Severe Manifestations of COVID-19 in Children: Rare But Important

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Q: *The testing that is now being offered in the community/drive thru sites--do we know if they are testing via antigens, antibodies, or both?*

A: To my knowledge, what is available is nucleic-acid amplification tests obtained by nasopharyngeal swabs. Most of these tests are batched (i.e., turnaround time at McLendon Labs within 24 hours), while some are rapid (<15 minutes); the rapid tests are in much shorter supply at this time. Antigen-based tests are being developed (these would also be swabs), but they are not likely to be as sensitive as molecular (nucleic-acid amplification) tests. Antibody tests are blood draws; I'm not aware of the community availability but these have much less of an application in the drive-through setting.

Q: *Has there been a correlation between BMI and disease severity in children, like there appears to be in adults?*

A: There was just a paper out in JAMA Peds (doi:10.1001/jamapediatrics.2020.2430) that suggests this is true, as has been our UNC experience. I don't think this (severe COVID in kids) has been looked at in broader epidemiologic studies.

Q: *Is there any important information about where our patients got their infection or where their family members got infected?*

A: I have not interviewed them all personally, but to my recollection, most have had symptomatic family members who may or may not have been diagnosed with COVID-19. We have a biased sample of sick patients, but the in-home attack rates seem to be very high in the patients we have seen. My suspicion is that occupational exposure is the mechanism of viral entry into many of the families we have seen; for example, the parent of one patient was an employee of the chicken processing plant in Sanford. I think access to testing is still an issue for many families in our region, and I also feel there is a need for more education about how the virus can spread within a household.

Q: *There have been recommendations of permissive hypoxia in patients who do not have a lot of respiratory distress. Is this still the recommendation now that we are doing more HFNC?*

A: I think respiratory care in general needs to be individualized for each patient, as we have seen no single strategy works for all patients. For instance, most guidelines stress prone positioning, however, patient 4 in our presentation did not tolerate it, and recent reports stress that not all adults benefit from prone positioning, and that it should only be used if patients feel it helps and are able to tolerate it. What we have seen in our patients is that in general, they seem to feel less dyspneic with higher flows and FiO2, even if their oxygen saturations are high, so I would not necessarily go with permissive hypoxemia.

Q: *Are there any signs or symptoms earlier in the course of the disease that predict later severe outcomes?*

A: No one to our knowledge has done modeling to show what constellation of sn/sx/labs predict a severe course or poor outcome, though we know certain abnormalities are statistically associated with severe/critical illness once it develops. I think the one thing that comes up repeatedly is a low lymphocyte count, however I'm not sure when in the disease course it has to be measured. Certainly a very low lymphocyte count that doesn't improve with therapy makes me nervous.

Q: *Regarding non-invasive ventilation (NIV) - if I understand correctly, BiPAP is not actually harmful but its requirement is a sign of rapidly impending resp failure. But if it is just a better tolerated form of positive pressure than CPAP in a covid+ pt, would it be acceptable to use?*

A: Correct, NIV is not thought to be harmful, the thought is that if someone is requiring NIV or BiPAP, that their disease has progressed so far as to almost certainly require intubation, and delay by using BiPAP or NIV at that point leads to increased mortality. If you STARTED with BiPAP, I suppose it would be acceptable, but I think there is a possibility of masking significantly worsening disease that is changing from microvascular disease with V/Q mismatch and likely compliant lungs that can be well managed with HFNC/CPAP to a more true ARDS picture with poorly compliant lungs that require high PEEP that still can occur in late severe disease.

Q: *Before COVID, we saw patients with severe lung injury and high level of systemic inflammation from vaping. There seems to be overlapping features. How do you differentiate them, especially in those who may test negative for COVID?*

A: You are right! History taking is still the best way to differentiate the two, I suppose. There have been suggestions that folks who vape are at higher risk for severe disease, but I don't think smoking or vaping have come out as significant risk factors consistently in all studies. This is an interesting question!

Q: *How many of the 4 abnormal labs should you have in order to qualify for starting LMWH as outpatient? Is there any value for daily aspirin for mild cases who are staying home?*

A: At this point in time, there are no formal recommendations for VTE screening as an outpatient and VTE incidence as an outpatient have not been reported. It may be a good opportunity to review with parents and patients the signs and symptoms of VTE when discharging. ClotConnect.org is a website managed by Dr. Moll, adult hematology colleague at UNC, which has helpful patient education handouts. This one in particular is nice and abbreviated. Aspirin use does not significantly reduce the incidence of VTE and can be associated with GI bleeding and easy bruising. At this time, there is no experience with using a daily aspirin for mild cases. However, I would consider thromboprophylaxis as an outpatient on an individualized basis particularly if a patient is considered to be a high risk for VTE, such as those known inherited thrombophilia (protein C, protein S or antithrombin deficiency) and encourage maintaining good hydration and mobility.

Q: *Since MIS-C presentations are associated with GI symptoms initially, is there any thoughts/research regarding IgA immunity?*

A: That is a great question but we really just don't know very much about MIS-C mechanisms. The diffuse involvement and similarities with Kawasaki disease suggest possible endothelialitis/vasculitis as a mechanism, and GI tract involvement might not be surprising in that hypothesis. I've also heard relative ischemia in the setting of cardiac dysfunction suggested, but it seems like abdominal symptoms are more common than you would expect. Perhaps arguing against IgA is the more diffuse involvement outside of the mucosa.

Q: *In MIS-C, is there evidence for actual infection and/or inflammation in the GI tract? (i.e., are these patients shedding more virus in their stool? do they have elevated fecal calprotectin?)*

A: We unfortunately do not know very much about MIS-C mechanisms, including in the GI tract. The diffuse involvement and similarities with Kawasaki disease would suggest possible vasculitis/vasculopathy. In the Belhadjer et al study from France and Switzerland, they did test fecal SARS-CoV-2 PCR, and only 6% were positive. It is unclear whether these patients had GI symptoms. None of the now 5 available case series of MIS-C noted fecal calprotectin measurements. Some anecdotal reports from places seeing MIS-C is these patients behave like they have underlying GI vasculopathy with poor absorption and needing IV steroids or other medications administered parenterally.

Q: *Could the need for higher PEEP (once intubated) also be related to the high number of obese patients with severe disease? Presumably this would need a multivariate analysis adding the risk factors (among the >900 publications)*

A: Absolutely, although I do think it has a lot to do with the pathophysiology of the lung disease. Late COVID does tend to change from high-compliance, V/Q mismatch pathophysiology to low compliance ARDS pathophysiology. In that situation, high PEEP is beneficial, similar to "old BPD"/hyaline membranes lung disease. The main "take home" message as far as ventilator management is to characterize each patient's physiology as best you can and tailor management to the individual patient, vs adopting an "across the board" strategy.

Q: *Can Dr. Willis explain testing newborns at 24 and 48 hours if infection doesn't occur until birth? Isn't a negative test at 24 and 48 hours expected? Is there evidence that newborns infected at birth will be shedding virus at 24 or 48 hours of age?*

A: Unfortunately, much is not known about this. My sense is that we are not seeing many infants test positive at that time point, but I don't think they knew that would be the case when the recommendation was first published. I am hoping that CDC or some other public health entity is looking at frequency of infection

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Q: *It seems that the remdesivir trials have been only in adults... is it permitted for use at UNC in kids? If yes, are data being collected to ensure peds have the same results as adults?*

A: Yes it is permitted for pediatric use. There are two dosage forms, and only one (lyophilized powder) can be used under 40 kg. The lyophilized powder is in shorter supply but is somewhat available. We would be willing to request it for a child of any age down to 3.5 kg. In recent weeks we have had adequate remdesivir supply for patients who meet inclusion and exclusion criteria, but that is not guaranteed. Unfortunately, there are not pediatric clinical trials that I know of, which would be very difficult to power in children. We are contributing to various registries and I think it will be possible eventually to do some comparative effectiveness studies. I think it's reasonable to extrapolate adult findings at least to adolescents for the time being.

Q: *It How do you distinguish acute COVID infection from MIS-C?*

A: This is a great question as there can be overlapping features between acute COVID-19 infection and MIS-C. Most children with MIS-C do not have acute respiratory symptoms and instead present with more persistent fever, GI symptoms, and other organ involvement. They are also more often testing positive for COVID-19 IgG and negative for COVID-19 by PCR. While some children with acute COVID-19 infection can have elevated markers of myocardial inflammation, the prevalence and degree of elevation seems higher among children with MIS-C.
