FAITH ROGERS: Hello, I'm Faith Rogers, host of today's program COVID-19: Keeping Up with a Moving Target. This is the May 27 update of DKBmed Radio's coronavirus educational series. Thank you for joining us.

As a reminder, we are providing twice weekly 15-minute webcasts and podcasts on Wednesday evenings and Friday mornings featuring the latest news, treatment updates, and clinical considerations, as well as answering your questions about COVID-19. 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 and CE information. To attest for CME and CE credit, please visit COVID-19.dkbmed.com. There you'll also find all of our previous COVID-19 programs and have access to other free CME/CE programs on a wide range of topics. The slides for today's webinar and previous webinars can be found under the resource tab.

Today's learning objectives are:

- **Describe factors is associated with secondary infections**
- **Discuss clinical effects of viral shedding**
- **Discuss current data pertaining to use of remdesivir**

With us today, we have Dr. Paul Auwaerter, the clinical director of the division of infectious diseases at Johns Hopkins School of Medicine. Thanks for your time, Dr. Auwaerter.

DR. AUWAERTER: Thank you, Faith, and I always want to acknowledge the generous support of DKBmed, The Postgraduate Institute for Medicine, and the Institute for Johns Hopkins Nursing. Additional resources and educational activities are available through DKBmed at their covid19.dkbmed.com site, so please visit.

As we are moving through cases, we show this map and I think it's no longer quite as relevant as it was. I think many of us acknowledge that COVID-19 is circulating in communities. It is still striking people who are living in more congregate and grouped environments or in larger families, people who may not be able to socially distance as easily, and also institutionalized settings, but the risks remain and many states have elected to move ahead and re-engage various sectors of the economy.

A number of these photographs circulated from a hundred years ago in the pandemic, and of course, the professional and college and other sports clubs such as youth leagues have all mostly ground to a halt. Some are reawakening, but these photos remind us that even back in the influenza pandemic, attempts were made to play sports or watch football, for example, and it'll be interesting to see exactly how this will work. Obviously, in many ways this virus is much harder to acquire outdoors. I think anything outdoors certainly lowers risks tremendously, even with a modest amount of social distancing.

But the really high-risk venues still remain large groups of people in environments where circulation may not be as good indoors. That can include churches and synagogues or retail shopping. These are things where wearing masks is helpful to help prevent unintentional transmission for people who may not realize they're sick, but these are all aspects that I think many are working out and also for colleges and universities that are trying to understand whether they can reopen safely in the fall.

For the rest of this webinar, I want to focus on some issues that are coming up frequently in hospitalized patient management for those of you who are right on the front lines and caring for patients. Many

know the well-acknowledged complications in influenza of experiencing so-called double sickening and secondary pneumonia, most famously with MRSA, but this can also include routine community-acquired pathogens. There's a sense that this may also occur frequently, especially in more critically ill COVID-19 patients.

A couple of studies are beginning to emerge for patients who have been stricken severely ill, landing in the intensive care unit, often with mechanical ventilation. A recent paper published in *Clinical Infectious Diseases* gave a range, looking at the literature, of 13-44%. Interestingly, this virus causes a low white count initially, and there's a sense that interferon is inhibited and there may be other immunological perturbations that allow nosocomial pathogens to set up shop especially well.

What's a little unclear is if this is any more common yet than anyone on a prolonged mechanical ventilator, but you see a number of the typical pathogens here: bacteria and mold such as Aspergillus, especially in patients that might be previously colonized, such as lung transplants. The time of onset of symptoms for secondary infection is anywhere from 10-17 days, and yet in this group, many unfortunately succumbed before their third week passed. These may be terminal events, possibly. It's difficult to interpret the literature precisely because many of these reports are coming from China and New York City, and understandably, clinicians have elected to give antibiotics frequently because these are patients that proceduralists don't wish to go and get samples from because of concern for aerosolizing the virus.

Antifungals are also administered in a subset, and I'll say at Johns Hopkins we use a β-d-glucan screen in the serum. This is a fungal marker to try to gauge risk for something like Aspergillus and whether to use voriconazole, and at least in these reports, corticosteroids were frequently used. I think this may be less likely in Europe or North America, but the whole concept of whether you use steroids to tamp down the hyperinflammation of COVID-19 is still something to be addressed.

Starting off with the Chinese guidelines many months ago now, an anti-il-6, interleukin 6, strategy using a monoclonal antibody called tocilizumab was in their guidelines. A number of centers have used this drug to some degree to try to cool down patients from a cytokine storm, which seems to be driving a lot of illness. This is a preprint from a group that looked at patients who had received both tocilizumab and those that didn't. Obviously, there are issues here, but their illnesses were relatively closely matched, so there wasn't a lot that seemed different. But if you look at bacterial infections, and not unsurprisingly, if you get rid of a vital interleukin response, there seemed to be more bacterial infections and at least a trend, although the numbers are very low for additional fungal infections. I think this will await more information because there are a huge number of clinical trials, using not only tocilizumab but other monoclonal antibodies such as clazakizumab, which is an anti-interleukin 6; anakinra, anti-il-1 drug that inhibits GM-CSF. Many of these are being studied. We'll get a better sense from randomized clinical trials about the true risk, but it’s something to be on the watch for, especially if these drugs are employed in your patients.

Another key question that comes up frequently in hospitalized patients is: we need to send this patient to a rehabilitation facility, we're doing another swab and the CDC had recommended that two swabs are needed to remove airborne and respiratory precautions, what do you do with someone in their fourth or fifth week of hospitalization and they still have a positive test? Is that person still infectious? We had some indication from this paper in *Nature* that looked at a small number, only nine patients, who are either mildly ill or asymptomatic.

I won't walk you through all the charts, but if you look at G, you'll see by day 10 none of these patients had a virus that could be cultured. This was about the same time that antibodies started to be made in earnest, with most patients having developed them by day 14, so you can think about from day 10 to 14 after onset of symptoms, that virus isn't being transmitted. But does this apply to sick and hospitalized patients? Patients who are under critical illness may have gotten steroids to suppress their immune systems and so on, and then just because you can't detect it by viral culture, which is a fairly insensitive assay, perhaps people still are infectious.

However, some interesting studies performed by what's often called the Korean CDC looked at so-called re-positives. These were patients who had been in hospital and were discharged with negative tests and then they were screened on average about 14 days after stopping isolation, many at home. Some of them had recrudescent symptoms such as just fever and so on, and of that group of 285, a number of these people were re-positive, so the virus was found again, but it was just by molecular assay, and the question was, are these patients infectious?

They used contact tracing of family members and other close contacts in 790 people, and in these cases, no positives or retransmission were found, so if there was a canary in the coal mine that these positives represented, it doesn’t seem to pose great infectious risk. That doesn't mean these viral remnants, which may not be fully intact viruses, aren't somehow creating some kind of immune response or recrudescent fever, but this has given us some reassurance that patients are no longer infectious. For anyone who might be two to three weeks into their illness, I think although there's still not definitive information on this, the chance of that person infecting someone else is really quite low. Some of these patients were tested 82 days after illness, and people can shed, at least by viral carriage, enough RNA to be detected by a nasopharyngeal swab. The CDC, which previously had managed these people with isolation and so on, have now determined because of this study that these re-positives do not require isolation.

A few words about therapies. Last week, preliminary results from remdesivir were published in the *New England Journal.* This is still a preliminary analysis. The last patient only completed their 28-day course, from what I understood last week, so the full analysis will probably be out in June. In April, a press release noted a reduced length of stay from 15 days to 11 days in the patients who received remdesivir, and this was therefore viewed as a positive result.

Further analysis showed that the drug, which is a nucleoside analog, is fairly safe, but looking at subgroups as in panel D, those who received high-flow oxygen or noninvasive mechanical ventilation, those who needed ventilators or ECMO and panel E seem to have a fair amount of overlap. These were probably patients later in their illness where maybe the antiviral properties of the drug didn't have as much effect, at least at this 14-day mark. As a minimum for these patients, there was not an observable difference.

However, in patients who required oxygen as you can see in panel C, there was quite a divergence, with the sense of the population that recovered who received remdesivir is greater. Although there wasn't a statistical benefit for mortality, there was certainly a strong trend, certainly in this C group, but that was also the largest group in this study. There is still more to be learned about this drug. But remdesivir, at least in the United States, has been a scarce resource. Many hospitals are allocating it to people in their first week or so of symptoms or the first 10 days or so, and those in the hospital for weeks, and so on based on this study.

Another promising treatment but yet still investigational and for which we do not have definitive answers is the use of convalescent plasma. A number of studies are underway, but this is the best study that I know of to date, again a preprint. It has not yet been peer-reviewed, but it's information from Mount Sinai in New York, working with the New York Blood Bank, and was one of the first to gather enough donors who had survived COVID-19 and then administered plasma to recipients. The group used historical matched controls with COVID-19, and there was a benefit at day 14 in oxygen requirements in those who received convalescent plasma. The odds ratio was relatively modest at 86%, but the survival, although with fairly broad confidence intervals and a hazard ratio of 19%, but this only applied to nonintubated patients, suggesting that if convalescent plasma should be given early in the hospitalization if it is to provide benefit.

Faith that's all I have for you this week, there's always much to be learned yet, and every week certainly brings more that we're incorporating into clinical practices. I think we have some questions.

FAITH ROGERS: Thank you for those updates. We will now continue to the listener Q&A.

Dr. Auwaerter, this is our first question: are there any predisposing factors or conditions that have been identified for the multisystem inflammatory syndrome in children outside of COVID-19?

DR. AUWAERTER: Faith, this really has raised a lot of concerns, of course the experience in the New York metro area where there have been over a hundred or I believe even 150 children who have been identified with this, but yet we're still learning about it. Two papers that have come out of the United Kingdom have suggested that, I believe, three-quarters of the patients were of Afro-Caribbean descent and the majority were male. The average age was 11 years. In New York City, there were older children, but the average age was around 8-1/2, and 64% of the initial group put together by the Health Department met Kawasaki criteria, but yet they were more ill. Most important was the word that most of these children did not have identifiable underlying health factors such as asthma, they didn't have obesity and so on. Certainly this will be looked at more closely as we're in the first few weeks of understanding this syndrome, but that's what we know now.

FAITH ROGERS: Thank you Dr. Auwaerter, our last question: are we any closer to more reliable serum antibody testing?

DR. AUWAERTER: It depends what you mean by reliable. A number of reliable tests are available now that probably mean you can trust that a positive result indicates you've been exposed and a negative one, as long as you've waited long enough after the illness, probably means that you didn't experience the novel coronavirus. The Abbott test has published very reasonable data.

The Centers for Disease Control serology, which some might consider the gold standard at the moment, is an ELISA-based antibody test that uses purified spiked protein, one of the key envelope proteins of the virus, and the CDC says that this is 99% specific and 96% sensitive, so it's not quite up to HIV standards but pretty darn close.

If you're asking if this antibody test means you're immune, that's a slightly different question. I don't think we know enough yet. We have to check for neutralizing antibodies, and it's also important that we're learning more and more that antibodies alone may not provide the kind of protective responses and that certain T-cell epitopes are also very important. We discussed that last week, which was a more vaccine-focused webinar, so anyone who's interested may want to take a look at that series.

We still don't have that immunological passport meaning “I know I'm antibody-positive and I feel I won't transmit it.” Part of this is because quite honestly, with influenza you can have evidence of antibodies, yet still harbor the virus and transmit. That's not likely in the first few months after illness, but what's going to happen later this year? If you do waning immunity and so on, I think it's best for everybody not to feel that this test gives them some kind of impenetrable armor, but still to practice social distancing and take care, especially if you have people at risk for ill health at home.

FAITH ROGERS: Thank you for those updates. As a reminder, to claim CME/CE credit please complete the evaluation at COVID19.dkbmed.com and select today's activity. You'll receive your certificate immediately after. Any questions or issues feel free to email us at the address listed.

For any questions, please send them to QA@dkbmed.com that’s Q as in question, A as in answer, at DKBmed.com.

Don't forget to access our resource center at 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. Again, thanks for joining us and thank you for your dedication to your patients with COVID-19. Thank you, Dr. Auwaerter.

DR. AUWAERTER: Thank you, Faith and thanks, very much again for listening, and for everyone that's helping on all fronts with the COVID-19 effort. This goes with great appreciation, and if you have questions please send them in and we'll try to get them answered.