2).

The point-counterpoint boils down to the following:

The case against use of ACEi/ARBs

- Patients with hypertension have more severe COVID19 disease (hard to tease away from age because hypertension goes up with age) (Source)
- ACE receptor quantity and expression goes up when you take these meds for 1-2 weeks or longer (Source)
- Late stage complications of COVID19 include inflammation of the heart muscle (which has significant ACE receptor expression); These medications might prime the heart to suffer overwhelming viral replication and tissue destruction (probability: low, evidence level: low, cost of being wrong: disastrous) (Source BMJ Source PeterGramPost Source Note also that it's hard to distinguish heart muscle damage specifically from multi-organ failure, which also occurs as a late complication of this disease.

The case for use of ACEi/ARBs

- These medications may block early interactions of the virus S protein with ACE by competitively occupying the binding site.
- Some hypothesize that the increased ACE receptor expression from these meds might actually preserve the function of the impaired cells for longer when they are under attack (though this also may just provide more sites for the virus to dock and enter new cells).
- These drugs are important medications with clear clinical benefit in heart disease and hypertension. Patients with more serious comorbidities have higher COVID-19 morbidity and mortality, so BP and CV protection (offered by ACEi and ARBs) cannot be dismissed.

Wildcard

- It may be that a short term pulse of these meds could help prevent/fight the virus, but be stopped within a few days so that ACE receptor expression doesn't increase in the late stage of the disease. Given how quickly the pandemic seems to be making its way through humanity, we may not ever have time to set up a trial for this approach. Instead, we may need to wait for, and rely on, retrospective, non-randomized case-control data from China and Europe. We are searching for these data every day, but to date nothing has emerged.

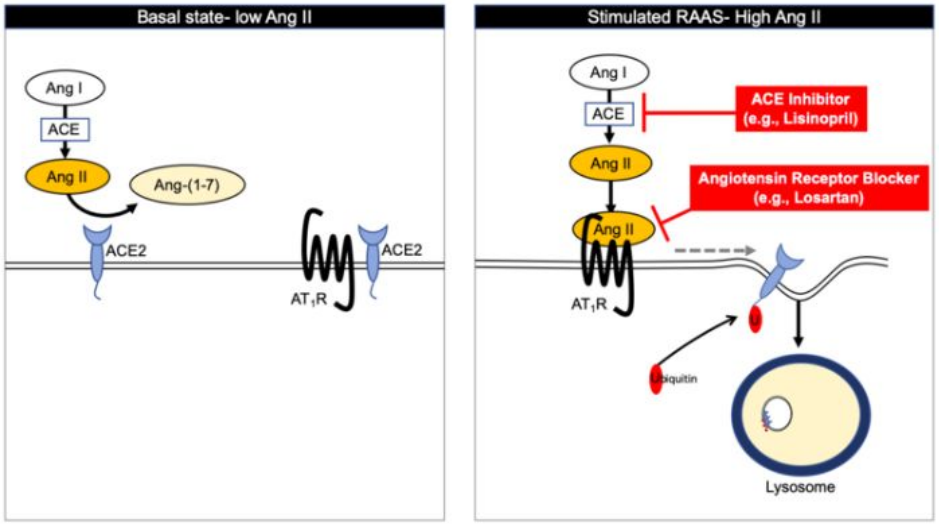


Figure: Type 1 angiotensin receptor (ATR1) blocker (e.g., Losartan) ubiquitized ACE2 and therefore could suggest that an ARB prevents Covid-19 viral entry.

Our Recommendation

As you might imagine, the correct decision is far from clear, and while we agree that it would be irresponsible for millions of Americans to stop their medications en masse, it requires a very individualized approach.

Global recommendations: Until we have more data (hopefully very soon), we generally concur with the *European Society of Cardiology* consensus statement, that the population should not be taken off of these medications en masse if they are already taking them--especially if one has had a recent cardiac event or kidney disease.

Personal recommendations: Talk to us and make a decision based on your specific case and risk tolerance. If you are on the ACEi/ARB solely for blood pressure control, it may not be unreasonable to switch to an equally effective alternate medication in the short term, until we have more data to support one way or the other.

Once again, do not make changes to your medications without consulting with your doctor, and keep in mind that this is all subject to change as the situation develops.

Appendix

Summary recommendations from several professional societies

Society	Summary of recommendations	Last Statement Update
European Society of Hypertension	Recommend continuing ACEis/ARBs due to lack of evidence to support differential use in COVID-19 patients. In those with severe symptoms or sepsis, antihypertensive decisions should be made on a case-by-case basis taking into account current guidelines	March 12, 2020
European Society of Cardiology Council on Hypertension	Strongly encourage continuing ACEis/ARBs due to lack of evidence to support discontinuing	March 13, 2020
Hypertension Canada	Recommend continuing ACEis/ARBs due to lack of evidence that patients with hypertension or those treated with ACEis/ARBs are at higher risk of adverse outcomes from COVID-19 infection	March 13, 2020
Canadian Cardiovascular Society	Strongly encourage continuing ACEis/ARBs and Angiotensin Receptor Neprilysin Inhibitors due to a lack of clinical evidence to support withdrawal of these agents	March 15, 2020
The Renal Association, United Kingdom	Strongly encourage continuing ACEis/ARBs due to unconvincing evidence that these medications increase risk	March 15, 2020
International Society of Hypertension	Strongly recommend that the routine use of ACEis/ARBs to treat hypertension should not be influenced by concerns about COVID-19 in the absence of compelling data that ACEis/ARBs either improve or worsen susceptibility to COVID-19 infection nor do they affect the outcomes of those infected	March 16, 2020
American College of Physicians	Encourage continuing ACEis/ARBs because there is no evidence linking them to COVID-19 disease severity, and discontinuation of antihypertensive therapy without medical indication could in some circumstances result in harm	March 16, 2020