VCHIP CHAMP VDH COVID-19

May 7, 2020 | 12:15-12:45pm Call Questions and Answers*

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Practice Issues – Testing Update – Breena Holmes, MD, VDH

VDH Public Health and UVMMC labs are now accepting nares swabs (front of nose). The CDC is now recommending full PPE for this collection method. We will continue to address this. We have an instructional video for proper collection (per CDC guidance) in development with Becca Bell, MD. The need for full PPE throws a wrench in this testing strategy. We do not have the supply chain of PPE for broad-based testing of kids in practices. Some talk about having kids do their own collection from the nares. We are awaiting a plan for test kit distribution. Please stay tuned. The testing task force is standing up pop-up sites for first responders and healthcare professionals who are asymptomatic. This effort is organized by VDH with the VT National Guard. Drs. Raszka and Lee will be on tomorrow to discuss issues with testing asymptomatic individuals.

Practice Issues – Pediatric Multi-System Inflammatory Syndrome – Matthew Hollander, MD, Pediatric Rheumatology, UVM Children's Hospital, UVMMC

I'm going to focus my attention on summarizing this inflammatory syndrome, which we're now recognizing is more in a spectrum characterized by features that overlap with Kawasaki disease, toxic shock syndrome, and more broadly, cytokine storm syndrome. Just as important, I want to convey that solid primary care awareness of these cytokine storm pictures will facilitate early targeted therapy and that's going to help decrease morbidity and mortality. To that end, preserving access to our primary care doctors is going to be very crucial. Dr. Raszka gave a very thorough background on the advisories put out by our colleagues in Europe sounding the alarm on this COVID hyperinflammatory connection. Getting back to last week, we already knew about the early Chinese reports about the increase in ARDS and elevated pro-inflammatory cytokines. Doctors back then were suggesting that immunomodulators that we already used in the treatment of a variety of conditions, including those in rheumatology could be used. So, what's changed? Some of the stories in the press that patients might expect us to know include pieces published in the New York Times and Washington Post just earlier this week about the experience in New York and a few other cities. This week the New York Department of Health reported 15 patients ages 2-15 with typical Kawasaki-like presentation. As of last night, that number is up to 64 cases reported in New York. A handful of cases have also been reported in other states, including the original California case report out of Stanford. In addition to the British advisory, at least 50 cases have been reported in Europe, notably in Italy and Spain. A cluster of 20 Kawasaki-like cases were reported earlier this week in Montreal. Interestingly, they all tested negative for COVID-19 using NP swabs.

So, how common is it? It appears to be a relatively small number so far. Larger registries to address this in the U.S. are currently being set up. It is going to be difficult to address whether this number is over or underrepresented in the press right now. I personally, I suspect we're underreported right now, because clinical teams are busy enough. For the time being, I would expect that the true number is lagging behind current reports.

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On the pediatric rheumatology listserv, there has been discussion about the connection between cytokine storm syndrome and morbidity in adults for over 2 months. The cytokine storm story is not new. It's been described in the infectious disease literature since the early 2000s. We're all very aware of the connection between CMV and EBV-associated HLH. Really in the mid-2000s with the H5N1 influenza, this term cytokine storm fell into the public domain. In the rheumatology community, we're aware of a subset of cytokine storm syndromes named macrophage-activation syndrome, which is a complication of many of our conditions, most commonly in up to 10% of patients with systemic onset juvenile arthritis. That condition shares genetic mechanisms with familial HLH, so there's a reason for that as well as other vasculitides, most commonly Kawasaki disease. Some have suggested trends in lab studies, rather than threshold values, will be more informative, so that's why I'm not going to give you hard numbers in terms of lab values Just know that lymphopenias, worsening coagulopathies, worsening liver function, rising ferritin all argue for targeting this immune hyperactivity before we start seeing end organ manifestations like ARDS.

I reached out to one of the pediatric rheumatologists at Columbia who was quoted in one of the stories referenced above. He agreed to share the protocol they're using. The nomenclature used to describe these patients is in evolution, but it's coming into focus that there are basically 4 phenotypes of children who are presenting with this COVID inflammatory syndrome. The first is the Kawasaki-like disease and we believe those kids are incidentally COVID positive. They present with typical Kawasaki disease symptoms, including rash, conjunctivitis, potentially dilated coronaries early on (less common), elevated platelets, D-dimers, and elevated BNP. Now there's been higher numbers of atypical Kawasaki disease with clinical manifestations including elevated D-dimers, elevated BNP and younger age and lower platelets, which you wouldn't expect to see so early on. Finally, there are two conditions with more post-inflammatory toxic shock picture, which look less like Kawasaki disease. These patients have more stark abnormalities in cardiac dysfunction, GI manifestations and bowel-wall thickening. This is well beyond what you'd expect of these non-specific findings in Kawasaki disease like gallbladder hydrops. In these cases, we're finding that the ferritins are only modestly elevated (500-1000). One case in Lancet reported up to 4,000. This is nowhere near where we'd expect ferritin levels in a MAS picture, in which we'd see ferritins north of 10,000. Cardiac features are all manner of abnormalities (mild to moderate), including biventricular dysfunction, valvulitis. All these children are requiring BP support. Without frank HLH picture/ toxic shock, all of these children will have unusual extra cardiac features and colitis. We've noticed on the laboratory side, lymphopenia (low lymphocytes), normal neutrophils and low platelets, which are not characteristic of normal Kawasaki disease. The most serious is frank toxic shock syndrome, which is well beyond the toxic shock presentation of Kawasaki disease. These patients present with highly elevated ferritins, initially normal platelets and highly elevated D-dimers. There is some suspicion in the adult literature that these kids might be at higher risk for coagulopathies, but there's no evidence to suggest that this is playing out on the pediatric side.

Now, what are some of these atypical features shared above? In general, the patients are a little bit older that you'd typically see with KD. Their presentation is marked with very low BP, GI symptoms and severe abdominal pain and diarrhea, which are less typical for Kawasaki disease. In general, there are more questions than answers. You'd expect there to be a difference in prevalence between ethnicities. Kawasaki disease tends to affect Asian children disproportionately. This new syndrome is being seen in all races, with some noting especially high incidence among those of African and Caribbean descent. Some have been hypothesizing that the lower incidence on the West coast could be due to different strains.

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Speaking of biomarkers, there have been more and more studies at specialized centers looking at interleukins. For our purposes, studying these and keeping track of them on the clinical side is not going to be very helpful. There is growing rationale for interleukin-6 TNF alpha blockade that we would use in our rheumatology conditions.

So, what does all this mean for patient care? COVID-19 now leads as the probable diagnosis for providers encountering febrile inflammation, so the opportunities for late or missed Kawasaki disease diagnosis are obviously a concern. A general pediatrician was quoted in the New York Times on May 6th saying something to the effect that there are a lot of unknowns about this condition and parents who have concerns about things like a rash should take their kids to their pediatricians. On the primary care side, you're undoubtedly going to see some concern from parents about this. My advice would be that if you're worried about your child for any reason, contact your PCP or medical home. I would emphasize that this inflammatory syndrome is very rare, and we have an incredibly cohesive medical community in this region.

Last week we heard that roughly half the cases coming from NY last week tested negative on swabs. We now know that number/proportion is higher. Staying on testing, there was a commentary published in JAMA just yesterday with a graphic displaying testing and collection methods and how we think that may evolve over time. Most centers recommend keeping a low clinical threshold for this KD type picture with basic labs like CBC, CMP, acute phase reactants (ESR, CRP), urinalysis. They also recommend routinely testing ferritin, BNP and complements if you have an inkling of concern about this post-inflammatory syndrome. The evaluation of abdominal pain is likely multifactorial with descriptions ranging from diffuse (ex: mesenteric vasculitis) to sharp pain that can mimic appendicitis, so just keep that in mind. Most folk will ask about high dose steroids, but those can cause bowel perforation, so they should not be used for patients with severe colitis. The bottom line is that any child that you're going to be worried about having this inflammatory condition should already have come to the attention of their PCP and be referred to the inpatient side for an echocardiogram and other testing.

Questions/Discussion

Q: What do I do if I'm in close contact of someone who is waiting for their test results? (This information is also included in a few slides.)

A: Breena Holmes, MD, VDH: You should all wait it out. People can be contagious for up to 48 hours before showing symptoms, so the recommendation is to quarantine for 48 hours or until the test results come back. If the test comes back positive, then continue to self-quarantine for 14 days. For health care workers, at UVM MC, if asymptomatic and a contact of a known COVID positive case, they are allowed to work if masked with active symptom surveillance. This general guidance was developed to avoid having large-scale healthcare worker shortages, particularly if there was a surge. The CDC has now changed their guidance for symptom-based isolation from 7 to 10 days after onset. We're pursuing a symptom-based strategy and just continuing isolation. The test-based strategy is problematic. The Governor is in support of the state epidemiologist and the health commissioner taking the studies that have come along that Bill mentioned that there is growing comfort that 90% of people will become systematic by day 12, so this has shortened the quarantine period by 2 days. 25,000 – 50,000 people (snowbirds) come back to Vermont in the summer. These individuals are of great concern to VDH. People in quarantine in Vermont will have the option to obtain a test for SARS-COV-2 on day 7 or later of they are in quarantine. They must remain in quarantine until they get the test results. If they receive a negative test, then they can end the quarantine early on day 9. 50,000 probably doesn't include day, weekend, and weekly vacations.

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A: If I tell parents that they must miss 2 days of work while they wait for test result for their febrile child, they won't let me test.

Q: Could you say how many rotations instead of seconds (re: nares swab testing)? That may be easier (i.e. vaginitis test is swirl around 10 times).

Q: How are the snowbirds being monitored to make sure they are complying with the recommendations?
A: Alex Bannach, MD, North Country Pediatrics: In Quebec, I have heard that the Health Department does phone check-ins to reinforce isolation with travelers.

Q: How will "snowbirds" even know what VDH wants?
A: Breena Holmes, MD, VDH: They'll know through a big media campaign using multiple platforms.
A: Ashley Miller, MD, South Royalton Health Center: There are signs on 91/89 down near me that say to isolate for 14 days if coming to stay (I'm on the NH boarder in central VT).
A: Kari McKinley, NP, Timber Lane Pediatrics: There is a large sign on the road exiting the airport.
A: Breena Holmes, MD, VDH: The contact tracing team reinforces isolation for patients who are positive.
A: Halle: There are signs entering VT by car from the Plattsburgh area of NY that request 14-day quarantine.

C: Ashley Miller, MD, South Royalton Health Center: *This is an interesting study:* https://forum.pediatricsupport.com/t/covid-19-re-emergence-what-parents-want-from-practices/3751.

Q: Is the mechanism at all similar to what happens with worsening clinical courses with sequential dengue infections?
A: Matt Hollander, MD, UVM Children's Hospital: I do not know about dengue.
A: Wendy Davis, MD, VCHIP: We can ask Drs. Lee and Raszka tomorrow.

C: Breena Holmes, MD, VDH: I am hearing from public health staff on this call that the quarantine policy changes are soon to be announced, so hold off on any change for now. There will be many documents and the website needs to be updated.

Q: So, it's like Kawasaki disease, but not?
A: Matt Hollander, MD, UVM Children's Hospital: What complicates the story is there are a variety of syndromes that are falling under this multisystem inflammatory syndrome. There are children who present with atypical Kawasaki's and they are generally older. There are children testing positive for COVID that have elements that are shared across Kawasaki disease and MAS, etc. So, they are sick and then 2-3 weeks later, there's this post-inflammatory response where they become much sicker. And we don't really know why that is.

Q: Have the majority of children had a relatively 'symptomatic' original illness versus mild illness, followed in 2-3weeks by severe illness? I'm just thinking about monitoring pediatric patients with symptomatic original/COVID illness.
A: Matt Hollander, MD, UVM Children's Hospital: Unfortunately, detailed courses for each child aren't published. What I gather from the listserv is that they have been relatively symptomatic originally and seem to get worse as opposed to a Kawasaki type picture where they get treated and then bounce back. That is not being seen or report here. It's more they are sick and they get worse.

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