HOST: Hello I'm Faith Rogers, host of today's program, COVID-19: Keeping Up with a Moving Target. This is the April 15th update of DKBmed radio's coronavirus educational series. Thank you for joining us. Our plan is to provide weekly 15-minute webcasts and podcast updates featuring the latest news and answering your questions about COVID-19. Please know that just as knowledge of COVID-19 is evolving, this program will evolve over time as new information warrants. We welcome your suggestions to make this as beneficial as possible.

Support for this program is provided by DKBmed. Today's program is accredited for ANCC and AMA PRA Category 1 Credits. Please visit our website at COVID19.dkbmed.com for complete CME and CE information. To access other free CME programs, and to view or listen to last week's content, please visit us at DKBmed.com.

Here are the overall learning objectives for the program:

- **Discuss symptoms and transmission of COVID-19**
- **Discuss risks, management, and precautions with COVID-19**
- **Describe natural history of COVID-19 illness**

With us today we have Dr. Paul Auwaerter, Clinical Director of the Division of Infectious Disease at Johns Hopkins School of Medicine. Dr. Auwaerter, thank you for joining us. Take it away.

DR: AUWAERTER: Thank you, Faith. I want to thank DKBmed for their generous support, and also the Postgraduate Institute for Medicine and the Institute for Johns Hopkins Nursing. And as already mentioned, you have the URL address for additional resources and educational activities.

As the pandemic evolves, New York City and its metropolitan area remain the epicenter of cases and, unfortunately, deaths, at least in North America. But this continues to evolve, and there are hints that the social distancing that has been invoked in many states has started to help bend the curve, but in other areas it's still increasing. This is something that will be watched quite closely. I also want to mention that the experiences in China and some of the European countries such as Denmark and Austria that are beginning to liberalize their social distancing will be watched very carefully.

For health care workers, there remains a divide between what is commonly done in Europe, as well as in North America. North America has always, at least with the Centers for Disease Control backing, preferred an N95 respirator or other similar devices on the chance that there's routine aerosolization of the virus. The CDC did loosen their requirements because of the intense demands on N95 masks and similar equipment. They are now allowing a face mask, which is the alternative seen on the right-hand side of the slide, from NHS in Britain. This mimics very much the WHO recommendation that droplet precautions are sufficient for protection unless there are aerosol-generating procedures. This is something that's being followed, and I do see that there's probably going to be a gradual change over time because, although aerosolization is certainly possible, it is probably not the brunt of the way the infections are being acquired.

The second recent big change last week was the CDC changing what they called close contact with suspected or confirmed COVID-19. Typically, this has been a 14-day quarantine. Now with the interim guidance is, anyone who's considered a key essential worker (list in the blue box) does not have

to obey that. That's to help avoid shortages in critical infrastructure workers, so I think the strict demands back when we thought the infection could be more contained with perhaps contact tracing and strict quarantine are being loosened. This is being followed, along with the fact that a fair number of people are probably asymptomatic, hence the earlier universal mask suggestions.

The Centers for Disease Control have also put forward information from 14 states on hospitalizations, and since so much of our early data was from China, I thought it was useful to try to compare. What is very evident here, though, is that there is very little age difference in the impact of this coronavirus. Much like in China, there are very few hospitalizations in the US for children and even young adults, but hospitalizations climbed significantly, especially in the oldest people. Looking at this group of the almost 1,500 patients, almost three quarters were over 50 years of age. There was still a slight male predominance, not very different than in China, as well as underlying health conditions. It remains unclear if hypertension's an independent one; there are some suggestions that it might be, but it could also just reflect an age variable. But it is clear that's a little different than other studies that obesity has become a significant risk factor, along with some of the others previously cited such as diabetes and heart disease.

The other point from this report is that it appears that Blacks suffered higher hospitalization rates than expected for their percentile of the communities from which they had taken this data. The reasons for this are by no means clear. A variety of factors have been suggested, whether it's genetic, whether it's comorbidities, body mass index, or perhaps socioeconomic factors. This will certainly be determined, and I would say in Baltimore we've certainly seen that this holds through in our community.

For the sickest patients in the intensive care unit, I thought it was worth contrasting their early experience at the University of Washington, whereas Italy, of course, had an earlier upswing in its epidemic and an older population and had much more ICU critical care experience. What you can see, interestingly, is the ages are very similar. (There's a typo on the slide: 56 to 70 was the general range.)

There were more women in the Seattle cohort as a percentage, and proning was used in about a third of patients in both locations, but with a higher mortality rate noted than in Italy, at least in this small number. I would say Johns Hopkins, although we have similar numbers to date, just 24 are critical care. People are reporting that they are proning patients at a much higher rate — north of 50% —and our mortality rate is under 5%. This is of course very early, and we have a younger population than either in Italy or University of Washington. But it may speak to the fact that certain amounts of supportive care rather than any kind of pharmaceutical intervention may make some differences, so that certainly will come about.

Speaking of therapeutics, the Infectious Diseases Society of America issued what they called a Living Guideline Document with a very strict grading format for giving recommendations. You can see them listed here, and the snapshot version is that because of the lack of evidence, almost any off-label drug at the moment has only been advocated for use in the setting of a clinical trial. Some have argued that this is the only ethical approach, given known risks and only theoretical benefit; others have said that well gosh, you know, we're faced with people in front of us, we have no knowledge, we're trying to make educated guesses and there are no trials available. So there's clearly a tension here, but this is a very — how should I say — dogmatic approach to giving recommendations, which is certainly one point of view.

The only one of note is the corticosteroid recommendation: they recommend against using corticosteroids as a conditional recommendation with very low certainty of evidence. The Critical Care Society did come out with guidelines saying that steroids in the ICU should only be used in accordance to standard procedures, for example, such as suspected adrenal insufficiency and other management issues, not specifically for COVID-19.

We await randomized controlled trials of remdesivir. In the news, it is of interest that the one trial on less severe disease was closed in China because of enrollment problems, so we won't know much about that. We will await the trial for severe disease, and also two trials in the United States that had expanded numbers of enrollment tripling or quadrupling the number required in the trial, which are all hints, perhaps, that the drug is not super effective, at least at the time that it's administered. This case series data which were presented recently in the New England Journal of Medicine had no comparator arm, so it's very hard to understand how effective this drug is. I would just mention, it's gotten the in news as saying this drug is helpful, but I think that remains a question mark.

This was 61 patients, about three-quarters of whom have completed a 10-day course. They were quite ill, as you might expect for compassionate use. People are fighting fires and they are trying something for their desperately ill patients. The majority, as expected, had comorbidities and, at least at the time that we put together this case series, they say that about 70% had improved, at least in oxygenation. Twenty-three percent were judged as severe side effects, but much of this just seems to have been potentially not drug effects, rather just the seriousness of their critical care illness. I don't think from this compilation that much of anything could likely be taken from these data.

I showed this slide earlier, and I just wanted to emphasize, as I've added the bottom row which is also another preprint. None of this has been published yet, but this was on chloroquine from a group in Brazil that looked at so-called high dose chloroquine at 600 mg twice a day vs a lower dose of 450 mg twice a day. Both are actually quite high doses of chloroquine. This trial is significant for the fact that, not unsurprisingly, there was a little impact on viral shedding. However, there was a concern for higher lethality and because of that that the higher dose of that arm was stopped. As we're accumulating more data, that probably points to the fact that at least in very ill patients, there can be untoward reactions from these medicines. My own personal opinion without data is that a lot of drugs look good in the test tube, because if they inhibit host cell protein synthesis and so on, they'll appear to inhibit virus. But once you get those drugs in vivo, you may not see that effect, and I think that will likely be the case with hydroxychloroquine and chloroquine.

Also, a group from France that does pharmacovigilance looked at a recent series over the past few weeks on just cardiac events, and found that the vast majority were in patients receiving hydroxychloroquine or that drug and azithromycin, including seven cases of cardiac death, 12 who experienced at least syncope, and the others with prolonged QT. At Johns Hopkins we are not advocating for using these drugs once patients are unstable or in the intensive care unit.

Lastly, I'll just close on a hopefully brighter note. Vaccine development, has, to my eye, been really explosive for COVID-19. You can see here the number of not only approaches that are listed, but those in preclinical phases of development, and even phase 1 safety profiles in progress. The WHO is estimated 12 to 18 months for developing an effective and safe vaccine. We'll have to see if that can be shortened, but one hopes this will lead to something that could help curtail or even end the pandemic if it doesn't happen earlier.

I think we have some time for questions.

HOST: Yes, thank you, Dr. Auwaerter, for those updates. We will now continue to the listener Q&A. To submit questions for Dr. Auwaerter of your own, please send questions to QA@DKBmed.com. That's Q as in question, A as in answer, at DKBmed.com. If we are not able to address your question in this session, we will try to address it in another session.

First question: What is the current evidence about antihypertensives and whether they play a role in a virus acquisition or in complications? Is there any thought regarding ACE2 being higher in males than females contributing to the higher number of males being adversely affected with COVID-19?

Those questions are at a high focus that the NHLBI, for example, is trying to help answer about the ACE2 molecule being a receptor for the novel coronavirus. At the moment, I would say there is really only mixed data and hypotheses, so this will be borne out as we look at a larger experience, which could be both the combination of looking at electronic medical records as well as prospective studies, to try to help understand this. I've seen data suggesting that being on angiotensin converting enzyme inhibitors or receptor blockers are protective, others saying that perhaps they're not, so I think this is unclear. More males than females tend to have hypertension, so I think this is impossible to really get at this time, and certainly there are no recommendations afoot at all for changing medications.

HOST: Great, thank you, next question: Some clinicians have suggested that some providers are using ventilators too aggressively. Can you please share your thoughts on that suggestion?

DR: AUWAERTER: Obviously this gets at several issues that I think have to rest at the moment with clinical judgment. I can tell you on the one hand, I've certainly heard critical care and intensivists suggest that they'd rather intubate before there's a crisis. We've seen some people with COVID-19 decline incredibly fast, and the idea would be you'd like to intervene before there's a code on the floor, or you have to bag someone, and so on. Obviously, just like with the old-fashioned preimaging evaluations of appendicitis, some people may not have needed to be intubated in retrospect, but I'm not sure there's a right or wrong answer. I am NOT a critical-care intensivist so I think at the moment we're not sure. Obviously, everybody would like something that's like Goldilocks with the porridge, just right, but I think people are trying to do the best they can and get people to the appropriate levels of care for safety. We've not had extraordinary problems to date extubating people that survived. Some people had prolonged ICU stays, but that has not been a routine issue beyond those that may already have advanced lung disease.

HOST: Thank you, next question: I am seeing more information that pink eye or conjunctivitis is a symptom of COVID-19. From what I have read, this is only a late-occurring symptom. Can you confirm or comment on this?

DR: AUWAERTER: There have been some reports of these issues either earlier or later in illness, I don't know how common it is and whether this has been looked into systematically, so I think we'll need to reserve some judgment on that, especially in later illness, when there could be other reasons for inflammation.

HOST: Thank you, our next question is: I have seen reports of clotting issues in people who are severely ill with COVID-19. Is there any guidance on anticoagulation treatment prophylaxis for hospitalized patients?

DR: AUWAERTER: So certainly, especially for patients who are quite ill who may not be terribly mobile or who are in the intensive care unit and paralyzed from proning and so on, there are reports of both deep vein thromboses and pulmonary emboli. Some centers have advocated for anticoagulation at rather significant levels to prevent this problem. It's unclear if this is occurring any more frequently in COVID-19 disease compared to other critical illnesses, but I would say there is some divide, because some have argued about not routinely anticoagulating at high level, and then others that do. I would say at the moment this is an issue lacking some data and people are trying to figure out best practice until there is one.

HOST: Thank you. Our next learner question: I've heard a few reports of the COVID-19 presentation being similar to high altitude sickness. What is the evidence on this and how would this change the treatment?

DR: AUWAERTER: I'm not quite sure I've heard this. High altitude sickness is triggered by a drop in oxygen tension, and of course that doesn't routinely happen. As far as I know when people are in hospitals, they're often at sea level. I suppose what this might be getting at is a concept that many patients sort of had air hunger or feel short of breath although their oxygen requirements aren't very high, which is a little different than we might see in some typical respiratory illnesses. It might be something similar to what we see in sepsis, where people can have increased respiratory rate and some lower oxygen saturations without really marked demonstrable findings on imaging.

HOST: All right, well thank you again, Dr. Auwaerter, for joining us today. To claim CE credit, please complete the evaluation at COVID19.dkbmed.com and select today's activity. Feel free to access our resource center on COVID19.dkbmed.com. You'll find a range of information, including the latest COVID-19 data and statistics, medical society guidelines, and resources in Spanish. To all our listeners, please be on the lookout for our next activity. We will send out an email when it is available next week. To submit questions for Dr. Auwaerter of your own, please send questions to QA@DKBmed.com. That's Q as in question, A as in answer, at DKBmed.com. Again, thank you for joining us and thank you for your dedication to your patients with COVID-19. Thank you, Dr. Auwaerter.