THERESA MAYLIN: Thank you, everyone, for joining. I'm Theresa Maylin, a senior education specialist. And on behalf of the Mayo Clinic School of Continuous Professional Development, I'd like to welcome you to the Mayo Clinic COVID-19 webinar series.

Before we get started, we'll cover a few points. The first is how to claim credit. If you'd like to claim credit, after the webinar, please visit ce.mayo.edu/covid0616. You'll need to log in to the site. If it's your first time visiting, you may need to create an account.

After you've done this, and you're logged in, you'll see an access code box. You'll need to enter today's access code, which is COVID0616. This will allow you to unlock the course, take a short evaluation, and then you'll have access to your certificate. This link and the code will be dropped into the chat box periodically during the webinar.

The second is how we'll facilitate questions. So you'll see at the bottom of your screen, circled here in red, is the Q&A function. If you have any questions during the webinar, we ask that you please enter them into this Q&A function. And this will ensure that the panel can see them.

There's also an up-voting function. So be sure to vote for the questions you'd like to see answered. The panel will take questions in certain segments during the webinar series. So during that section, make sure you enter your questions that are relevant to that topic.

Today's learning objectives. By the end of this session, you should be able to determine how SARS-CoV-2 and COVID-19 affects pediatric patients. You should be able to describe clinical guidelines for treatment and management of COVID-19 in pediatric patients and define multisystem inflammatory syndrome in children, abbreviated as MIS-C.

And today we'd like to welcome Dr. Charles Huskins. He's the chair of the Division of Pediatric Infectious Diseases. And he's a professor of pediatrics.

CHARLES HUSKINS: Thank you very much, everyone, for joining us this morning. This is a really important topic. I'm glad that you're here to listen to the discussion and ask questions. We have an outstanding group of speakers to talk about the various topics. I'll keep their introductions brief to allow the most time for discussion.

First, we have Dr. DJ Hall, who is the chair of the Division of Pediatric Hospital Medicine and an assistant professor of pediatrics. Next slide, please.

Dr. Nipunie Rajapakse is a consultant in pediatric infectious disease and an assistant professor of pediatrics. Next slide. Dr. Rana Chakraborty is a senior associate consultant in pediatric infectious diseases and a professor of pediatrics. Next slide. And Dr. Emily Levy, who is a Mayo clinic scholar, clinical fellow in pediatric infectious disease, and assistant professor of pediatrics and pediatric infectious disease and pediatric critical care medicine.

Next slide, please. So I want to begin just by making sure we're all on the same page with various terms that will be used. So the first is SARS-CoV-2, which stands for Severe Acute Respiratory Syndrome coronavirus 2. This is the name of the virus that causes the disease COVID-19. So when we use the term COVID-19, we're talking about coronavirus disease caused by the SARS-CoV-2.

The third term is what we call MIS-C, which is multisystem inflammatory syndrome in children. We'll go through these through the presentation. Next slide, please.

So this is the agenda for the topics today. We'll start with a discussion of the epidemiology of COVID-19 in children. We'll then move on to perinatal infection, critical illness, treatment of COVID-19, MIS-C, and then we'll end with concluding comments and questions. So let's begin with the epidemiology of COVID-19 in children. And we'll ask Dr. Rajapakse to lead us through that discussion.

NIPUNIE RAJAPAKSE: Thanks, Dr. Huskins. So as of today-- June 16th, 2020-- globally there are over 8 million cases of COVID-19 that have been reported-- about 430,000 deaths. Here in the United States, there have been about 2 million cases and over 110,000 deaths.

There have been some challenges that I think have hampered us somewhat from understanding the true burden of disease amongst children and what proportion of these cases are amongst children. Some of these have been related to the limitation in testing availability, and also the higher likelihood that children are asymptomatically infected or have mild infection, and therefore may not have been tested or confirmed to have infection. And this has hampered our ability to completely understand the burden of infection amongst the pediatric age group.

In countries that have had large outbreaks and widespread community transmission, especially early on in the pandemic-- so countries like China, Italy, here in the United States-- approximately 1 to 5% of all confirmed cases have been reported to be amongst children. As of June 1st here in the US, it's estimated about 3% of total cases have been in kids.

We do know that children of all ages can be infected with the SARS-coronavirus-2 virus. There have been reports of infections in premature neonates, ranging up to obviously the adolescent and young adult age group as well. Most cases in pediatrics-- when they have looked especially at clusters-- seem to be related to household transmission and exposure to usually an index adult case within the household.

This has been a very interesting finding. I think from what we know about other respiratory illnesses-- especially viruses like influenza-- children seem to be very efficient transmitters. However some of the early data looking at transmission suggests that possibly that may not be the case for this virus, and that children may be more likely to acquire it from adults. I think it's still an active area of study but we need to explore further as well.

Most children-- as we have heard-- are more likely to develop asymptomatic or mild to moderate infection. And most of these kids can be cared for at home, with many recovering over a one-to-two-week period of time. Hospitalization rates of children in the United States have varied anywhere from 6 to 20%, based on the MWR report from April. And less than 2% have generally required critical care admission.

Thankfully deaths have been rare in the pediatric age group, though they have certainly been reported. There seems to be some risk factors that Dr. Levy will be mentioning later on for more severe illness. But some deaths have occurred even in previously healthy kids with no obvious risk factors. And so it is an important consideration, especially as we look at many areas starting to reopen.

CHARLES HUSKINS: Thanks very much, Dr. Rajapakse. COVID-19 is primarily a respiratory disease. But there are other presenting symptoms as well. Dr. Hall could, you take us through some of the ways children might present with COVID-19 illness in both the outpatient and inpatient setting?

DJ HALL: Certainly. I agree that the majority of patients are similar in presentation to adults in that they will present with respiratory illnesses. Fever is by far the most common presenting symptom, with more than half of children having fever if they're going to have a symptom at all. In early reports between fever, cough, and shortness of breath, that would occur and over 70% of all children. And by and large, this was the primary reason for children to be admitted to the hospital-- would be respiratory distress, if it were to occur at all during acute illness.

Interestingly though-- and because there's a lot of less common symptoms that have gotten a lot of attention. And these occur from anywhere to 10% to 30% of children. And they can range from a very mild sore throat to there've been admissions nationally for severe sore throat, which have led to dehydration-- additionally headache and significant GI symptoms with nausea, vomiting, diarrhea, and abdominal pain, which can mimic symptoms of appendicitis.

Other things that have gotten a lot of attention have been some of the dermatological manifestations. And that can range from just mild rash to some of the things we've seen with COVID toes, which is more of a rash that can appear on the acral surfaces.

We here locally have also noticed-- what has been reported nationally-- that fever can be the sole presentation in infants, particularly infants under 30 days of age. So while we do know that children, particularly infants less than a year, can have severe respiratory symptoms as being the reason for hospitalization, we've seen a lot of children be hospitalized in that age group of investigating fever in a neonate.

CHARLES HUSKINS: Thanks very much. Most kids with COVID-19 can be managed as outpatients. What kind of counseling are you providing for families? And what sort of follow up do you recommend? And is this the same for all children? Or should children with significant comorbidities be handled differently?

DJ HALL: Yes. To echo what Dr. Rajapakse said at the beginning of the talk, the majority of children do have mild or moderate symptoms and do not require anything where they would interact with a hospitalist or be in the hospital setting. And simple viral treatments that pediatricians would recommend for all patients are what we're recommending as well. And that would be pain control with acetaminophen.

Early on there was controversy around the use of NSAIDS. However that has now been approved. So use of ibuprofen is appropriate as needed for pain or discomfort. We focus a lot on fluid management and trying to avoid dehydration.

Here we counsel families on specific signs and symptoms to watch for. That is done both at the time of diagnosis but also through ongoing follow up with nurse phone calls. And at that time they assess for signs of respiratory distress, so things such as grunting, tachypnea, retractions, but also signs of dehydration, and then early signs of shock.

So signs of poor perfusion-- such as cold, clammy skin-- would all be signs that they should watch for. But by and large, we're not seeing that in a large portion of the children. And so many are able to manage it at home with just simple measures of fluid management.

CHARLES HUSKINS: And anything else about children with more serious comorbidities that we need to pay attention to?

DJ HALL: So I think for children that have underlying pulmonary disease-- even things as simple as a mild asthma-- but certainly children of chronic lung disease, congenital heart disease, underlying renal dysfunction, or autoimmune diseases, such as diabetes or children that we have placed under immune suppression for other reasons-- they do likely have a higher risk of having more severe illness and therefore more frequent check in is probably what's provided.

Interestingly though a lot of the children, through case reports-- with illnesses such as cystic fibrosis and even oncologic patients-- continue to do well even with acute infection. But we have a lower threshold to see those patients in an emergency department or a hospital setting.

CHARLES HUSKINS: Thank you very much. I don't see any questions on this section. So we'll move on to perinatal infection. Dr. Chakraborty, what do we know about infections in pregnant women and neonates?

RANA CHAKRABORTY: Thank you for the question, Dr. Huskins. There's a lot of emerging data coming out right now from this and touch base on that. Initially from some of the reports from China, some of the complications of SARS-CoV-2 infection included miscarriage, premature labor, and fetal distress.

In the last few weeks, we've received a report call from France. We looked at over 600 pregnant women who have infection. Thus far about 181 have delivered. Of this group 35, or about 6%, have a critical form of COVID-19 infection, requiring critical care, related most often to respiratory disease.

The risk factors and the disease severity appear to be associated with age greater than 35 years and prepregnancy obesity. And then there was also preexisting diabetes, previous pre-eclampsia, and gestational hypertension or pre-eclampsia. One woman from this group died. And one neonate born from this cohort died from complications related to prematurity.

Last week in the BMJ, there was an article reported in the UK. And that pretty much showed-- it was very similar to the French data. Over there in the UK, they reported that Afro-Caribbean, an ancestry from the Indian subcontinent, were also seen as significant risk factors for poorer outcomes. Most infections appeared to occur in the second or third trimester.

Fortunately there doesn't appear to be any definitive evidence of intrauterine infection in the literature to date, although a number of investigators do report placental dysfunction and the presence of inflammatory cells in the placenta noted by histology. Now in terms of newborns and the neonates and the outcomes, some of the most comprehensive data we have were on 33 neonates born to mothers with COVID-19 in Wuhan.

A report came out in March of this year. And basically of those 33, most infections were classified as mild. Of three neonates who had symptomatic infection, the most serious illness that was noted were actually related to complication prematurity, asphyxia, and sepsis, rather than from a SARS-CoV-2 infection, per se. And what was being over here in our practice in Rochester and in southern Minnesota is a similar pattern thus far.

CHARLES HUSKINS: Thanks very much. So when the baby's born, what do we do? What about separation versus rooming-in, testing, et cetera?

RANA CHAKRABORTY: Again, this is an evolving area of investigation. There is still quite a lot that we don't actually know. A number of guidelines have already been put forward by the Center for Disease Control and Prevention from the American Academy of Pediatrics and from the World Health Organization.

Currently what we're recommending is that any newborn may room with the mother or receive care in a separate room, especially if the mother is symptomatic. However the risks and benefits should be discussed. And an informed decision should really be made between the neonatal teams, the obstetrician, and the mother.

The current guidelines coming out from the CDC, the AAP, and the WHO really state that mothers with COVID-19 may breastfeed but should really take steps to mitigate postnatal transmission of infection to their neonate. And so these interventions to mitigate-- as I'm sure you're well aware of-- include frequent handwashing, practicing respiratory etiquette, wearing a mask, and when in close contact-- i.e., within 1 to 2 meters or 3 to 6 feet with the infant.

So far SARS-CoV-2, the virus has not been detected in any breast milk samples. An uninfected designated caregiver may also express breast milk in order to reduce the potential risk of transmission. And in terms of testing, the CDC, as of three weeks ago, recommends testing of all SARS-CoV-2-exposed newborns by RNA PCR on nasopharyngeal swabs.

CHARLES HUSKINS: Great. Thank you very much. And I think that's at 24 and 48 hours they recommend that testing, right?

RANA CHAKRABORTY: Right.

CHARLES HUSKINS: And if the baby's not going to be there for 48 hours, you can do it before discharge?

RANA CHAKRABORTY: Yes. That is the recommendation.

CHARLES HUSKINS: Great. Thanks. We do have some questions. We'll get to those in in subsequent sections because I think they pertain to those sections. So we'll move on now to talk about critical illness. And we'll ask Dr. Levy to help us with this. So what do we know about which children are more likely to develop critical illness, Dr. Levy?

EMILY LEVY: Thanks for the question, Dr. Huskins. So as Dr. Hall said earlier, the vast majority of children do well and are not critically ill. There are far less children who are critically ill than adults. Initial observational studies from Wuhan told us that children very infrequently experience severe disease. And they only had in the 10s to less than 10 number of children admitted in the initial reports we're receiving. And certainly very few children received critical care.

In terms of the risk of different children, there have been conflicting reports regarding very young infants. Initial reports from China and some from Europe predicted that very young infants were at higher risk than school-age children. However more recent reports from the United States have not necessarily borne out that risk factor. It does appear that very young infants are at higher risk to present with respiratory symptoms, versus the other symptoms that Dr. Hall mentioned earlier, for instance GI-type symptoms.

As we see more evidence, obesity appears to be emerging as one of the strongest risk factors for severe illness, particularly in older children, which is similar to what we've seen in the adult population. I'd like to highlight two specific reports of JAMA Pediatrics that have come out more recently.

One is a cross-sectional sampling of 48 children that required pediatric ICU-level care in Canada and the United States in the first couple months of COVID-19 here in America and Canada. And one is across-- and one is a single center study on outlining risk factors for severe disease, which they defined as mechanical ventilation. In both those studies, obesity emerged as a major risk factor. Adolescents were more likely to be sick than school-age children. In the cross-sectional study, more than 50% of children admitted to the PICU were older than 11.

One of the other factors that emerged for severe disease was medical complexity, which was defined in various studies as technology dependence or children who require tracheostomy and mechanical ventilation, as well as multiple underlying comorbidities, like chronic lung disease. In both these studies-- the cross-sectional study and the single center study looking at severity-- infants did not appear to be at higher risk for severe disease. That is young infants were admitted and were part of the cohorts, but they didn't appear more likely to develop extremely severe critical illness than the other patients in the study. And in the cross-sectional study of PICU patients, only 17% of the patients were infants less than 1 years old.

There was a lack of disproportionate effect on immunocompromised patients. So although, again, immunocompromised patients were admitted and we're included in these cohorts, it wasn't that the more immune compromise you had, the more severe your illness was, as we see in some other infectious diseases. As Dr. Hall mentioned, in general DKA, asthma, and sickle cell disease have also emerged as risk factors for COVID-19 in children, as they have for adults and seemed to indicate potential development of more severe disease.

And then there were some lab markers that indicated the likelihood of disease-- patients presented with lymphopenia-- but that seemed to have no prognostic value about the severity of illness. Elevated inflammatory markers did seem to predict a more severe course at admission, so higher CRPs and procalcitonin indicated that a patient may have a more severe illness.

CHARLES HUSKINS: Thanks very much. What about the general approaches that you'd take to critical care management-- recognizing we'll get into other elements of treatment specific for COVID too in just a second?

EMILY LEVY: Sure, yes. Good question. So as we've mentioned, the majority of patients who are admitted are admitted with fever and upper or lower respiratory tract symptoms. Approximately 75% of patients that require critical care have lower respiratory tract symptoms, so similar to what we've seen in adults, but actually lower respiratory illness burden than what we've seen in adults.

Children may also present with very severe GI symptoms, some even prompting surgical procedures looking for acute abdomen and then very occasionally present with shock. So in general for respiratory failure, this is standard pediatric ARDS management. That is low tidal volumes, permissive hypercapnia, permissive hypoxemia, higher peep settings, conservative fluid management-- which is important to realize as these children are initially being admitted-- and occasionally deeper sedation.

We've seen in pediatrics, just like an adult populations that bacterial coinfection is common with COVID-19. And so having a lower threshold to consider bacterial coinfection and consider antibiotics to treat that is appropriate in this disease. One of the single central studies reported that 18% of their patients had bacterial coinfection during their admission. And that included patients who were intubated, so who were mechanically ventilated.

Trialing non-invasive ventilation is appropriate in these patients. The current SCCM recommendations for adults does not say that you can't use non-invasive ventilation. So although CPAP and BIPAP do have some aerosolization risk, and may prompt infection control considerations, intubation also has a very high aerosolization risk. And so in general the pediatric critical care world is not recommending against non-invasive. If CPAP or BIPAP would be appropriate to trial, we can trial that in these patients for support prior to intubation.

When intubation is considered, the patient should be intubated by the most skilled practitioner. That means ideally the child is in a center where there is a most skilled practitioner by the time you might need to intubate the child. In the critical care world, we may consider steroids, neuromuscular blockade, or iNO for refractory ARDS cases. That would all be done in an ICU.

In general in pediatrics, prone positioning has less supportive evidence than in adults, just in general for ARDS management. And that's because we have had less rigorous trials supporting it at this point, not that we have evidence against it. In the cross-sectional PICU study that I mentioned earlier, only two patients receive prone positioning of the whole group of patients. But it is reasonable to trial it in a patient with severe ARDS. And as we collect more evidence in this disease, we may see that it has similar benefits in critically-ill children, as what we're seeing in adults.

In terms of shock management, it's rare for children to present with COVID-19 in septic shock. For adults SCCM is recommending norepinephrine for first-line vasopressor management. In children I would use the typical septic shock management recommendations that we have from the SCCM Surviving Sepsis Guidelines. And we don't have particular evidence about any one vasopressor.

SCCM guidelines recommend against using IVIg or plasma exchange in these children as standard therapies. And I know Dr. Chakraborty is going to talk a little bit more about specific therapies later on in the session. We recommend considering prophylactic anticoagulation early. In general critically-ill kids are at higher risk for thrombotic complications. And in particular COVID 19 has been shown to carry a very high risk of thrombotic complications.

And then again, just to emphasize that early transition into a tertiary level of care center or a center with a PICU, if a child has known comorbidities or seems to be presenting with a severe case is reasonable, there have been a couple of uses of VV ECMO so far for these children in the United States. And certainly we've seen that ECMO support can be useful both in adult populations and in the international pediatric population.

CHARLES HUSKINS: Thanks very much, Dr. Levy. I see a fair number of questions coming in on daycare and school. We'll get to that in just a second. But Dr. Levy, could you just quickly comment on sequelae and time course-- how long do these kids stay in the ICU-- that sort of thing?

EMILY LEVY: Yeah. So it really depends upon severity. It appears to be tied more to ARDS severity than anything actual individual about COVID-19. The longer one is mechanically ventilated, typically the longer the ICU subsequent courses. With severe ARDS we see ICU courses anywhere from 5 to 14 days at times.

CHARLES HUSKINS: Great. Well thank you very much. That's a nice segue into the treatment section of our discussion. So Dr. Chakraborty, could you give us an update on what we have for specific treatments?

RANA CHAKRABORTY: Yes. Thank you. What I think is important to recognize is the actual viral life cycle. And I won't get into too many technical details. Suffice to say that many of our treatments have been directed either towards the virus itself and some of these drugs we know about or to the immune response. And sometimes a combination of both treatments are applied, especially to severely critically ill patients.

So if we could forward first, and I'll speak about the first-- the rationale. If we look at the life cycle, we have these spike proteins. And they need the host cell receptor. That's ACE2, which you may have heard of, and also the coreceptor, TMPRSS2. So when you've heard about the use of monoclonal antibodies, these appear to be specific for that interaction between the spike protein and the receiving receptor, which we think is ACE2.

If we forward again-- if you press forward again-- yep. On the other hand, a drug that's evolving and we're looking at is camostat mesylate. And that blocks of TMPRSS2, which we also think is quite important in the actual interaction between the virus and between the receptors on the cell surface. But that hasn't gone very far into clinical trials, at least here in the US. Hydroxychloroquine, which we've probably heard a lot about, had a rationale-- at least in vitro-- in terms of where it may act, especially in terms of working endosomally within the cytoplasm of cells.

And if we go to the next part of the slide-- thank you. And then you heard about the rationale for using ritonavir-boosted lopinavir, which is still used as a drug against HIV. And the rationale here was looking at the stage of protease cleavage and proteolysis, per se. Next slide-- or next component.

Remdesivir, which you begin to hear about shortly in terms of its clinical efficacy, on the other hand, inhibits viral RNA polymerase. And that is also the mechanism of action of the drug favipiravir. Forward.

And then there's immune response modifiers. And I'll also mention a couple of these, tocilizumab and sarilumab. And these drugs are actually looking at the inflammatory response-- in other words, the immune response. So we've spoken a little bit about the antiviral effects, including the monoclonal antibodies-- remdesivir and favipiravir-- and then here we've got immune modulation and its potential benefits. And I'll talk a little bit about the trials that have come about and their efficacy in terms of improving patient outcomes.

If we go to the next slide. And this really reemphasizes the viral response phase, which is present and was described earlier this year, and then the effects of the host inflammatory response or the cytokine storm, and what they're associated with-- for instance ARDS, elevated inflammatory markers, for the host inflammatory response, and the viral phase, which is more associated with the constitutional symptoms that Dr. Hall described earlier.

I think that's the end of my slides here. So those are the principles in terms of the mechanism of action of the drugs. What is the evidence in terms of clinically? What do we see in the patients? And what's actually been reported?

Well in May of this year, there was some data coming out about the efficacy of remdesivir. This is a multi-center, multinational, double-blind placebo-controlled trial, which is randomized. It was in adults with lower respiratory tract infection from SARS-CoV-2. Patients were either assigned to remdesivir or placebo for 10 days with the primary outcome being time to recovery.

There were more than 500 patients in each arm. So this was very well powered. And in the remdesivir group, the median recovery time was 11 days compared to 15 days amongst those with placebo. The mortality by 14 days was 7% with remdesivir and close to 12% with placebo.

There were adverse effects noted in about 21% of the remdesivir group and 27% of the placebo group. The authors here therefore concluded that remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19 and who had low respiratory tract infection.

Now in terms of what is available for children right now, remdesivir is available on a trial basis or by compassionate use from its manufacturer. It's also available by emergency use authorization in children under 18 years with confirmed COVID-19 and severe manifestations of disease.

Now in terms of the evidence base for the use of convalescent plasma therapy, we had an article that was published just on June the 3rd in JAMA-- the Journal of the American Medical Association. This was an open, label multi-center, randomized controlled trial. It was from Wuhan, China. There were over 100 participants, although the investigators were looking at targeting 200 into the trial.

They put about 50 into the standard treatment and about 50 into a group that receive standard treatment, plus convalescent sera. The primary outcome was clinical improvement within 28 days. And what they were able to show was basically that clinical improvement occurred within 28 days in about 52% of the convalescent plasma group, compared to 43% in controlled.

They concluded that in patients with severe or life-threatening COVID-19, convalescent plasma therapy did not result in significant clinical improvement within 28 days. But there is a caveat, which was that the interpretation was limited by early trial termination because the study was underpowered. And this was because with the outbreak taking place in Wuhan, they had planned to enroll a sample size of 200 and weren't able to reach that sample size because there were fewer cases occurring in that city with the advent of lockdown and a number of the other interventions that had taken place.

So a similar multi-center trial is currently being undertaken through Mayo Clinic. And there will be a multi-center pediatric arm to this particular trial.

Now in terms of immune modulators-- and speaking a little bit about their effects-- I mentioned tocilizumab. And the clinical evidence base comes from a report in the proceedings of the National Academy of Sciences here in the US from our colleagues in China. Here they again had patients with severe or critical COVID-19 in the city of Anhui, in China.

They were given tocilizumab, which is an anti-IL-6 drug, in addition to routine care. And within five days, the Investigators reported that 15 of 20-- or 75% of the group studied-- had lower oxygen intake. CT scans improved in about 90% in the lymphocyte percentage, which is often associated with a precipitous decrease, which was noted in 85% of patients, which turned to normal in about half of patients by day five. No adverse effects were observed. And all the patients were discharged on average at day 15.

Finally, the other drug I was going to talk about was anakinra. This blocks interleukin-1 and has had its use in patients with hyperinflammation. Retrospective study published in May basically showed that-- from Milan-- that again that treatment with high doses anakinra was safe and associated with clinical improvement in 72% of patients they followed-- the number was 21 or 29 patients-- with reductions noted inflammatory markers as well.

So there are a number of products that are available on the market. And there's finally one note today that's come out from a large trial coming from Oxford, which again is multi-center-- actually just today-- and I read it actually in the media and from the BBC-- about the benefits of dexamethasone as a potential intervention, which may be important in more resource limited settings, where you may not have access to drugs like anakinra and tocilizumab and remdesivir. I think I'll stop there. Thank you.

CHARLES HUSKINS: Thank you very much. I know there's a lot of interest on day care and school. And so we're going to try and save the last 10 to 15 minutes for that. But before we get to that, we're going to just have a brief update on MIS-C from Dr. Hall and Dr. Levy.

DJ HALL: So quickly, something that's come up quite a bit in the news as probably the most severe complication that we're seeing surrounding coronavirus in children is MIS-C. Dr. Huskins gave us a definition of that earlier. But the CDC has now recognized this as being a reportable disease. It was first reported in Europe. In the United Kingdom they noticed a cluster of cases. We have since seen a cluster of cases in New York and several different areas throughout here in the United States.

The epidemiology of this is somewhat interesting in that it can occur in any child under the age of 21. However it seems to have a predilection for children of older elementary school age to adolescence, so children from the 9 to 13-year-old range. The symptoms are reported here on the screen, but typically are three to five days of fever followed by more severe and organ involvement. This can include cardiac impairment or signs and symptoms of shock.

There is some overlap around Kawasaki disease. But I think Dr. Rajapakse can share a little bit on some of the quick initial investigations, which are highlighted here by the CDC, but also that she can share some expertise on.

NIPUNIE RAJAPAKSE: Great. Thanks, Dr. Hall. So I think one of the really critical things that we have seen so far when you look at lab findings in children presenting with this syndrome is marked inflammation, so elevation of things like C-reactive protein, ESR-- erythrocyte sedimentation rate-- ferritin, those have been essentially universal across all of the cases that have been diagnosed thus far.

When you look at the complete blood counts from these children, a few things of note have been reported including leukopenia and specifically lymphopenia, as well as neutrophilia and thrombocytopenia. There have been noted to be-- especially in children with cardiac involvement-- elevation of some of the cardiac markers, so troponin and pro-BNP. And then some children have presented with concerns for coagulopathy as well and elevated D-dimers.

Many of these children, given recognition of the potential at least for cardiac involvement, have had echocardiograms performed. And the most common findings reported have been findings of myocarditis, especially left ventricular dysfunction. Some children have been found to have-- either at the time of diagnosis or later on in their course of illness-- coronary artery dilatation or aneurysms, which has been part of the reason why there have been parallels drawn with Kawasaki disease, which is the most common cause of these that we see in children.

In terms of other testing, so temporarily, there seems to be a relationship with this SARS-coronavirus-type-2 infection. A majority of children reported in the literature have had antibody or positive serology. Some have still had positive PCRs. And some have presented with both positive PCR and positive serology as well. But the large proportion presenting with positive serology is another clue that helps with the hypothesis that this is likely a post-infectious type of inflammatory syndrome.

Testing has been conducted in many cases to look for other infectious etiologies. There's some crossover with other infectious syndromes, like toxic shock syndrome. And while some children have tested positive for other viruses, generally they have not been able to identify any co-infection that is occurring frequently amongst these children. Certain lab findings have been found to be predictive of higher likelihood to progress to critical illness or more severe presentations like shock, including higher CRP, lower lymphocyte counts, and neutrophilia, as well as [INAUDIBLE] anemia.

To contrast a bit with Kawasaki disease, which many pediatricians or people who care for children are probably familiar with as Dr. Hall mentioned, the age group of children presenting with MIS-C seems to be older, so median age range from 7 to 9 to 11 years of age. And we have seen a disproportionate number of cases occurring amongst racial and ethnic minorities, specifically within the black population and the Latinx community.

And I think that's an area that we need to understand better. We do know that those children, like adults, have been disappointingly infected with SARS-coronavirus-2. But there may be other factors playing into that observation as well.

And when they've done comparisons between children diagnosed with Kawasaki disease prior to the COVID-19 pandemic, generally looking at inflammatory markers, children with multisystem inflammatory syndrome seem to have greater elevation of inflammatory markers as compared to prior cohorts of Kawasaki disease. So I think we still have a lot to learn about this syndrome. And there's a lot of research underway. And some great articles that have come out in the last few weeks describing these cohorts of children. But those are some of the initial observations at least that we've been hearing about.

CHARLES HUSKINS: Thanks very much, Dr. Hall and Dr. Rajapakse. Dr. Levy, we've got a couple of minutes. I've heard the management of MIS-C described as good old fashioned ICU care. Is that true?

EMILY LEVY: Dr. Huskins, that is true. In fact on my notes, I had a bullet point that said, this is supportive, good old fashioned critical care. In contrast to patients with primary COVID-19 disease-- like Dr. Rajapakse Dr. Hall said-- this is a post infectious inflammatory disorder, we believe, and not an active infection. And these patients are very likely to present with shock and myocardial dysfunction.

They should be managed in a center with both PICU and ECMO capability and also with ped subspecialists who are used to managing cytokine storm. That includes rheumatologists, infectious disease doctors, also, ideally hematology, immunologists, and cardiologists would be involved in their care. More than 50% of them-- in terms of the official reports we have so far-- present with vasodilation and myocardial dysfunction shock.

There was one report of 58 children from the UK-- from a group called the PIMS-TS group-- and they reported that 62% of them had myocardial dysfunction, which resulted in [INAUDIBLE] heart failures and low cardiac output syndrome. 5% of that group were required to VA ECMO. The vast majority of respiratory distress in this population is secondary to shock. So they are less likely to require mechanical ventilation for primary respiratory distress. But of course that can be part of the management of shock. And they are likely to acquire fluid overload during their course because of the management shock early on.

In terms of medication, if Kawasaki disease criteria are met, either atypical or typical, we're still treating these patients per standard Kawasaki care. And that's IVIg and aspirin. We're considering high dose steroids in all cases, whether it's a Kawasaki disease type patient or a patient with less typical Kawasaki disease presenting symptoms and more severe shock.

We're considering early anticoagulant, both prophylactic and treatment levels, which is stratified by symptom severity and the level of myocardial dysfunction the patient has. And then as several people have mentioned, echocardiogram are part of the hallmark of care for these patients because they are very likely to develop coronary artery aneurysms. They are more likely to develop them in patients with Kawasaki disease from what we've seen in initial reports so far, although we don't have final data on this at this point.

Because these patients are likely to develop coronary artery aneurysm, we know in terms of Kawasaki disease outcomes that typical Kawasaki disease outcomes are good. But if a patient does have a coronary artery aneurysm, that can complicate outcomes. We're seeing less death in these patients. But we have very little data about long term morbidity and survival outcomes. And we do know from the Kawasaki disease literature that patients with coronary artery aneurysms often require long term anticoagulation and have a higher lifetime risk of acute coronary events.

Lastly, I'll just mention that there are many clinical specialists who are considering immunomodulatory agents in these patients, such as anakinra, infliximab, and tocilizimab. Those are anti-IL-1, anti-TNF, and anti-IL-6 respectively. We don't have a lot of data about this as of yet. And so more data will be needed as we continue to understand this disease, the children it affects, and how to manage it.

CHARLES HUSKINS: Great. Thanks very much. Well we've got about 10 minutes left here. And the topic of daycare and school is one that many people are interested in. So Dr. Rajapakse, I'm going to ask you to address that. And then, Dr. Hall, I'm going to ask you to make a couple of comments about some of the unintended consequences of what might happen in the COVID era in terms of other health outcomes for kids. And then we'll take whatever remaining time for remaining questions at that point.

So Dr. Rajapakse, what should do we do? Daycare, yes? No? High risk kids, any kid-- what kind of precautions should we take? And what about school?

NIPUNIE RAJAPAKSE: I think this is a really critical question, Dr. Huskins. And I think it's a complicated one. And I think there's not going to be one answer that fits all situations. Obviously schools are closed early on in the pandemic because of concerns regarding transmission of infection within the school setting. This has been-- in outbreaks of influenza especially-- found to be an effective measure to prevent large outbreaks and community transmission.

But there are very real negative consequences from having kids out of school, especially for prolonged periods of time. And I think those need to be carefully weighed along with the risk of infection when we make these decisions going forward about if and when to reopen schools. About 20 million children in the United States depend on schools for breakfast and lunch programs. And we have seen [INAUDIBLE] security become a significant issue having to keep them at home.

Millions of children also depend on school systems for their health care. And so that's been another area that we have seen kids struggling. I think firstly it is important to have public health professionals-- infectious disease specialist-- pediatricians involved in the discussions around reopening of schools. And I think a lot of these discussions will depend on the local epidemiology and what is going on in specific areas.

If and when schools do reopen, I think they will look different than what we're used to. There have been proposals about different types of measures that can be put into place to reduce the risk. But really none of these will reduce the risk all the way to zero in most areas.

And so some things that have been proposed are strategies like staggered drop off and pick up times to avoid a lot of crowds of people congregating at the school, distancing of desks-- obviously space considerations come into play-- keeping children in small groups and restricting mixing of groups-- such that if there is a case within a group, it will be a relatively confined number of people that may be exposed to that child-- and then symptom screening not only of the children themselves but of everyone within the household and recommendations that if anyone in the house is sick that the child should not be sent to school.

I think those are some of the things that have been proposed going forward along with other measures, like masking of children and teachers. And continuing to offer alternative strategies I think will be very important and helpful, especially to some of the children that may be at highest risk, or may live in a home with someone who is very high risk. So continuing to offer some of the virtual learning setups that have been put in place already will be an important consideration going forward as well.

So I think it's a complicated issue. I think a lot of people will need to be involved in the discussions of how to do this safely and when it is safe to do so. There's still a lot of questions about what is going to happen through the fall into the next influenza season and whether we will see both flu and COVID-19 circulating. And I think we have a bit of time now over the summer break here in the United States to try and understand this infection better, understand transmission better, and try and figure out what we can do to reduce the risk.

CHARLES HUSKINS: Dr. Hall, do you have any additional comments on that?

DJ HALL: Just to echo what was mentioned earlier, I think that there's many concerns around children being out of school. In addition to the issues that surround food and security, we also know that when children aren't in school there's an increase in screen time. There's a decrease in exercise. There's also a change in overall mental health, as we see.

Studies have already reported increased risk of anxiety and depression in children who are removed from the social environment. The other unintended consequences of social isolation are keeping children in the home of places where they may be exposed to potential child maltreatment. And all of those are things that we have to be really cognizant of as we're continued to advocate for pediatric care.

Additionally we've seen pediatricians and telemedicine providers doing the appropriate thing by delaying well child care. But this has also created to delay in vaccines and a delay in other types of care that children need for conditions such as ADHD or more common diagnoses that could have been managed in the clinical setting. So we're going to have to be vocal and be an advocate for children because they're impacted in many ways because of the changes we've made secondary to coronavirus, and maybe even more so than the virus has impacted children at the medical level.

CHARLES HUSKINS: Great. Thanks very much. I still see some questions with concerns about kids with high risk conditions-- asthma, diabetes, these sorts of things-- in terms of what their risks are with school. I'll just comment. Anybody else, feel free to add to this. I think the general principles of masking, social distancing, hand hygiene, and surface disinfection are really critical. And that's true no matter where you are-- in the home, in the daycare center, in the school, in the hospital, et cetera.

So I think we have good evidence that those kinds of interventions can have a very significant impact. It doesn't necessarily mean it's going to eliminate any effect. But it can have a very significant effect. We just have to do them carefully and consistently. Anybody else with any comments on that topic?

We have a couple other questions. Let's see, I'm going to ask Dr. Chakraborty, could you comment briefly on vitamin D? Do we know anything about that?

RANA CHAKRABORTY: There has been some discussion with vitamin D. And it's that lower levels may be associated with worse outcomes. It's probably worthy of further investigation, knowing also that there are large populations that seem to have been affected by coronavirus who have historically also had low vitamin D levels.

And in this respect you talk about the African-American, Afro-Caribbean populations, and also folks from the Indian subcontinent and the UK. They've historically had low levels. Maybe there's an association. But it's also multifactorial. And there could be other issues related obviously to hypertension, impaired glucose tolerance, and so on and so forth. So it will take a little time to tease out, but may be worth looking at further.

CHARLES HUSKINS: I see a couple other questions about the immune system and potential immune effects. I think at this point, I would just add I think it's too early to really know what the potential effects down the road might be on the immune system. Hopefully children will recover without difficulty and there won't be any long term effects. But I think that's an important question that we need to address in the future.

So I'm going to stop here because I think we have some housekeeping to close with. Theresa?

THERESA MAYLIN: A reminder on how to claim credit. If you'd like to claim credit, please visit ce.mayo.edu/covid0616. You'll need to log in. And if you haven't created an account on the site before, you'll need to create your account first.

Then on the site you'll be able to click the Register tab. Underneath that tab, you'll see this box for an access code. In that box you'll enter COVID0616 and hit Unlock. This will allow you to start the course. Once you're in the course, they'll take a short evaluation. And then you have access to your certificate.

Thank you, everyone, for joining us today.

CHARLES HUSKINS: Can I make one quick comment too-- which is--

THERESA MAYLIN: Yes.

CHARLES HUSKINS: --thank you very much for your attention. Thanks for the great questions. And thanks to the presenters for their expertise and great discussion. So thanks very much. Have a great day.