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NAUDIA L. JONASSAINT: Today, I've been given the task of really talking about COVID-19 and the liver. And then I think I'll try to catch us up a little bit on time but also just go through some things that I think are temporally pertinent in regards to this. So I have no financial disclosures.

So as many of you already know from the popular press, SARS-CoV-2 is part of a single stranded RNA virus to which SARS, that was identified in 2003 for the first time in MERS, which was identified in 2012 for the first time, are part of the same family. And this virus is pretty common in mammals and also in birds and get its preface of corona from the fact that, as you can see on the left, it has a crown-like appearance around the virus itself.

So the general transmission of the disease, COVID-19 overall is fairly resilient and contagious. So it spreads fairly rapidly. And we know now that it spreads through sneezing, and coughing, and also close contact. What remains [INAUDIBLE] particularly as we see the cases of COVID-19 surging is that the virus is thought to remain viable for two hours to 14 days. So depending on the surface, and the carrier, and the fomite where it really is carried, this can be a long lasting virus.

What we call the R naught in regards to its transmission for COVID-19 is about 2.2. And what this essentially means is that for every index case of COVID-19 that's identified, you can expect about 2.2 additional illnesses to be identified secondary to that. Also pretty scary about it is that the doubling time-- and this has been different over the course of the disease transmission-- is about 7.2 days.

So in regard to the COVID timeline, what we know is that index cases were identified for the first time in China in December of 2019. Several unexplained pneumonias popped up in Wuhan, China. And as you can see on the right here, this is the wet market thought to be associated with the first cases. And on December 31, the World Health Organization was alerted about those unexplained pneumonias. And by January 3, the first BAL was done for the index case and identified the presence of this novel coronavirus.

By March 11, the World Health Organization had declared a global pandemic. And this is pretty scary, because I left to go to Puerto Rico on March 8. And when I came back, essentially, we were essentially in lockdown at that time. It was interesting, because I had had a friend at the CDC that was saying, whatever is being reported is worse than Americans anticipate. And she was saying, you shouldn't be traveling. You shouldn't be going anywhere. This is really, really bad. And at that time, I think we were still kind of very, very much in La La Land in regards to this and what was essentially headed our way.

When you look at the overall timeline, just over the first month of the pandemic, it's pretty shocking. So as I noted before, the early alerting by the WHO was on December 31. And as I said before, by December 3, there was already essentially the BAL that identified that index case. The seafood market was actually closed on the first of the year in China. And as you can see, over the first month of the pandemic it was pretty extreme. So from January 1, again, we were still here in the United States, I think probably significantly unaware of what was going on around the world. But there had already been over 200 identified fatalities and over 10,000 cases across 23 countries in the world.

So SARS-CoV-2 presents, as you all know, as a typical flu-like illness. And really, what happens is that the main things that happen are fever and cough, but there are some other symptoms. And from what I've heard from people who have been infected, the fatigue and the overall sense of myalgia is pretty profound. People feel run over by a bus. It's also important to realize that there is a small amount and a small percentage of patients that will have gastrointestinal features as possible presenting features of SARS-CoV-2. And again, another profound mechanism of this is really the profound lymphopenia which is thought to be associated with the severity of disease.

So the Chinese Center for Disease Control was really the first to really quantify how this would be segregated. And what they really identified was that 81% of the cases of SARS-CoV-2 were going to be fairly mild, reported to have fever, dry cough, and mild dyspnea with a respiratory rate of less than 30 as part of the illness. And then, the ongoing levels of severity will go up over time with severe disease being reported in about 15% of cases and really being identified as a respiratory rate of greater than 30 and lung infiltrates greater than 50% within 24 to 48 hours of onset of symptoms.

The more critical cases will result in respiratory failure or septic shock and multi-organ dysfunction and failure. And we'll talk a little bit about what is believed to be the manifestations and the common manifestations of this in the setting of the liver. But as we well know, probably between 20% and 40% of these cases will actually result in death.

So liver function test abnormalities are one of the clinical features of COVID-19 infection. And what you can see here in this paper on respiratory research is that probably somewhere in between 15% and 30% of cases of SARS-- or SARS-CoV-2 or COVID-19 will have LFT abnormalities. Much of what we know suggests that-- and it's unclear. But much of what we know suggests that the severity of disease may also be related to whether or not we see these liver function abnormalities.

And many times, these liver function abnormalities can be very mild. And I think some of the concomitant liver disease that we see, really, the severe AST, ALT into the thousands, and then some of the things that Shaw had talked about before in regards to vanishing bile duct syndrome, or profound cholestasis as a manifestation of overt cholestasis with rise in the bilirubin would be less typical and I think are associated sometimes with overlapping cholestasis of sepsis in some of the other more profound illnesses.

The mechanism for liver disease and COVID-19 is really unknown. And it's postulated that very well many mechanisms may be going on here. One may be a direct cytopathic response. So essentially, COVID-19 or SARS-CoV-2 is entering into the cells and causing pathology. Another proposed mechanism is that there is just an uncontrolled immune reaction. So there is essentially a cytokine storm that happens that you can see here on the right side of the screen, and that that leads to a profound liver injury.

And then the other ones are two that we typically see many times in hospitalized patients for other reasons, which is overwhelming sepsis and what I talked about before in my last slide, which is this idea of cholestasis of sepsis. And I think the traditional teaching that I was taught is that cholestasis of sepsis typically doesn't go beyond bilirubin of between 2 and 11. When you get beyond that realm, you're really talking about probably something that doesn't just include cholestasis associated with sepsis but another concomitant disease process. And then lastly, the drug induced liver injury seen in this case, where many things may be going on there, and I'll talk a little bit about specifically the drug induced liver injury associated with COVID-19 specific medication.

So though I think the underlying etiology of the disease process is unclear, what is clear is that the angiotensin converting enzyme 2 is thought to be critical for the entrance of COVID-19 into cells. And what we know more now than we did previously is that the ACE-2 seems to lie predominantly on the cholangiocyte, which is interesting, because we don't see a profound-- the typical finding in COVID-19 is not a profound cholestatic injury but one of hepatocellular injury.

But we also realize that there is another leading cell surface binder, which is TMPRSS, which is present on hepatocytes. And this has been demonstrated both in in vivo or liver organoids and also in the liver itself, that both of these may actually have some interplay. It is clear that TMPRSS is present on hepatocytes. And it's also clear from the organoid studies that have been done is that when you [INAUDIBLE] that ACE-2 is also positive on liver progenitor cells.

So what is going on here is it's critical to understand that these two things might be critical in regards to COVID-19 entering the cell. But in addition, it's still unclear why ACE-2 is predominantly on cholangiocytes but COVID-19 seems to present more so with hepatocellular injury. And I think part of that is because, again, drug induced liver injury sepsis and profound overwhelming multi-organ failure, I think, overwhelm sometimes the clear presentation of COVID-19 as it relates to liver disease.

So this study looking at *Journal of Hepatology* just really looked at overall the cumulative probability of clinical deterioration. And essentially, what is shown here is that as you have an increase in all of your liver enzymes going from the hepatocellular picture in ALT and AST to GGT alk phos and bilirubin, which are more profound cholestasis, as we can see the cholestatic enzymes, I think, portend a poor prognosis.

And again, I think that that is because probably, cholestasis of sepsis and other things such as drug induced liver injury and in addition to that, the vascular injury that Shaw had alluded to from the ASLD findings are maybe overwhelming these people who have profound or more profound cholestatic liver injury. But again, the predominant picture is one of a hepatocellular injury.

So I did want to just briefly talk about this idea of remdesivir and how this leads to liver function test abnormalities. So just to steep you in the background, this is really given as an intravenous infusion. And there is some talk of there being an inhaled form of remdesivir coming forward in the near future. But this is typically given over a five to 10 day period of time. It's converted intracellularly into an active triphosphate. And as a result of that, the ATP competes for incorporation into the viral RNA.

There have been, as you all probably know, mixed outcomes regarding what the benefit of the medication in regards to time to recovery. And there's unclear mortality benefit. And I think overall, this is really right now being used for those people who have severe COVID-19 and those people who are hospitalized as a result. And ongoing studies in regards to whether or not all symptomatic patients should be exposed to the medication.

The pattern of liver damage is predominantly one of that of a hepatocellular injury. And I think, again, when you start thinking about cholestatic liver injury and COVID-19, you really are probably dealing with someone who is severely ill from COVID-19 itself. The damage is, as reported, typically transient. And as I said before, I think some of the damage may be overshadowed and confounded by the severity and the level of COVID-19 exposure.

The last thing that I wanted to talk about specific to the liver and GI tract is this idea that the GI tract is a possible mode of transmission. There had been some reports earlier in the COVID-19 pandemic about a very, very large apartment structure in China where there was clearly an exposed family that had been exposed in Wuhan and then two families that were actually along the same drainage pipe system and the fact that there may have been aerosolized products coming from stool actually in the toilet for that shared system that may have led to fecal-oral transmission.

So as we know from previous, the SARS COVID identified previously in 2003, the RNA was detected in stool. So fecal-oral transmission is hypothetically and theoretically possible. About 3% to 79% of people will develop GI symptoms. And it seems more so in the 20% range, so middle of the road in regards to this. But in a study that was done in publishing gastroenterology, when they looked at 73 patients, 53% of those patients had positive stool RNA. And 23% of those patients were still shedding RNA in their stool after having a negative respiratory sample.

And for those of us who are hepatologists and still scope from below, I think it's just important to remember the diligence that needs to be taken in regards to making sure that handwashing and all of those things are done with fair vigorousness after patients that have been exposed to COVID-19 are being taken care of. So this is in general where we are. And this is taken directly from the CDC website with total cases now in the United States really over 14 million as of yesterday, and then, again, the deaths in the United States somewhere in the range of the 270,000 range, actually probably close to 280,000 as of yesterday.

So what we know really is the worldwide pandemic is surging again. And if that is unclear, then these numbers should certainly make it obvious to us. The overall number of cases worldwide are over 60, nearing 66 million, and the number of deaths over 1.5 million. And as you can see here, the United States, in something that you don't want to be number one in, is leading the track.

And that is in comparison to countries like India and Brazil, which we know are very, very highly populated, particularly India itself. And Brazil, remember, is as large as the continental United States and are really still behind us in regards to the number of deaths and cases. Now, some people may say that this is secondary to testing. But again, if we overall look at the death rate across the board, at least via an attribution, we still are winning the race in this regard.

I think it's also important to steep us in our local understanding. And this is just to show you the first time, when there was a surge of COVID-19 in the United States, we in Southwest Pennsylvania were fairly spared. I think we saw what was happening to our East coast colleagues. And we shut down pretty quickly in regards to this. But between November 22 and December 3, the cases in Pennsylvania have nearly doubled over that period of time.

So when we talk about the number of cases in the surge, this is going to be, I think, very, very significant for us. And I think that that's why the temporal importance of this talk is really important, because many of you all know within the system Presby had to open new ventilator beds yesterday, because there were no longer any ventilator beds at Presby yesterday.

So I think it's also important to talk about the fact that the hospitalization and death rate by age and by some other parameters is different. And here, we can just see that obviously older age is a risk factor for both hospitalization and a significant risk factor for death. And obviously, for those people that are over the age of 65, the risk of death is fairly profound.

In addition-- I think that this has been part of the news and is ongoing-- is that there is also a significant amount of racial and ethnic differences when we talk about COVID-19, both in terms of cases, hospitalizations, and death. And much of this is attributed to the social determinants of health, access to care, and the fact that there are increasing risk factors in populations, particularly Latinos and Blacks in regards to diabetes and other risk factors that put you at greater risk for acquiring COVID-19 and also having poor outcomes.

So I think we do have to recognize that we would be remiss to not understand that there are disparities in liver disease health exacerbated by the COVID-19 pandemic. And I think some of the problems are that there are some delays in diagnosis. There's also an overall decrease access to care, a lack of treatment, and increased exposure in some populations as opposed to others.

And I think some of the proposed solutions to this in my mind are really a very, very vigorous telemedicine platform. And as many of you all know, we went to 98% telemedicine other than for our transplant evaluation patients when we were initially surging. We have not taken on that solution this time thus far. And then, some flexibility in resource allocation. So thinking about the human resources, meaning physicians, nurses, et cetera, the physical plant, how many hospital beds and machines do we have in order to take care of these patients?

And then medications, which came up in the previous surge and I think now is going to be less of an issue as we understand the importance of corticosteroids in this population, which for right now we do not have a limitation on. And then the fact that the antivirals are more available now than they previously had been. And then we also, I think, have to think about PPE and also start to think about vaccine hesitancy in some of our most vulnerable populations. And as you know, the vaccine hesitancy amongst Latinos and Blacks is amongst some of the highest in populations. But they are most likely to be frontline workers moving forward.

When we think about overall what effect COVID-19 has had that may have an undue effect on liver disease patients, we can see obviously that liver related mortality-- we can see the difference in liver related mortality in this study that was done looking at the 30 day cumulative probability of overall death in patients with COVID related mortality versus liver related death. This is having a profound effect on our patients. And I think we have to understand that for those people who are decompensated that come into the hospital, they are going to be at increased risk if for some reason they, in fact, do contract the virus.

This is a paper done early on in the COVID-19 crisis by Moon et al. Looking at the case fatality rate. And as you can see and would be reasonably appreciated, as you move from chronic liver disease without decompensation to the higher levels of decompensation with liver disease up to Child's B-- sorry-- Child C cirrhosis, the case fatality rate rises over time. And I don't think that that's anything that we wouldn't expect.

In addition to that, as we would also expect and often happens to our patient when they are hit by something concomitant, whether it be pneumonia, UTI, sepsis, et cetera, there is also an increase in the overall decompensation rate in those patients who have chronic liver disease and acquire COVID-19.

So this paper out of Italy I thought was very, very interesting. And I think overall, I put this here just to say that this really looked at the COVID-19 deaths as opposed to all cause mortality. And what this tells me overall-- and this is something that has been written about in *The Times, The Wall Street Journal*-- is that people who are dying from the all cause mortality during the COVID-19 pandemic has actually increased.

So it's not just disease attributable to COVID-19 infection, but overall that people are succumbing to probably their chronic diseases, not just chronic liver diseases, but all chronic diseases more so. You probably have seen some of the common press in regards to people with attributing their chest pain to something not wanting to go to the hospital, and then dying of MI in that setting. So the question is, how much disease is going undiagnosed during this period due to people's fear for accessing care?

The other thing is that I think that COVID-19 is going to have an overall effect-- and I think Dr. Rogel talked about hep C elimination earlier-- but it's going to have an overall effect on our ability to eliminate things that we've been looking to eliminate. So the international goal of eliminating hep C worldwide, there was a paper done in the *Journal of Hepatology* looking at this and just basically overall says that treatment starts of new diagnoses are going to decrease over this period of time.

And this is a proposed model of how many undiagnosed cases there will be decrease in the number of new cases of hepatitis C between 2020 and 2030, with just a delay in one year of HCC program, the delays in treatment starts which near 800,000, and then overall the number of viremic infections and the number of incident HCC and liver death attributable to those delays.

I also wanted to just talk briefly-- and this did not happen to us, because again, as I said before, in Southwest Pennsylvania we were fairly spared in regards to the last surge of COVID-19-- but this is just something that we should keep in mind as our cases seem to be increasing over time. We can see here that organ procurement and transplantation during the COVID-19 pandemic are inversely proportional to each other. So the number of transplanted organs over time-- and this delineates it by type of organ-- goes down as the number of COVID-19 cases surges. So this is just really, really important to understand.

The last thing that I want to talk about is this idea-- and I don't know if you all have heard about this-- is this idea of long haulers. So there is what people are calling long hauler syndrome and that we don't fundamentally understand, because we are only, what, nine months, 10 months in-- well, I would say 12 months into COVID. We do not understand what the long term ramifications for people are long term. And this is just an article about this long haul syndrome and the NIH starting to understand and convene a two day meeting sponsoring this idea of coming to an understanding what the long term effects of COVID are-- increased shortness of breath, long term pulmonary disease.

And the fact that I think that this is going to have an undue effect on people who are more likely subject to pulmonary disease, diabetes, et cetera, and I think is going to make it harder for those populations. And I recently am part of a grant that we're submitting with Temple University to look at not only vaccine hesitancy amongst the Latino and African-American population, but also looking at the phenotyping and genotyping these people that have either non-severe COVID or severe COVID and trying to figure out those people who are going to have long standing effects from this, from a pulmonary standpoint and cardiac standpoint.

So just in conclusion, I think the power to improve the health of our world lies in equitable and sustainable solutions. I think chronic liver disease and cirrhosis has an increased mortality from COVID-19. And I think the study from Italy clearly shows that there is an excess death in 2020 that's not fully accounted for by just COVID-19 related deaths. The international hep C elimination is at risk secondary to the COVID-19 pandemic, and that we need to understand what the effect, I think, in our area nationally and internationally what the effect of organ procurement and the rate of transplantation will be in the setting of COVID-19 surging again.

I also think that there has been a longstanding pandemic of poverty, lack of access and treatment, as well as diagnosis, and that COVID-19 has just exposed those kind of long term systemic issues in our population. And I think as liver disease doctors, we are going to be forced to address this more and more moving forward.