This Week in Virology

TWiV 949 Clinical Update

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Guest: Daniel Griffin

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pdf of this transcript available (link)

Vincent Racaniello: *This Week in Virology*, the podcast about viruses, the kind that make you sick.

[music]

VR: From MicrobeTV, this is *TWiV*, *This Week in Virology*, Episode 949, recorded on October 27, 2022. I'm Vincent Racaniello, and you're listening to the podcast all about viruses. Joining me today from New York, Daniel Griffin.

Daniel Griffin: Hello, everyone. Joining us today from Hawaii, Vincent. [chuckles]

VR: Yes. I'm on the Big Island today where it is 11:00 AM. For you, Daniel, it's just the end of the day, right?

DG: I wish it was the end of the day. It's only 5:00 PM. [laughs] Lots more day to go. [chuckles]

VR: Let's jump in.

DG: [laughs] We will. All right, I'll start with my quotation. “Never be afraid to raise your voice for honesty and truth and compassion against injustice and lying and greed. If people all over the world would do this, it would change the earth.” That was William Faulkner. This is from the speech he gave when asked by his daughter, Jill, to speak at her high school graduation University High School in Oxford, Mississippi, 1951. I'm a huge Faulkner fan, and I actually was reminded of my interest in Faulkner by a recent book I read, *Breathless*, right?

VR: Yes.

DG: David Quammen is also a big Faulkner fan.

VR: Yes, he studied it.

DG: Faulkner had a bad influence on me.

VR: Why is that, Daniel?

DG: I had read *The Unvanquished* right before high school graduation, so I decided, much like the character, I could cut my hair with a pocket knife. Who needed a fancy barber?

[laughter]

DG: I love Faulkner. I love the way his sentences just go on and just how much it's about the language. Let's get right into it. Polio, an interesting week for polio. I think I can say that. As our listeners may or may not have heard, Dr. Janelle Ruth, the CDC's team leader for domestic polio, announced that they are in discussions with New York State and New York City colleagues about the use of the novel oral poliovirus to stop the current transmission of polio here in New York. Not sure that's going to happen. I've been around you too much, Vincent.

[laughter]

DG: Not enough optimism. There was an article recently in CNBC by Spencer Kimball. I'll put a link in the show notes, or someone else will put it in for me, actually. I was really impressed. Some of the things I was impressed by was that he really seemed to get vaccines and what they do. He points out, as we have discussed, that although the inactivated vaccine that most of us have gotten is highly effective at preventing paralysis, it does not stop transmission of the virus.

It doesn't keep you from getting infected, doesn't keep you from spreading infection. The oral polio vaccine is effective at stopping transmission of the virus, but this is temporary. A nice article, hopefully, keeping people on target with what vaccines can and can't do.

VR: Daniel, the problem I have with this is that we don't look for poliovirus in sewage elsewhere so it's very possible that it's throughout the U.S. To just focus this on New York is misguided for one. Secondly, this new OPV, nOPV2, has only been used for a short time. We're hoping it doesn't revert, but we actually don't know. I think it may not be a good idea to fill our wastewater with nOPV2 because we're not sure what's going to happen to it.

DG: [chuckles] You mean it might actually revert? We scientists might be wrong about it being revertant resistant. It might revert just like oh my gosh.

VR: I would never bet on a virus not to mutate.

DG: Yes. I think that's what viruses do. Anyone who believes otherwise - What is it? *Jurassic Park,* life finds a way. There's a lot of truth in that statement. The *MMWR* "Progress Toward Poliomyelitis Eradication - Pakistan, January 2021 through July 2022," so a bit in the news about polio lately. Just background here, after reporting a single wild poliovirus, WPV1, case in 2021, Pakistan reported 14 cases during the April 1 through July 31, 2022. As per this report, Pakistan and Afghanistan are the only countries where endemic wild poliovirus transmission has never been interrupted.

All but one of these 14 wild poliovirus type 1 cases in Pakistan have been reported from North Waziristan district in Khyber Pakhtunkhwa. They also report that an outbreak began in Pakistan in 2019 has been successfully contained. Giving people an update on what's going on out there. The next article is the one that I thought was really the most interesting. I am

hoping that we can regain some confidence in vaccines, which really were damaged, was eroded during the last couple of years. This was an article. You don't have to read it. I'm going to tell you what's in there.

The article, “Polio by the Numbers - A Global Perspective,” was recently published in *JID*. It's a really interesting article looking at our world with polio vaccines versus a world where the polio vaccines had never been created. I don't know how many of our listeners or watchers saw the TV series *Counterpart*. That was a two-season TV series that aired, and I think this is important when it aired, December 10, 2017 through February 17, 2019. In this drama, there are these two initially identical worlds that are created due to an experiment in East Germany, and then the worlds greatly diverge after a severe flu pandemic.

I remember watching this show and thinking, "That's really interesting. They got all this footage of people walking around East Berlin with masks on.” Initially, the one world supposedly remains much like our world, but then the other has this pandemic, and you see these scenes of people wearing masks. In 2022, looking back on this series, *Counterpart*, I'm not sure which of those two worlds is more like our world.

Now back to the paper. In this publication, the researchers use this *Counterpart*, the two worlds. They estimate that because of polio vaccines, five million cases of paralytic polio were prevented 1960 to 1987. Another 24 million cases of paralytic polio prevented 1988 through 2021. In this counterfactual world with no vaccines in our world, about 30 million cases of paralytic polio have been prevented. They even talk a little about the impact of the global polio eradication initiative. When people have hesitancy, just a reminder of just how incredibly powerful vaccines can be. Influenza. The *MMWR,* “Influenza and COVID-19 Vaccination Coverage among Healthcare Personnel, United States 2021 through 2022.”

In a lot of places, this is strongly encouraged that healthcare personnel get influenza vaccination. But, as we see here, healthcare personnel influenza vaccination coverage was 79.9% during the 2021 through 2022 season. They mentioned 87.3% completed primary COVID vaccination, 67% of who received a booster dose. Influenza primary COVID-19 and COVID-19 booster coverage was higher among healthcare workers who reported employer vaccination requirements for these vaccines and was, this is painful, lowest among healthcare workers in the long-term care setting environment. In that environment where we have our highest risk, most vulnerable people.

RSV. Not to be left behind, we are seeing a rapid increase in cases of RSV. You know something is going on when your mother calls you up asks about, “What is this new virus?” It's not a new virus, mom. This is already overwhelming some hospitals. As I mentioned, a tripling of cases just over the last two months based on CDC surveillance data. We're already at basically last year's peak and here we are still in October. This is part of that tripledemic that people are talking about. Some exciting data though on RSV vaccines was presented at IDWeek. I will just mention one of the studies.

There's a lot background here on RSV and why it's taking so long, but the article, “Phase 1/2a Safety and Immunogenicity of an Adenovirus 26 Vector RSV Vaccine Encoding Prefusion F in Adults 18-50 Years and RSV Seropositive Children 12-24 Months,” was published in *JID*. This is basically the results of a small randomized double-blind phase 1/2a

placebo-controlled study with 12 adults and 36 RSV seropositive children randomized to different doses of the vaccine or placebo at day one and day 29 with six-month immunogenicity and one-year safety follow-up. Interesting, RSV infection was an exploratory outcome in children. That's of course what we're all going to care about.

No vaccine-related serious adverse events were reported. That's encouraging, small sample. They give us baseline geometric mean titers showing increases. Not sure if we know exactly what that translates into. Here, RSV infection was confirmed in fewer children that received the vaccine. That was 4.2%, than placebo, which was 41.7%. Almost a tenfold reduction. You got a hand up there, Vincent.

VR: Yes. Given the delay, it's easier to raise my hand to ask a question.

DG: [laughs]

VR: Did they actually look for blocking infection, so they did PCR on these kids?

DG: At least my understanding was that this was infection-confirmed. It was not just screening people with PCRs. It was symptomatic, confirmed to be RSV. We're doing PCR to confirm RSV in most cases.

VR: OK.

DG: I should say in most cases because a lot of our urgent care centers have these quad antigen rapid tests, which are really nice. Someone comes in, they've got some upper respiratory symptoms, and we'll go ahead and we'll look for influenza A and B. We'll look for COVID and we'll look for RSV with these rapid tests. If you have more than one, it makes sense. As far as treatment, it's going to guide treatment, but also it's going to help with prognosis. We'll talk about some data in the future. If you have more than one thing, not surprising, your likelihood of progressing to hospitalization, your likelihood of a worse outcome increases.

Ebola, next week. People are, "Why, Dr. Griffin, haven't you been talking about Ebola? I understand you're heading to Uganda in a few weeks. What's up with Ebola?" I have been keeping my eye on it. Next week, we will be recording at the annual meeting of the American Society of Tropical Medicine and Hygiene. I will add some information about the current situation with Ebola in Uganda at that meeting.

Now to the monkeypox. Still trending down in terms of new cases being diagnosed per day, but we are now up to six deaths, maybe more from the monkeypox. Just announced that two people here in New York had died. Two people in Chicago, a man in Nevada died over the last week. With monkeypox virus, always the question about how much did that play a role in the death? One of the concerns, and maybe the WHO is right on this, is that we are seeing more severe infections. This has me concerned that we're missing a lot of the mild cases. I don't think that suddenly the monkeypox has become more virulent. When a higher percent of the cases are more severe, you worry that's just that we're missing all the less virulent cases.

We did hear about the JYNNEOS vaccine. An impressive number here in the *MMWR*. “Receipt of First and Second Doses of JYNNEOS Vaccine for Prevention of Monkeypox - United States, May 22 - October 10, 2022,” early release. We heard that by October 10, a total of 931,155 JYNNEOS vaccine doses had been administered in the United States. Almost a million doses so really impressive. Remember that we're still learning here. If you get diagnosed with monkeypox, if you make the diagnosis of monkeypox, let's get folks involved in the STOMPTPOXX.org trial to see if our antiviral works.

COVID. Right up front in the COVID section, I want to start with an article that actually addresses a concerning challenge for us. This is the article, “Distinguishing SARS-CoV-2 Persistence and Reinfection: A Retrospective Cohort Study,” published in *CID*. Here's the scenario. A person had COVID recently and their PCR is positive admission, what to do? Here, all individuals at a large academic medical center who underwent a SARS-CoV-2 nucleic acid amplification test, I like they call it that, not a COVID test, greater than or equal to 45 days after an initial positive test, both tests had to be between March 14 and December 30, 2020, were analyzed for potential reinfection.

Inclusion criteria required having at least two positive NAATs collected at least 45 days apart with a CT value of less than 35 on all the repeat tests. For each included subject, the likelihood of reinfection was assessed by viral genomic analysis of all available specimens that had that CT value less than 35, a structured CT trajectory criteria, and a case-by-case review by infectious disease physicians. We start with these two infectious disease specialists up at Massachusetts General Hospital in Boston. They are tasked with categorizing the patients as either being low or moderate to high clinical suspicion for reinfection based on chart review.

They're asking the ID, "What do you think?" The ID doc says, "Ah, I think this is just remnant. Viral shedding, as people tend to say. No need to worry here." Then they get CT values, but the ID clinicians don't have access to that yet, and then they go ahead and they get genomic data to really ask, "Is this that prior infection or is this a new infection that is distinct?" They found, and this is a bit frightening, that clinical and CT value-based assessments fail to identify 1/3 of genomically supported reinfection. A third of the time, we're getting it wrong as ID docs. A third of the time, that CT value is not giving us the information. A lot for discussion here.

A couple of things that were disturbing here, I will say. Immune-suppressed people with CT values that stayed in the 20s for past two months, as they described here, are they still infectious? How does this impact our utilization of private rooms? I don't know if I shared my discussion with the Germans who thought we were all crazy putting all these people with COVID in the same rooms and not doing any sequencing. Perhaps SARS-CoV-2 can recombine. We're just creating these little mixing pots in our hospital. A little challenge here and may be necessary to redefine how we approach re-infections and infection control issues. Vincent, I don't know if you had any thoughts.

VR: What we're saying here is that a fraction of the time, these are re-infections, because the genome tells you it's a different virus, let's say. Correct?

DG: Yes.

VR: That's one thing just to clarify so that people understand that it's not persistence. In some cases, it's persistence. The other issue is you're worried about putting people in the same room because you're worried that these different viruses are going to recombine. I would say this has been happening for two years now. Two years plus out there in the wild, these viruses have had the opportunity to recombine. It's happened. Nothing untoward has come of it, so I'm not sure that's an issue that should drive how you're housing these patients.

DG: Yes. I think that's important. The first part is pretty straightforward. Someone comes in, we say, "Does this person need isolation?" A third of the time, maybe we're getting it wrong. We say, "No, they were positive 50 days ago. This is probably just from that infection." Maybe we're missing a new infection and we're putting someone - We have billions of people participating in the evolution of SARS-CoV-2 out there in the world.

Children, COVID, and vulnerable populations. This was, I thought, a little sobering. According to the Government Accountability Organization, they are attributing 25% of maternal deaths in 2020 and 2021 to COVID-19. As they say, COVID-19 contributed to 25% of maternal deaths in 2020 and 2021. Just continuing to point out which populations are high risk. Some updates on vaccines and children here. The CDC's independent vaccine advisors voted 15 to 0, that's unanimous, Thursday, 10/20/2022 to add most COVID-19 vaccines offered in the U.S. to the childhood, adolescent, and adult immunization schedules. Just some background here because I know this has been taken out of context, I'm going to say.

The immunization schedules are updated every fall before going into effect the following year. The COVID vaccine’s inclusion on the schedules does not constitute a mandate, particularly for school children. This is the purview of states, localities, jurisdictions depending on local laws. The committee also unanimously voted to add COVID-19 vaccines to the Federal Vaccines for Children Program. This is important. This move allows the shots to be provided for free to children of families who might not otherwise be able to afford them such as those who are eligible for Medicaid, underinsured or uninsured, Alaskan Native, American Indian.

Also adding COVID vaccines to the routine childhood immunization schedule is the first step in potentially getting the shots covered by the Vaccine Injury Compensation Program, which is a more established program that allows for those who may have had vaccine injuries to pursue settlements from the federal government rather than the vaccine manufacturers. I will comment, we're hearing that the prices on these COVID vaccines may be over $100 per shot. The idea that we're going to have free access for the underserved I think is very important from an equity point of view.

Human Health and Services would also have to formally add vaccines to the VICP and Congress would have to pass legislation, so there's a lot that needs to go on here. A lot of this is really a move toward an acceptance that COVID is here to stay. Just one more vaccine in the list of vaccines we use for preventable illnesses. I will point out one thing which I think is interesting. There's already over 20 states that actually have state laws on the books that prevent wide mandates for COVID vaccines. It's an interesting move at the state level.

The pre-exposure period, I'm going to do a little bit of a reminder on masks next time because people seem to have forgotten their effectiveness. Remember, this is the time when I tell people you should have a plan. Part of that plan is getting your COVID vaccination. We did get a little bit of movement here. Novavax got approval EUA as a booster on October 19, 2022. This is a change.

Let me read the revised fact sheet. What exactly does this mean? Novavax COVID-19 vaccine, Adjuvanted, is authorized for emergency use to provide a first booster dose to individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and to individuals 18 years of age and older who elect to receive the Novavax vaccine Adjuvanted because they would otherwise not receive a booster dose. Little subtleties here. This is a first booster dose, this is not a second, third booster dose. It's the same dose. It's 0.5 milliliters of the Novavax vaccine at least six months after completion of a primary vaccination series.

“Dr. Griffin, but does this stuff work?" There is some data here. I was able to find a pre-print. I should say it was shared with me, so thank you. The pre-print, “Novavax NVX-CoV2373 Triggers Potent Neutralization of Omicron Sub-lineages.” Here they report that after a third dose of Novavax, there were high titers of antibodies against Omicron BA.1 and BA.4/5 with responses similar in magnitude to those triggered by three doses of an mRNA vaccine. Not sure we know exactly what that means, but that's the data that we've been working with.

We also heard last week Moderna says Omicron booster response stays high through three months. Interesting on a few levels. One is that the booster was approved August 31, and here we are with three months of data. I just want to point out that a lot of people are like, "They released these boosters and they never gave them to people." Obviously, if we have three months of data, this means human beings had gotten this vaccine prior to approval. I do know that the mouse data was what was presented, but we did actually have human beings. We had safety. That was a myth that boosters were released prior to being giving to human beings, but it's a myth with long legs.

This people will like or not like, it depends if you enjoy exercise, but the article, “Association Between Regular Physical Activity and the Protective Effect of Vaccination Against SARS-CoV-2 in a South African Case-Control Study,” physical activity and the protective effect of vaccination against SARS-CoV-2 in a South African case-control study published in the *British Journal of Sports Medicine*. This is another one of these test-negative case-control studies that they use to estimate the risk of having an associated COVID-19-related hospital admission among individuals who were unvaccinated compared with those who were fully vaccinated with the J&J vaccine.

196,444 participant tests were stratified into these three measured physical activity subgroups, low, moderate, and high activity, to test the hypothesis that physical effect is an effect modifier in the relationship between vaccination and hospitalization. Vincent, I have to say, I'm wondering if you just forgot about vaccination and just looked at low, moderate, and high activity and exercise.

Anyway, they reported that vaccine effectiveness against a COVID-19-related admission among vaccinated individuals within the low-activity group was 60%, 72% for moderate,

85.8% for the high-activity group. Compared with individuals with a low activity level, vaccinated individuals with moderate and high activity levels had a 1.4 and 2.8 times lower risk of COVID-19 admission respectively.

VR: That's very impressive, don't you think?

DG: I'm trying to figure out is it the exercise or is really the exercise and the vaccine.

VR: Plus the vaccine, yes. [crosstalk] In line with that, Daniel, someone asked last night, does it matter what time of day that you get the vaccine? Is it better in the morning or does it not matter? Do you have any thoughts on that?

DG: It's really critical that you get it in the evening. No, I'm joking.

[laughter]

DG: I can't say that we've studied that, but it's an interesting thing to think about. We get our AM cortisol surge. Would it be better to get it in the evening because maybe there's going to be more reactogenicity, more immune response? I don't think we know. It's interesting. We've been using vaccines for so many decades. These seem like interesting studies. Let's get antibodies and T cells, let's vaccinate one group in the morning and one group in the evening. Then you worry now that's going to be a problem because what we all have to work in the evenings because the best time to get a vaccine is 9:00 PM, right?

VR: Sure.

DG: Maybe we don't want to know, Vincent.

VR: Yes.

[laughter]

DG: Don't let science stand in the way of your lifestyle. COVID passive vaccination, Evusheld, so tixagevimab co-packaged with cilgavimab, still recommended for adults and pediatric individuals 12 years of age and older who have moderate to severe immune compromise or may not mount an adequate immune response, or can't get the vaccine. We did get the article, “COVID-19 Outcomes in Solid Organ Transplant Recipients Who Received Tixagevimab-cilgavimab,” (Evusheld), “Prophylaxis and/or Bebtelovimab Treatment,” so mAb treatment, “in a Nurse-driven Monoclonal Antibody Program During the Omicron Surge.” This was published in the journal *Transplantation*.

We have an interesting table looking at those that developed COVID-19, those that were hospitalized, those that died. Seeing here in the Evusheld 150/150 group, about 28.5% developed COVID-19. We can compare that to the 150 and then later they get 150/150. I don't know if people remember when we bump the dose in the middle. With an N of 35, nobody in that group developed COVID, nobody got hospitalized, nobody died. If we looked at just the higher dose, the 300/300 just given upfront as one, we saw 7.6% develop COVID-19, only 1.2% were hospitalized, less than 1% died. Just more data, but really it's hard. No placebo group here so just hard to sort out what the exact impact is here.

This is the depressing part of today's talk. The article, “Omicron Sublineage BA.2.75.2 Exhibits Extensive Escape from Neutralising Antibodies,” posted as a preprint. In this context, I'm fine with bringing this up as a preprint as this is really a neutralizing antibody information. There's a table looking at the neutralization of the different monoclonals out there with the different variants, and unfortunately, not looking great for the tixagevimab-cilgavimab. They actually put them together at BA.4.6 not doing well, BA.2.10.4 not doing well, BA.7.5.2 not doing well. I assume this is pseudovirus neutralization assays.

I couldn't really sort that out from the preprint, I shot an email to one of the authors, so hopefully, I get some clarification. Concerns going forward to patients who are relying on this for protection as we see more of these variants. Moving into the early viral upper respiratory phase, this is really a reminder. Number one, the number one recommended treatment is Paxlovid with that 89% to 88% reduction in the unvaccinated, probably about a 75% reduction in the vaccinated. We keep hearing about this rebound. I have to say, this is impacting negatively people getting this tremendous benefit.

Recently, I had a 68-year-old, had some medical issues, was carrying some extra weight, and we had a really long discussion because they were not sure with all the negative things they had heard about Paxlovid. I laid it out for them, I said, "OK, here's where you stand. Before we had any therapies and vaccines, about 20% of folks were ending up in the hospital. Your risk probably was a little bit higher at baseline, let's say, 30%. You got your vaccines. Let's say we drop you down to 3, that's 1 in 30. We can drop you down to 1 and 300 if we add Paxlovid to this." Sometimes you really got to walk through with people.

The goal is not to turn this into a five or six day illness. The goal is to keep people out of the hospital. The goal is to keep people from dying. The goal is to keep people from progressing when they end up on a ventilator with permanent damage to their lungs. Just really tough, let's focus on the science. Number two, remdesivir. About an 87% reduction based on that *New England Journal of Medicine* article if given in the first seven days. Really difficult to get access here, but a great option when we have access. Number three, head to head a little bit inferior to the first two choices, that's our bebtelovimab, our monoclonal. The science we have suggests this should not be your first but your third choice.

Number four, molnupiravir with about a 30% reduction. Avoiding the steroids, avoiding the antibiotics. Hopefully, patients are then doing well and most of them are not progressing to severe second-week early inflammatory. That's where we have less effective tools, steroids in the right patient at the right dose. Remember, this is only about a 17% mortality reduction. Not an 89% reduction in progression but only a 17% mortality reduction. Anticoagulation, pulmonary support, maybe remdesivir if we're still in the first 10 days but diminishing returns, immune modulation.

I will say there were some interesting presentations that IDWeek revisiting immune modulation. We got some results from the ACTIV-1 IM looking at infliximab and abatacept versus placebo for COVID-19 pneumonia. Infliximab is a TNF-neutralizing monoclonal and abatacept is a soluble cytotoxic T-lymphocyte associated protein 4 analogue that prevents antigen-presenting cells from delivering that co-stimulatory signal and activating those T cells. More immune modulation for week two, the rebound period, I like to call it the early inflammatory phase.

The primary endpoint for time to recovery was not statistically significant. Interesting, the secondary outcome was mortality at day 28. This occurred in 10% of the infliximab patients compared to 14.5 of placebos odds ratio 0.59 in 11% of the abatacept patients versus 15.1% of placebo patients there. Patients on low-flow oxygen and those with higher levels of CRP appeared to benefit more. Little data mining, I think, when you start breaking it down there, but I'll just say that, but not data to suggest that restrictive stewardship criteria where we only give this to people on high levels of pulmonary support that are the least likely to benefit. Think about that as we start considering these newer agents.

Also our old friend or is it a new friend, sabizabulin. [laughs] These are the results of a subgroup analysis of a phase three trial of ADA patients with a documented comorbidity who also needed oxygen by mask or nasal prongs. Deaths were significantly lower among those receiving oral sabizabulin compared with those on placebo. 5.2% versus 27.6% with a P value of 0.0090. This was reported by Dr. Paula Skarda of Regions Hospital in St. Paul, Minnesota. Patients that ended up getting sabizabulin also saw significant reductions in length of hospital stay, 13 versus 24 with placebo, days spent in the ICU, 4 versus 17, or on a ventilator, 3 versus 17.

Interim analysis, the full trial population which included patients with a WHO score of 4 to 6 showed a 51.6 relative reduction in mortality at 60 days with this oral microtubule disruptor. An FDA advisory committee is slated to meet next month to discuss whether the data are sufficient to support the EUA of sabizabulin in patients with moderate to severe COVID-19 at high risk for ARDS. This may be the right therapy for those sicker individuals.

We also had the article, “Tocilizumab Versus Baricitinib in Hospitalized Patients with Severe COVID-19: An Open Label, Randomized Controlled Trial,” published in *CMI*. As in the title, these are the results of an open-label randomized control trial addressing whether or not baricitinib was non-inferior to tocilizumab for immune modulation in COVID-19. Impressive that toci's become the gold standard to which you don't want to be inferior. The primary outcome was mechanical ventilation or death by date 28. Secondary outcomes included time to hospital discharge by day 28, change in WHO progression.

The authors assigned 251 patients with COVID-19 to receive toci, that was 126, baricitinib, 125, plus standard of care. They found that baricitinib was non-inferior to toci for the primary compositive outcome of mechanical ventilation or death by day 28. Baricitinib was non-inferior to toci for time to hospital discharge within 28 days, and no significant difference in WHO scale at day 10 as far as severity. More on the immune modulation front.

I will close as I always do with no one is safe until everyone is safe. This pandemic continues with hundreds of people dying per day here in the U.S., hundreds more if not thousands more around the world. Pause right here and thank you for everyone who does this, go to parasiteswithoutborders.com and click on the Donate button. Every small amount counts and we are really close. This is going to drop on Saturday with just a couple days left in our Floating Doctors fundraiser. Help us reach our goal, help us provide that potential donation of $40,000 to Floating Doctors.

VR: It's time for questions for Daniel. You can send yours to daniel@microbe.tv. Josh writes, "For a high-risk individual recently infected with SARS-CoV 2, does it make sense to take

multiple treatments? My grandmother is in her 80s, a kidney transplant recipient boosted recently on Evusheld, thanks to *TWiV*, she tested positive for SARS-CoV-2. Her hospital, having ruled out Paxlovid, is giving her bebtelovimab. Would it helped for her to also take remdesivir? It's hard to tell whether of the four recommended early treatments, Paxlovid, remdesivir, bebtelovimab, and molnupiravir, each patient is supposed to take only one or take as many as seems safe."

DG: This is great, and hopefully, this is a learning lesson for us. We do not know how people do when they get multiple therapies. We've talked a little bit in some of our *ID Puscasts* about sometimes when we give multiple antibiotics for bacterial infections, actually people do worse than if they are on the one best therapy. That's different with tuberculosis, it's different with HIV, so it would make sense, it seems to make sense giving someone a monoclonal, giving someone an antiviral that works by another route. We don't know, we need to do the studies.

There's anecdotes out there, there's people doing this out there, but ultimately like everything else we need to have that humility to say this is an interesting question. We need to ask it properly. We need to get the right science because COVID is here to stay. These decisions are going to continue to be in front of us. Once these are licensed, we don't want people doing willy-nilly. We want evidence-based guidance giving us the best outcomes for our patients.

VR: Lillian writes, "I've heard you speak many times about not giving steroids in the early phase of COVID treatment, and I'm wondering if you could explain in layman's terms the science behind this, so to speak, and why it's not a good idea. An acquaintance of mine just tested positive for the second time and was definitely given steroids early the first time. I wanted to be able to pass along your knowledge with a more detailed explanation other than to just tell them it's not a good idea as I know they will ask me why."

DG: [laughs] I think the real why is we've studied it. There are a couple of articles, and we'll leave links in the show notes. One study actually looked at people getting steroids during the first week, and overall progression to severe disease and hospitalization was increased six-fold if they gave those to folks during the first week with oxygen saturations greater than 94%. They actually had a mortality increase of 35%. Another study where they did greater than 20 milligrams per day of prednisolone equivalent, that had an associated hospital admission odds ratio of 2.5, more than doubling cardiac events, almost tripling your risk of pulmonary embolism. Then, again, a 3.5-fold increase of mortality.

The science, we studied it. It's associated with increased risk of progression, increased risk of death. Why is it? What's the mechanism? What do we think the mechanism is? We think it's during the first week when your body is trying to respond to the virus and prevent ongoing viral replication. You're basically shutting it down. People who've been vaccinated and get steroids, they say, "Why did you even bother with the vaccine?" Here was your chance for your primed educated immune system to jump in, and you just turned it off with the steroids. That's the mechanistic idea behind the science.

VR: Mary writes, "Please speak to when baseline LFTs PT/INR and eGFRs are needed for three-day remdesivir prior to administration and whether retesting during the course is

needed. Since the course is so short and it can take more than 24 hours for outpatient lab results to be available, it's likely that timing for the second and third dose may roll around before test results are known."

"Was this retesting initially recommended for a longer course of remdesivir? The PINETREE study suggests that outpatients with mild to moderate COVID-19 administered three-day remdesivir may not require baseline creatinine if they weigh over 48 kilograms. What about baseline LFTs and PT/INR? What about retesting? Any insights you have would be appreciated."

DG: These are great questions. The eGFR, for our listeners, that's really an estimate of kidney function, estimated glomerular filtration rate. Initially, when remdesivir first came out, there was a lot of hesitancy to use it in people that had compromised renal function. At this point in time, there's a lot of literature, there's a lot of experience using remdesivir independent of kidney function, so I'm not concerned about kidney function. Also, good evidence that remdesivir does not cause renal failure, so just I'll put that out there. You can send me hate mail, but no, search it, look at the literature. At this point, we feel like remdesivir is a very kidney-safe medicine.

What about liver function tests? What about elevated liver function tests? There is a rare situation with the liver function tests, those AST/ALT, the transaminases are five-fold or more above normal where it's recommended that we not do remdesivir. Again, that was based on these early trials, 5, 10-day courses. With a 3-day course, I think you can look at the risk-benefit there.

A lot of the settings where you're going to be able to give IV remdesivir, you could probably get a comprehensive metabolic panel back pretty quickly. Again, it's a risk-benefit. If you've got someone that you're worried about that's high risk, here's your opportunity to reduce the risk of progression by close to 90%. I think it's reasonable to go ahead and then try to get the data when you can.

VR: Finally, Kathleen writes, "Thank you for discussing the recently reported occupational exposure of the nurse to monkeypox virus resulting in an infection. As reported in *MMWR*, the needle stick occurred when recapping the used needle by hand before disposal. I think this might be a very good teachable moment. I can't help myself as a clinician and safety professional to remind never recap a needle. If one must absolutely cover the needle prior to disposing in a sharps container, then utilize the one-handed technique. Just my two cents when discussing the needle stick that results in a Jenerian pustule four days later. Thoughts?"

DG: [chuckles] Yes. Kudos. I was listening to the *MMWR* podcast weekly briefing and just as they described the exposure when the person was recapping the needle. Come on. Let's be more careful.

VR: That's *TWiV* weekly clinical update with Dr. Daniel Griffin. Thank you, Daniel.

DG: Oh, thank you so much. Everyone, be safe.

[music]

[00:46:07] [END OF AUDIO]