Update on SARS-CoV-2 / COVID-19: General Guidance

March 19th, 2020

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Pharmaceutical update

We will be devoting the bulk of today's update to the rapidly changing therapeutic landscape.
We will address personal protection, the extraordinary underestimation of cases in the U.S. (and resultant implications) in a subsequent update.

Preliminary clinical trials data started trickling in yesterday, but it is premature to narrow in on a specific protocol until we absolutely have to. We are viewing the medications list below as a toolbox to be accessed in the right combination at the right time.

Hydroxychloroquine plus Azithromycin

Two protocols are currently being circulated. The first is a preliminary clinical abstract from France showing successful reduction in COVID19 viral load using hydroxychloroquine and azithromycin in combination (Raoult et al 2020). Azithromycin is an antibacterial agent with some immune-modulating properties (commonly known as a "Z-Pak") that has a synergistic effect with chloroquine for the treatment of malaria--meaning, the meds work in combination better than either alone. The azithromycin was added to patients who were considered "severe." The big caveats here were that the study was small, it was poorly controlled (the control group were people who refused treatment or were at another hospital or treatment center), unblinded, and the end point was viral load in mucous, not faster recovery from the infection. They have not released their raw data. The French government will set up a new trial to independently confirm results.

Takeaway: We are considering the combination of chloroquine/hydroxychloroquine + azithromycin for our patients with moderate to severe illness: this is on a case by case basis.

Chloroquine vs hydroxychloroquine

- We generally consider the two medications to be roughly equivalent in humans (500 mg chloroquine vs 200 mg hydroxychloroquine). In-vitro testing (Yao et al. 2020, Liu et al. 2020) showed a higher inhibitory effect for hydroxychloroquine, however, human dosing studies comparing the two for antiviral usage have not been done. Apart from the above mentioned study, nearly all human trials for SARS1 and ongoing for SARS2 have been using chloroquine. All guidelines published from China/Italy in this outbreak so far use chloroquine (Gao et al. 2020)
- While it's generally true that hydroxychloroquine is less toxic than chloroquine, this is more of a concern for long-term use. For a course of treatment that lasts less than five years and does not exceed a certain dose, the risk of ocular side effects for either drug appears to be small, especially for those under 60 who do not have renal or liver function impairment.

Ritonavir/Liponavir (Kaletra)

The second protocol was published in the *New England Journal of Medicine* yesterday examining the repurposed, existing anti-viral Keletra (ritonavir/lopinavir) (Cao et al. 2020). This study was more rigorously done than the above study, and concluded that the medication had no effect on survival.

We should not, however, abandon hope for this medication. This study enrolled only critically ill patients, and the average day on which the medication was started was day 13 from symptom onset, which is nearly the median day of death from the virus! All this tells us is that Kaletra doesn't work when you start it on a patient who is almost dead. For those patients who started before day 12, there was a modest but detectable improvement. Again, this drug should absolutely continue to be studied in our view and we are not ready to write it off.

Takeaway: We now have 4 drugs that may directly impact the course of the infection: chloroquine, hydroxychloroquine, azithromycin, and Kaletra.

It cannot be overstated that isolation is still the best defense, and that you should not take any of these medications alone or in combination without consulting with your doctor first.

Other promising pharmacologics:

- Favipiravir has shown promise as a treatment of COVID19 virus in both reducing duration and improved lung condition. The drug is currently being studied in both Japanese and Chinese clinical trials. Early results indicated that it is more effective in treating milder cases, decreasing illness duration, while it has been less effective in treating more advanced illness.
- Camostat mesylate which has a novel antiviral mechanism is under investigation in Japan; we are following this closely.

From our previous update on March 17: There are currently reports out of Italy and France circulating on the potential for anti inflammatory medication (NSAIDS) to aggravate COVID19 virus progression. Although these reports are not robust such that a definitive conclusion can be made, it is our conservative recommendation to our patients to avoid NSAIDs (e.g., Aspirin, Naproxen, ibuprofen, Aleve, Advil) until we acquire additional information. If needed we recommend Acetaminophen (i.e., Tylenol).