This Week in Virology

TWiV 603: Cloudy with a chance of coronavirus

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Guest: Daniel Griffin
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This is a partial outline only of Dr. Griffin's update on COVID-19 clinical situation

Listeners have provided a lot of good feedback on his discussions sharing his experiences and sorting out what to do next

Still seeing loss of smell and taste with COVID-19 infections and is more pronounced than just nasal congestion. In fact, this occurs with minimal to none nasal congestion

1. In most cases it is transitory, 1-2 weeks
2. It begins with a disruption where foods taste chalky, which does improve

Other manifestations we have seen in our patient population of 0.5 million people in involve almost every specialty

1. Skin: patients may feel that their skin is sort of buzzing, vibrating, or burning.
   Not only subjective findings are being reported but objective findings ranging from rashes (some are quite impressive) to: vasculitis and thromboembolic or ischemic changes. Some patients have even presented with black toes
   There may be more skin issues in children and dermatologists are making the diagnosis

2. Neurological impacts: patient presents with a history of falling. Sometimes it is due to balance: one gentleman said that he had to hold on to things and when he lost his grip, down he went.
   Sometimes it is a direct neurological manifestations (as reported in JAMA and NEJM) where there is a whole range of neurological affects: sometimes they are falling secondary to hypoxemia or, especially in some of the younger patients; they just lost the strength. The general malaise and weakness is knocking them down. We aren't seeing as much true encephalopathy but there is some, presenting as glassy-eyed with a zombie-like stare, especially in cases of hypoxia with requirements of high oxygen in the ICU. However, there has been full-fledged encephalopathy, where the patient is confused, combative, and even hallucinating. Chris Cuomo described hallucinations. Last week Dr. Perlman was discussing a possible neurotropism vs. medication effects while the blood brain barrier is open. But the symptoms have been seen both in patients on medications and also not on medications. There have been arterial occlusions to the brain, presenting as strokes
   A lot of times outpatient docs will get a call where the patient says "I just feel really unsteady, my balance is bad" and this is their COVID-19 presentation

3. Chest pain: usually occurs in the second week. This can be a combination of things,

such as a direct cardiac problem but the virus itself seems to be able to directly or through a secondary process impact the heart. There were a few patients that on evaluation appeared to be having an acute MI, but catherization showed clean coronaries, so it is part of the viral syndrome. We have a patient now undergoing evaluation and we are concerned because she is a woman in her 30s, who should not have CAD but does have severe chest pain, which could be consistant with that diagnosis

4. Kidney: a recent publication showed an EM of podocytes with viral particles within the podocytes. We are seeing renal effects from the virus as well as dehydration because people aren't eating or drinking. The lungs are managed by keeping them dry, which is not so great for the kidneys. So fluids have to be liberalized in some patients

5. Surgical issues: in the outpatient setting, at times patients are frightened of going to the hospitals even with obvious appendicitis symptoms and perforated appendicitis is more common. They have to be treated for the COVID-19 infection and the complications inherent in a ruptured appendix with the overwhelming inflammatory milieu affecting healing and coagulation problems. There is so much COVID-19 that the usual problems outpatient docs see regularly are now much more of a challenge

6. Hypercoagubility: we are seeing people who have made it through to the second week and are feeling better, only to develop a clot. There was someone recently, who thought they were better but on week 2, developed a big clot in his leg. This is now occurring in the outpatient setting at the tail end with patients who didn't require hospitalization. It is not easy to treat these patients because of the increased risks. Prophylactically treating them may cause harm because of a medication effect of a medication that they didn't necessarily need.

On TV 700-800 people in the area die every day with COVID-19 in the hospitals, but we are seeing about 200-300 people dying at home. Part of these numbers are due to COVID-19 cases but part of them are due to people failing to seek medical care because of COVID-19.

7. Outpatient coagulopathy: we are now seeing so many clots in the outpatient setting- Patients presenting to the ED with large PEs

8. Common hospital course: patient is admitted and started on a little O2, which increases to require a Venturi mask. This then progresses to full high O2 concentrations.

Treatments: ***IL-1 inhibitor Anakinra*** (normally for RA) has been used but hospitals have moved away from this as it has not seemed to help but rather to harm by shutting down the immune system for a prolonged period of time. This has necessitated other antimicrobials as they developed fungus in the blood or other infections and ultimately died. Again, you can potentially do harm with the treatment so we have stepped back there

Steroids and IL-6 inhibitorTocilizumab*:* a recent study published on 40 patients showed that within three days 75% dropped O2 requirement, 90% did well (in contrast to *remdicibir (? Spelling)*where only 60% did well). We are continuing to have that experience and finding that the combination is becoming

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Dr. Daniel Griffin's update on COVID-19 clinical situation:

> the standard of care as it seems to be keeping people off the ventilators. This regimen decreases the O2 needed and prevents the late stage high O2 requirement. This has been a positive experience for us but we are waiting for more studies because evidence based medicine is much preferred over "cowboy medicine" We need large placebo controlled blinded studies to confirm that this is actually true

One of the things that we are running into is that the first week we are dealing with a virus but subsequently there are lot of immunology issues in the second and third weeks. To their credit TWiV has interviewed many immunologists recently. However now, we are starting to deal with a lot of hematology problems

Next in line for TWiV should be hematologists. We are doing a lot better with avoiding the cytokine storm, keeping people off ventilators, as we know that mortality is very high when ventilators are used. Therefore not using the ventilator is a positive thing. However many patients are having clotting disorders even when they are on. what we think, is full dose anti-coagulation

Not only are we seeing pulmonary emboli but the renal doctors will be trying to do dialysis on a patient and the IV keeps clotting off. So we are starting to see a mix of things:

1. a small percentage of patients re developing inhibitors to the clotting cascade that is much like a lupus anti-coagulant, The Russel Viper Venom test is used to determine if the lupus inhibitor is present. These patients need to be anti-coagulated in a slightly different way – Vitamin K (rat poison) is used
3. Others who are on full high dose low molecular weight heparin seem not to be responding appropriately so we are looking for alternative treatments and waiting for publications to help figure this out in the next week or so. However, upon discharge, patients who have had a significant amount of disease go home on blood thinners such as coumadin or the novel anticoagulants: meds that act directly on Factor Xa, or thrombin

Another problem is the people who have been on 100% O2 for weeks and are not really better and we have not figured out what to do. Some may be undergoing thromboembolic disease and when SOME of them are placed on anti-coagulation, SOME of them get better.

We have had a few patients who have already received IL6 receptor inhibition early on but now are sitting at a plateau where they were the sickest of the patients. We thought that they would require ventilators but a second dose of IL6 *Tocilizumab* allowed the O2 requirement drop from 100% to 40-50% within a 24hour period, One patient had been on 100% for 13 days and his wife called begging us to try something. That night the hospitalist gave him a second dose and by the next afternoon O2 requirement dropped by 50%

Another group continue to get worse, despite anticoagulation and a second dose. We have tried BAL (broncho-alveolar lavage) on these patients, where a tube is placed into one of the branches of lung where fluid is placed in and then aspirated out. We have tried this because on CT scans the air spaces appear to be full of something that contains a lot of inflammatory cells. The washes are coming back with histiocytes, lymphocytes, neutrophils, eosinophils, and no fibrin but lots of this gunky plastic-like thick material that is filling the air passageways. We don't know what this is, but we have a growing number of patients that need to be on oxygen and we

are not really sure about how to treat them. It will probably require a multifactorial approach, with people who will have different reasons of why they aren't coming off the O2

We want to show that people who have been in the intensive care unit for 3-4 weeks are virus free, once we get them out into the world but they are still PCR (via nasal swab)positive for weeks. This has been discussed on TWiV – but we don't know if this represents viable infectious particles or just remnants

To obtain the specimen a swab of mucus is collected from the middle turbinate and then we send it off for the qPCR (quantitative PCR). In the study we did in Seattle we compared qPCR on the middle turbinate swabs vs the anterior nares. The average quantitative number in the Seattle study was 14, which is high. The anterior nares are coming up at about 32.This number would be a good way to determine if we are making some progress, if the qt levels dropping. The cut off at most labs for a positive is 37 but there is quite a difference between 14 and 35

(for the listeners' who are not familiar with the qT for quantifying), the virus load is like a golf score – big number is less virus, low number id more virus – bassackwards from what you would expect

Several times it was pointed out how the virus is important in the first week, and the cytokines in the second week or third week. The question was asked about whether the first or second week is relative to when the patients were presenting or actually infected? Clock starts at the day of symptom onset, which may be difficult to determine from the patient history. This would be the first day that you feel like you are not doing OK, not necessarily really bad, but you feel like you are coming down with something. This is important because there tends to be this clockwork like progression: mildest cases – not much symptoms beyond a day or two. Children, for instance, seem to be responding almost memory-like.. They get a fever for a day or two and then they are all better. Very short duration. Mild disease – they have symptoms until about day six and then are better and that's it, Then there is the next level, where patients say 'the first week I must have had something else but it's the second week when I really got the COVID' This was described really well on a previous TWiV, where Ian did a great job; it is that second week where you really feel what we think is the cytokine response, and really feel terrible. That's the point where people feel bad enough to end up in the hospital or they feel terrible but are able to ride it out at home. People with comorbidities tend to have that crash, decompensation at about day 7, whereas younger healthier people who decompensate do it on day 13 or 14. Once you get past that window you should get better except that we are now seeing thromboembolic complications that actually happen at the end of the second week into the third week

The last time hospital admissions were discussed, they were described as two inches under water. Now they are two inches above water. There is enough oxygen and beds. The census dropped just a little which means instead of being above capacity we are just below the limit, which is huge. The census of all 22 hospitals had been up to 3,600 and now it is down to 3,200 of patients with COVID. We are doing a better job of keeping patients off of ventilators. We aren't sure about the long term effects 0f hypoxia on the nervous system but these people look pretty good and we know what happens when we use the ventilator. Admissions are better, census is better, but the death rate is holding steady. It is about 700 in the hospitals and the deaths at home are 2-300. This does not include the nursing home deaths. The challenge is where do we go from here.

Quantity of ventilators was adequate. We didn't have the Italian experience,, which was when a patient in their 40s or 50s came in, they would have probably been OK but they were sick

enough to require ventilator support for a short period of time but there were not any vents, so those people would just die. We did get close to that point but we never got there and I think that is huge and thank everyone for the cooperation with social distancing.

Social distancing is difficult psychologically so people have adapted the restrictions to social 2-3 family cohort distancing or small quaren*teams*, where three or four young people will stay together and live in the same home. Modifications are necessary if social distancing is to be sustained for any lengthy period of time

Transcribed by Dr. Karen Lawson