FAITH ROGERS: Hello, I am Faith Rogers, host of today's program, COVID-19: Keeping Up with a Moving Target. This is the May 6 update of DKBmed Radio's coronavirus educational series. Thank you for joining us.

As a reminder, we are now providing TWICE-weekly 15-minute webcasts and podcasts featuring the latest news, treatment updates, and clinical considerations, as well as answering your questions about COVID-19. These will be available on Wednesday evening and Friday morning. Sign up at COVID19.DKBmed.com to be sure you get the latest updates.

Today's program is accredited for ANCC and AMA PRA Category 1 credits.

Please visit our website for complete CME/CE information. To attest for CME/CE credit, please visit COVID19.Dkbmed.com. There you will also find all of our previous COVID-19 programs and have access other free CME/CE programs on a range of topics.

Today's learning objectives are:

- **Describe testing priorities for COVID-19 illness**
- **Review remdesivir data and what is known from randomized controlled trials**
- **Discuss tissue injury mechanisms in COVID-19**

With us today we have Dr. Paul Auwaerter, Clinical Director of the Division of Infectious Disease at Johns Hopkins School of Medicine. Dr. Auwaerter, thanks for being with us today.

DR. AUWAERTER: Thank you, Faith, and glad you're listening today. I want to acknowledge the generous support of DKBmed, the Postgraduate Institute for Medicine, and the Institute for Johns Hopkins Nursing. For additional resources and educational activities, please go to COVID19.dkbmed.com.

We're now well into our second month of the novel coronavirus across the globe, also in the United States, and one of the issues as we're moving along is that certain states are proceeding with different levels of relaxation of social distancing, and others are maintaining them. I think this will be quite challenging at times, and in two to three weeks, we'll see what kind of impact these changes may be having.

For the time being, perhaps on the good-news side, the CDC has updated their testing recommendations. I think this reflects that there is an increasing testing capacity generally, but there is still an emphasis on certain higher-risk populations to get tested, and perhaps tested more promptly. A lot of you may be already familiar with these, but we might just want to just touch on them. Obviously, anyone who's hospitalized, that's a no-brainer. Health care workers, anyone who lives in congregate living situations, people who are homeless, for example, in shelters, people in nursing facilities, first responders, and so on.

The others, besides people already having suspicions of COVID-19, include asymptomatic people. This is the first time that this has been emphasized in a sort of simplistic manner here. That includes people who may be in certain racial or ethnic minority groups that are disproportionately affected. This has been identified because of increased rates of hospitalization compared to presence in the population, such as African Americans, Hispanics and Latinos, and then certain Native American tribe nations such as the Navajo. The asymptomatic people could be part of a surveillance or public health interventions, as

well as just routine screening, for example, in prisons, homeless shelters, or any kind of institutional setting. I think as testing capacity expands, we'll be seeing this more and more.

However, if you've been listening to this program in the past, you know I have reservations about antibody testing. You can see the last bullet on this slide says the CDC has no current recommendations for antibody testing. This really reflects the influx situation of antibody tests where we don't yet know how well they perform: is it sufficiently accurate to be certain we are not seeing a lot of false positives? As well as whether these tests reflect that people have protective levels of immunity.

I want to spend a little time on some therapeutics, because this has become big news over the past week. The drug remdesivir, which was originally proposed as a treatment for Ebola, does have effect against coronaviruses. It's an antiviral, you can see here in this schema, that when a virus enters a host cell and has to replicate RNA to make proteins that then assemble new variants, that this drug remdesivir, which is only available IV, is metabolized to a prodrug. This active molecule, GS 4400 1524, interrupts the polymerase protein of the virus that's generated by the host cell and therefore stanches further viral replication.

We know this works well in the test tube, but the question is how well has it done in clinical trials. The gold standard is always a randomized controlled trial, and the first one of any significant degree out of the box was this trial from China which was halted prematurely. They had difficulty with study enrollment; they only had 237 patients. This was, though, a sicker population. People could have symptoms up to 12 days, but they needed to have lung involvement, and the overall findings compared to placebo were no improvement. There is no improvement in mortality or clinical effect, and perhaps most worrisome, there was no effect on the viral load, meaning there is no clear impact when this drug was administered.

There were some trends in the group that received the drug before 10 days, and this is perhaps hopeful, because we know from studies on influenza that the earlier you use antiviral therapy in that respiratory infection, the more likely you'll see a clinical impact. So perhaps a drug was just given too late. However, the one that made the splash, we really have minimal data, and that was discussed by Anthony Fauci and in a press release in late April, on a randomized controlled trial, also in patients with lung involvement. They got a higher dose on the first day of intravenous load, followed by daily dosing for up to 10 days. This was over a thousand patients, and it was 68 sites. Lots of centers participated, so you don't have much trouble trying to mimic real-life experience. Interestingly, I was surprised that this trial showed an impact, but the impact was that there was a decreased length of stay by 31%, meaning that people that got placebo left the hospital at 15 days, and those that got the study drug left after 11 days.

For mortality, there was a trend, but it didn't turn out to be statistically significant. As with any quality RCT, there is a data safety monitoring board, and that board did not suggest halting the study early because of clear and convincing benefit of treatment. But the decision was made on an interim data analysis to announce these results, and indeed, the trial is going to adapt or pivot and change to incorporate a new drug therapy, suggesting that remdesivir is now something of a standard of care as an antiviral against this coronavirus.

I do want to point out some things that have made people pause. The original study design was changed just a few weeks before, and had an 8-point severity scale. Instead, they changed to a revised primary endpoint of time to recovery. These sorts of things are usually frowned upon. This drug then got FDA

authorization under the emergency use authorization to treat hospitalized patients. You can see here that anyone who's quite ill in the ICU or on ECMO can get treatment for up to 10 days, whereas five days is suggested if patients are hospitalized and have lower blood oxygen levels or require supplemental oxygen.

This drug currently is being distributed. One and a half million doses were provided by Gilead to the federal government, but hospitals, for example our hospital, as of today, had not yet said how or whether they will receive drug outside of clinical trials. I know we'll still see how much drug is available, there's approximately enough doses for some 100,000+ people to receive a treatment course.

I'd like to conclude with a few things that we're beginning to really just be amazed at. With this coronavirus, there are so many questions. Most people have no symptoms or mild illness if they're infected, and yet 5%-10%, or even more, depending on the age and comorbidities of the population, have dramatic disease that is life-threatening. Most people know about the tissue lung injury that occurs in the lung that might precipitate something like ARDS, but we see renal failure with significant frequency. In people who are in the ICU, we end up seeing MIs, pulmonary emboli, and DVTs. About half of people who are ill have elevated liver function tests, there are strokes, some people present with diarrhea, there's smell loss, conjunctivitis. To me, thinking back to when we were just learning about HIV and having opportunistic infections, in a way HIV was a simpler virus to understand because there is sort of a lockstep physiology with that virus in the CD4 cells.

Here, there's a lot that we still yet have to learn, but for ARDS, our critical care colleagues have tried for a while to figure out interventions. Classic ARDS from bacteria tends to be a problem of neutrophil activation and mucus and debris with lung injury in response to certain danger signals that might be provided by bacterial endotoxin or others. However, although there have been no promising drugs that have worked well for this kind of ARDS, this is not the ARDS of coronavirus. So the standard ARDS is not what we tend to see, and it's a little more complicated. This slide is a lung injury that probably is very similar to what we understand influenza does when it causes ARDS, although it does it at a lower frequency than this coronavirus.

This is a process where activation within endothelial cells, and engaging with the ACE2 receptor somehow triggers intense inflammation. It also seems to be a disorder of regulatory T4 and T8 cells, that all combine, as you can see on the bottom, to produce lung injury with accumulation of fluid, additional macrophages, also fibrin and scarring that causes problems with diffusion of oxygen and lung compliance. However, if people survive, they tend to have less of this kind of lung injury situation. Why those triggers occur in some we think may have to do with certain genetic signals, perhaps from host responses, as well as occasionally they may have specific polymorphisms that are with a given virus, as we can see sometimes in severe influenza. Stay tuned and we may know more.

One of the things we initially discounted was that a lot of patients in the ICU seemed to have clots. This can happen even in any critically ill ICU patient, but this virus that binds to the ACE2 receptor on endothelial cells in this cartoon seems to cause vasoconstriction, so the vessels constrict in response to inflammation, or precipitates clot. This has driven what seems to be a fairly high incidence of strokes, MIs, pulmonary embolus, and DVTs, so this has precipitated some interesting debate about whether to anticoagulate all patients at a higher intensity, or even full-level anticoagulation in certain patients. A lot of this is being driven now by some accumulating experience, for example in Italy, where many patients ended up in the ICU. Prophylaxis was done in all their patients who ended up in the ICU, yet there is still

a substantial amount of problems, with thrombosis seen in nearly 30% of people in the ICU — despite the prophylaxis — having clots. These cases were diagnosed in the first 24 hours, which suggests that perhaps the clots were already in formation. This didn't seem to be because these patients were in a DIC profile.

France also had a fairly high incidence, a much lower number of patients, only 26, but you can see for those that were in the ICU and anticoagulated, in 100% of people there they found clots. In the Netherlands, also 31% findings of clots. In China, 20% of those patients had a cardiac injury, although there's debate if all that is due to thrombosis. This is still being sorted out. We haven't seen a lot of excessive bleeding, so I think there is certainly a trend toward anticoagulating more aggressively certain high-risk individuals. That, of course, includes people who end up in the ICU.

Thank you very much for listening. Every week we are learning more and more about this fascinating but devastating virus. Unfortunately, we do not have time for questions and answers this week. They'll return next week. Thanks so much for listening.

FAITH ROGERS: Thank you again, Dr. Auwaerter. A programming note: we do not have time for Q&A today as we will be recording an interview with Karin Huster, who has recently worked as a field coordinator in response to the coronavirus (COVID-19) pandemic in Hong Kong. She now volunteers as one of the coordinators on the homeless response for COVID-19 with Seattle King County Public Health. Dr. Auwaerter and Karin will discuss infection prevention control, health promotion and mental health activities packages targeting the most vulnerable populations. Please be on the lookout for this interview this Friday.

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Don't forget 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 of our listeners, please be on the lookout for our next activity this Friday. We will send out an email when it is available later this week. Any questions can be submitted by sending them to qa@dkbmed.com.

Again, thanks for joining us and thank you for your dedication to your patients with COVID-19.