

Good afternoon. I'm Commander Ibad Khan and I'm representing the Clinician Outreach and Communication Activity (COCA) with the Emergency Risk Communication Branch at the Centers for Disease Control and Prevention. I'd like to welcome you to today's COCA call: Multisystem Inflammatory Syndrome in Children Associated with Coronavirus Disease 2019. Today's webinar will be closed captioned. The CC button in the Zoom webinar platform to enable closed captioning is located either on the top or bottom of your screen.

All participants joining us today are in listen only mode. For participants using the Zoom platform to access today's webinar, if you are unable to gain or maintain access, or if you experience technical difficulties, the archived video of this COCA call will be available shortly on COCA's webpage at emergency.cdc.gov/coca a few hours after the call ends. Again, that web address is emergency.cdc.gov/coca. Continuing education is not offered for this COCA call.

After the presentation, there will be a Q&A session. You may submit questions at any time during the presentation through the Zoom webinar system by clicking the Q&A button at the bottom of your screen and then typing your question.

If you are unable to ask the presenters your question, please visit CDC's COVID-19 website at www.cdc.gov/covid-19 for more information. You may also email your questions to coca@cdc.gov.

If you're a patient, please refer your questions to your healthcare provider. For those who have media questions, please contact CDC Media Relations at 404-639-3286 or send an email to media@cdc.gov. For more clinical care information on COVID-19, you may contact CDC's COVID-19 Clinical Call Center at 770-488-7100. The center is available 24 hours a day.

Again, that number is 770-488-7100. We would like to remind clinicians to please refer patients to state and local health departments for COVID-19 testing and test results. Clinicians should not refer patients to CDC to find out where or how to get tested for COVID-19 or to obtain their test results. Also, please continue to visit emergency.cdc.gov/coca over the next several days, as we intend to host more COCA calls to keep you informed of the latest guidance and updates on COVID-19.

In addition to our webpage, COCA call announcements for upcoming COCA calls will also be sent via email. Subscribe to receive these notifications by going to emergency.cdc.gov/coca/subscribe.asp. Again, that's emergency.cdc.gov/coca/subscribe.asp.

Please share the call announcements with your clinical colleagues. I would now like to welcome Dr. Sapna Bamrah Morris, the clinical team lead for CDC's COVID-19 response. Dr. Morris will kick us off with a brief introduction, then she will turn it over to Dr. Ermias Belay, the special investigations team lead for CDC's COVID-19 response to provide a short update. Following Dr. Belay will be today's first presenter, Dr. Michael Levin, professor of pediatrics and international child health and Imperial College in London, England.

Following Dr. Levin will be our second presenter, Dr. James Schneider, chief of pediatric critical care medicine and associate professor of pediatrics at Cohen Children's Medical Center. Then today's third and final presenter will be Dr. Vincent Marconi, who's a professor of medicine and global health at the Rollins School of Public Health at Emory University School of Medicine.

Please note that Dr. Morris and Dr. Belay will not have presentation slides. The slide presentations will resume when Dr. Levin begins his presentation. I would now like to turn it over to Dr. Morris. Dr. Morris, please proceed.

Thank you, Commander. I'd like to start by thanking our speakers who are here today to share their experience and expertise. I would also like to acknowledge the inter-task force workgroup that has been formed here at CDC, as well as our field team and partners helping us to learn more about this multisystem inflammatory syndrome in children, or what we're calling MIS-C. Since the start of the pandemic, we've been learning about how infection with SARS-CoV-2 manifests in patients. We've seen the spectrum of asymptomatic infection to severe COVID-19 with substantial morbidity and mortality.

In adults, the immunopathogenesis is becoming a bit more clear: an early viral replication and response phase, a second non-severe symptomatic phase, and, in some, a third severe respiratory phase, often leading to the need for critical care and mechanical ventilation. It is apparent that, in adults, some of the most severe complications resulting in increased morbidity and mortality are linked to a cytokine release or a cytokine storm during and after this third phase. While some of these mechanisms have been described, we have a great deal more to learn about optimizing care and treatment. Dr. Levin and Dr.

Schneider will be sharing their experiences seeing pediatric patients presenting with the new multisystem inflammatory syndrome that is temporally related to infection with SARS-CoV-2. We've also invited Dr. Marconi to share what we have learned about the inflammatory component of COVID-19 in adults and some of the treatments that are currently being studied. We hope this serves to describe aspects that may be similar but also to highlight the differences in the presentation in children and adults. Now I'd like to introduce two of my CDC colleagues, first Dr.

Matt Oster, who's a pediatric cardiologist. Matt will be joining us for the Q&A session. I'm sorry that I neglected to list his name on the slide. Secondly, I'd like to introduce Dr. Ermias Belay, who's a pediatrician and the associate director for science for the Division of High Consequence Pathogens and Pathology.

As Dr. Belay is coordinating our CDC work group on MIS-C, I would like to ask him to share a brief summary of our current activities.

Thank you, Bamrah, and good afternoon, everyone. Since MIS in children was first reported here at CDC, we've been learning more about this condition, as Dr. Bamrah indicated. We've formed a work group to better understand and learn about this disease. And this work group developed a working case definition, which by no means is perfect and will be revised as more data become available.

On May 14, the CDC issued a health advisory on the MIS in children, and this healthy advisory was widely circulated among clinicians in the public health community in the United States. The health advisory described what we know about MIS at the time and it outlined our working case definition and requested clinicians to report suspected cases meeting the case definition to local and state health departments. We're working with the local and state health departments to establish a national monitoring system to better understand the burden and assess any potential risk factors for MIS and its temporal association with the COVID-19 pandemic. And we also try to better define the different clinical phenotypes of the illness. We developed a case reporting form to capture some critical data regarding the clinical, the laboratory, and epidemiology characteristics of this illness.

And as the COVID-19 pandemic continues and probably even through the fall, we urge clinicians to contribute to this national monitoring system by reporting cases to their local and state health departments. At this point, I would like to introduce Dr. Michael Levin to start sharing his experiences with the group here. Dr. Levin.

Hello and thanks very much for the invitation to share the experience we've had in the United Kingdom with you. And I'd like to start just by acknowledging that the data I will be presenting was developed by a wide group of pediatricians working at several London hospitals: Imperial College, NHS Trust, Great Ormond Street Children's Hospital, and the Evelina Children's Hospital, as well as a number of other hospitals. And I'm presenting on behalf of all of them. So I think that perhaps the only good news there was on the COVID epidemic seemed to be that children had mild disease. And as the disease arrived in the UK, I think that was the general pattern.

Most children seemed to have very mild disease. Few ended up becoming critically ill. And so there was a surprise amongst a number of us working in several London hospitals -- if I could have the next slide. Towards the end of March and the pandemic had arrived in the UK in early January and cases were increasing during February, and it was sort of towards the end of March that a number of pediatricians started noticing an unusual illness. And we had children who were admitted to pediatric intensive care units, critically ill with a very unusual syndrome.

They had been unwell with variable symptoms, often including sore throat, headache, but particularly abdominal pain and vomiting. Some of them had rash. Some of them had conjunctivitis or conjunctiva injection, raising concerns about a similarity to Kawasaki disease or Staphylococcal toxic shock syndrome. And this problem progressed rapidly to shock and organ dysfunction. And the children had a remarkably similar laboratory appearance in that they had very marked elevation of C-reactive protein, marked elevation of neutrophils, profound lymphocytopenia, elevated D-dimers.

And we started to notice some had marked elevation of troponin and brain natriuretic peptides, so suggesting a cardiac injury. The majority of our children were negative when tested for SARS-CoV-2 by PCR. And between the end of March and the end of April, we collected 37 cases from eight hospitals in and around London. And because there seemed to be a syndrome distinct from other pediatric entities, we felt it was necessary to systematically review the cases and attempt to establish a case definition. If I could have the next slide, please.

So in order to develop a case definition, all cases were systematically reviewed and the clinical and laboratory data placed on a database. The results were reviewed by a team that consisted of pediatric infectious diseases clinicians and intensive care clinicians. And in particular, we focused on had there been exclusion of other causes of shock and multi-organ failure, including bacterial sepsis, Staphylococcal toxic shock syndromes, infections associated with myocarditis such as enterovirus and macrophage activation syndromes. And after this review, we felt that this disorder was sufficiently unusual and sufficiently distinct from conditions that we knew about, that we alerted the National Health Service in the UK on the 24 of April. And if I can have the next slide, please.

On the 27 of April, the Royal College of Pediatrics and Child Health -- which is the body connecting pediatricians in the United Kingdom -- issued guidance for a disorder that we termed "pediatric multisystem inflammatory syndrome," temporarily associated with COVID-19. And we use temporarily because at that stage the association wasn't clear and still remains unclear as to the exact mechanism by which this upsurge in cases is related to the pandemic. The case definition which we used was a child presenting with persistent fever, inflammation with neutrophilia, elevated C-reactive protein and

lymphopenia. Evidence of single or multiple organ dysfunction of which shock, cardiac, respiratory failure, renal, gastrointestinal or neurological disorders were possible. And with an additional set of set of features, which we listed in an appendix which I'll come to.

In addition, to meet the case definition, we had to have excluded other microbial causes, including bacterial sepsis, staphylococcal and streptococcal toxic shock syndromes, enterovirus infection, and autoimmune disease. And SARS-CoV-2 PCR could be positive or negative, and antibodies were usually positive, as I'll come to. Next slide, please. So the cases identified in this relatively short period came from a number of areas, shown in the red dots, around London and the south of England. The age range was one to 16 years, with a median of 11 years.

There was a male predominance with 62% being male. And most of them were completely healthy children previously, with only a small number of children having the common comorbidities. One child had epilepsy. One child had asthma. But generally these were healthy children.

Next slide, please. A striking feature in this first description was that there seemed to be a predominance of children from black African, Caribbean, British ethnicity, who accounted for about 46% of the cases. Whereas in London, they account for 13%. And in overall England and Wales, about 3%. The proportion of white patients seemed lower than the proportion of white people in London or in the rest of England.

And there was also an increased proportion of South Asian, Indian Asian, British, with 11% in our series. London has a high incidence for this group, but it's higher than the rest of the UK. Next slide, please. The clinical presentation after the prodromal illness was the predominant presenting feature was shock and with evidence of myocardial failure. And 75% of the patients had shock, 51, with clear features of myocardial impairment.

A rash occurred in just over half of the children. 30% have had conjunctival injection. And 20% had mucous membrane inflammation or red, cracked lips. So a low proportion having features that were similar to Kawasaki disease. A striking feature was that abdominal symptoms were very prominent with a number of the children having abdominal pain, vomiting, diarrhea.

And three children were actually severely worried enough that they ended up having a laparotomy to exclude appendicitis or intussusception, with no obvious findings, suggesting a surgical cause. Renal injury was common with raised creatinines, but only one child required renal replacement therapy. And unlike adults with COVID, only a third had predominantly respiratory problems. And generally the major management problem was not a severe respiratory failure. Next slide, please.

The laboratory features were really quite striking. Patients had marked anemia with a median of 84. And they all had neutrophil elevation and very marked depression of lymphocyte counts, with a median of 0.6 lymphocyte counts. Platelets tended to be low.

There was elevation of D-dimers, suggesting coagulation activation. But despite this, the ferritin levels were elevated and fibrinogen levels were markedly elevated. I've already mentioned that troponin levels were elevated. And in the patients that it was measured in, pro-BNP or BNP was markedly elevated. And C-reactive protein in all the children was markedly elevated.

If I can have the next slide, please. Radiological findings on chest x-ray, there was a range of findings. Some patients had normal findings. Some had bilateral pleural effusion. Others had patchy consolidation.

Some had focal consolidation or atelectasis. Those patients that underwent a CT scan of the chest all had some areas of nodular ground glass opacification. Abdominal ultrasound or CT abdomen was undertaken in many of the patients, with evidence of bowel inflammation, distention, thickening of the bowel, and in particular intra-abdominal lymphadenopathy. Next slide, please. The cardiac findings were striking.

A significant proportion of them -- eight out of the 19 -- who had echocardiograms initially had evidence of impaired left ventricular function. Coronary artery dilatation or aneurysms was present in a significant number of children. So five out of the first 19 had evidence of coronary artery dilatation. And one child had a giant coronary artery aneurysm. Next slide, please.

The management of the patients is that all were treated in high-dependency or intensive care. The majority required fluid resuscitation. The majority required inotropic support. And then a range of other immunomodulator treatments were given, largely because of the extreme evidence of inflammation in laboratory findings, and also because some of the patients had features suggestive of Kawasaki disease. Intravenous immunoglobulin was the commonest immunomodulator used, with 62% of the patients receiving it.

And then we had some receiving immunoglobulin and steroids. And then there were a range of other immunomodulators -- Anakinra, Infliximab. And some received Azithromycin as part of COVID treatment. Next slide, please. The outcomes was that the majority of patients responded quickly to treatment.

Two children required extracorporeal membrane oxygenation. And one child died as a complication of ECMO with an intercranial thrombus and then hemorrhage. In general, the patients had a slower response than we see in many other infections. And a number of them took quite a considerable amount of time to come out of intensive care. Next slide, please.

SARS-CoV-2 results, only a third of the children were PCR positive for SARS-CoV-2, and often only after multiple testing from repeated respiratory samples, bronchial samples and stool. In contrast, a high proportion of the patients were positive for antibody. And when we first started seeing the patients, antibody testing wasn't easily available, but subsequently, a very high proportion of these patients are antibody positive against SARS-CoV-2. Next slide, please. So the question that, in reviewing the patients, we had was, what was this illness? There were obviously some features reminiscent of Kawasaki disease, somewhat similar to the syndrome of Kawasaki disease, shock syndrome.

There were features of staphylococcal, streptococcal toxic shock syndrome. There was some features suggesting macrophage activation syndromes with marked elevation of ferritins and extreme inflammation. And there was some similarity to a syndrome that we saw a lot during the 1980s, haemorrhagic shock and encephalopathy syndrome. But that generally tended to affect younger children. And there was some evidence of overlap with the features of autoimmune conditions.

But we found no evidence of staphylococcal or streptococcal. And if I could have the next slide, please. In order to compare these patients with Kawasaki disease and Kawasaki disease shock syndrome, we were very fortunate to have had a long-standing collaboration across the Atlantic with Jane Burns and

her group at Rady Children's Hospital in San Diego. And Jane has a data collection of children with Kawasaki disease, which includes over 1,000 children with Kawasaki disease. And it's a remarkable tribute to the willingness of clinicians to share information and pool resources in investigating COVID and new diseases.

In that we telephoned Jane Burns and asked if we could compare these new patients to her database. And 24 hours later, Jane and her team sent us the complete database. And so I'm showing you results that are a collaboration between the UK and the San Diego group. Next slide, please. So this slide summarizes the features comparing the new syndrome -- which we called in red "pediatric inflammatory multisystem syndrome.

In blue is the Kawasaki disease patients. And in yellow, Kawasaki disease shock syndrome. And then the black is toxic shock syndrome caused by either staphylococcus or group A streptococcus -- which we had connected as part of an EU-funded, multicountry study called Perform. So the first box shows that the children with the multisystemic inflammatory syndrome were older in age significantly. Their white cell counts, in the next box, was significantly higher than Kawasaki disease or Kawasaki shock syndrome, though overlapping that of staphylococcal toxic shock syndrome.

The neutrophil counts was significantly elevated relative to Kawasaki disease or Kawasaki shock. The lymphocyte counts were markedly depressed compared to Kawasaki or Kawasaki shock. Hemoglobins were significantly lower than all the other groups, as is in that middle panel. The platelet counts were lower than Kawasaki or Kawasaki shock syndrome. C-reactive proteins were more elevated significantly than either Kawasaki or Kawasaki shock or toxic shock.

And the albumin levels were also markedly lower than those seen in Kawasaki or Kawasaki shock. And in the bottom panel, the ferritin levels were significantly elevated compared to Kawasaki or Kawasaki shock, as were troponin levels and D-dimers. Next slide, please. So I think the conclusion from our comparison of the laboratory features and some of the clinical features was the syndrome seemed distinct from Kawasaki disease and from staphylococcal toxic shock syndrome. It seemed to be a new and unusual childhood illness, which was emerging really a month behind the COVID epidemic curve in the UK.

And it had distinctive laboratory features which differ from other syndromes, with marked troponin elevation, D-dimers, high CRP, and particularly markers of cardiac injury. Next slide, please. So this slide just shows the time course of the emergence of the syndrome in the UK, with the red curve showing the cases of the pediatric inflammatory multisystem disorder. And the blue cases showing the overall COVID positive PCR in London. And what we can see is that the new syndrome has emerged about a month after the curve of the COVID epidemic.

Next slide, please. Also, this is the distribution again from the UK Public Health laboratory service data, which with the age distribution and also the severity of the disease, and what you can again see is that, in children -- in the bottom part of the bars -- virtually all the children were discharged. There were very few deaths and very few had ongoing care. So it was a very mild disease until the emergence of this syndrome. Next slide, please.

So what is the mechanism? Well, I think we do know, but the timing after the COVID-19 curve, the majority of patients being negative for virus but positive for antibody, would suggest that this illness is mediated by the development of acquired immunity to COVID rather than by direct viral injury. Next slide, please. Since we established the case definition for pediatric inflammatory multisystem disease in

the UK, we've also become aware of a widening definition and widening numbers of cases. First of all, the red at the tip of the pyramid is the pediatric inflammatory multisystem syndrome, temporarily associated with SARS-CoV-2. But in addition, throughout the UK and in many European countries, there are now reports of typical Kawasaki disease appear in children with coronary artery injury, with all the usual features of Kawasaki disease, but with a large upsurge in numbers.

And increasingly, we are seeing children with no features of Kawasaki disease, no multiple organ failure, but with persistent fever and with elevated inflammatory markers -- raised CRPs, raised ferritins, raised neutrophil counts, and lymphopenia. And it would seem that this is a widening spectrum of disorders which probably have a common mechanism. Next slide, please. The emergence of these three disorders seem to have raised a number of urgent research questions, most of which we don't know the answers of yet. Do patients progress from the less severe form -- the febrile child with raised inflammatory markers -- to the more severe forms if we don't treat them? What is the risk of coronary artery aneurysms of each group? Because if there is a significant risk in all three groups, then treatment as for Kawasaki disease might be needed.

What is the relationship of all three disorders to the pandemic? Do anti-inflammatory drugs and immunomodulators such as immunoglobulins, steroids, anti-TNF, anti-IL1, and so on, improve the outcome and reduce the risk of coronary artery aneurysms? What are the mechanisms? And are there biomarkers which distinguish each group from COVID and from other conditions? So those are the questions that we've been grappling with in the UK and really need to be addressed at a multinational level in order to pool resources. Next slide, please, and that's my final slide. So in the UK and in Europe, we have two studies which are attempting to address some of these questions. The first is Diamonds, is a EU-funded grant which was awarded. It's led from our group at Imperial College.

But it includes 11 countries in Europe. And it aims to understand the biology of the disease by undertaking RNA transcriptome analysis, proteomic analysis, and genetic analysis, not only of COVID or this emerging spectrum of disease, but all infectious and inflammatory diseases. And we're attempting to recruit patients to these studies, which are now up and running in 11 EU countries in the UK. And the last study that I'm going to mention -- which we think is perhaps another way of trying to address some of the issues -- and it's a study that we've termed "the best available therapy study," or BATS. And it is an anonymized, multicountry study of the best treatment for the pediatric inflammatory multisystem syndrome, the Kawasaki disease associated with SARS-CoV-2, and the febrile inflammatory syndrome.

And the principle of the study is that we're inviting pediatricians all over the world to enroll patients. And each clinician -- we know pediatricians generally give their best treatment for their patients. And at the moment, because we don't know which treatment works, we don't know whether the treatments that usually work in Kawasaki disease will work. We are comparing the rates of normalization of inflammatory markers and the rates of development of coronary artery aneurysm as well as time on ventilators and inotropes in all patients who are entered into the study. And while this isn't a randomized controlled trial -- and we would much obviously prefer to be doing a randomized controlled trial -- the cases have emerged too rapidly to be entered into the trial.

And this study will let us propensity match by severity at enrollment, so that we can actually get an idea of which treatments may work and also whether there is progression from the milder forms to the more severe forms. And we think it's possible to do propensity matching, because we've got very good biomarkers of disease severity, or the severity of inflammation in terms of the CRP, the ferritin, the troponin, the BNP. And we've also got clear endpoints. So we are hoping to be sending out invitations to research teams and clinicians in many countries towards the end of this week, inviting people to

participate and submit their patients. It's an online, anonymized database, so would be welcoming of patients.

So last slide, please. I just want to say that we have had so much to learn in such a short time. And I know that pediatricians across Europe and the United Kingdom have pooled patients, have worked together to try and understand this disease. And we've had wonderful collaboration across with the teams in the United States such as Jane Burns's team in San Diego. And we're very keen to work on this in a collaborative way.

Last slide is just to again acknowledge -- if you could go to the last one -- that Diamonds study is an EU Horizon Twenty funded study, which is supporting recruitment of patients. And again, acknowledging all my colleagues at the different hospitals and the NHS and Royal College of Pediatrics and Child Health, who led the alert. Thanks very much.

Thank you Dr. Levin, for sharing your critical insight on this rapidly evolving matter. I believe we have Dr. James Schneider following your presentation. Dr.

Schneider, if you would please commence.

Great. Thank you very much. I appreciate the opportunity and the invitation to participate in this academic activity together and share some information about our experience in New York. If you could go to the next slide please. Next slide, please.

There we go. And we'll go to the next slide then. So first off, again, a warm thank you to everyone for listening, for participating. Dr. Levin, that was an outstanding description of what's been going on and you guys have really led the charge on identifying this and helping us understand it.

In fact, it was the awareness that was shared from the UK in late April that led us in our institution as well as I think most of us here on this side of the Atlantic to recognize that there is this new syndrome that children are presenting with. And we've learned already a lot from you and we continue to learn together. And obviously, the investigations that you're undergoing right now, I'm sure many of us would be willing to help as we are learning together as a community about this syndrome. What I'm going to share is some experience here in our institution. And for those who are not familiar with Cohen Children's, we are a large tertiary children's hospital which the one children's hospital is part of a 23-hospital health system here in New York.

And we capture a very broad net in our area. And I'm part of a 37-bed pediatric intensive care unit that pretty much offers all therapies known to critically ill children. And the data I'm going to share with you now are our experience. We've reported now to the New York State DOH -- I believe it's now in the mid-40s or so. I think it's 43 or 44 patients who have had this syndrome.

And initially, we were using a definition that was extrapolated from the original reports. And they all fall under the similar paradigm of children who had fever for at least four days with any of the following clinical findings of gastrointestinal symptoms, rash, conjunctivitis, oral mucosal changes, respiratory symptoms of cough or even neurologic symptoms. Again, similar symptoms that we often see in Kawasaki disease. These children also had to have significant findings of inflammation, so elevations in the C-reactive protein, ferritins. Also cardiac involvement with troponin or B-type natriuretic peptides.

And lastly, there were clinical features that either fell under different categories of those that were classic Kawasaki-type symptoms or those with incomplete Kawasaki symptoms, as you see. And these were the predefined characteristics from American Heart. As well as kids who did not necessarily fall under either of those two categories, however they were presenting with significant cardiogenic and/or distributive shock. And so then -- if we could go to the next slide, please. We were now obviously just given this new case definition through the CDC, which is helpful to at least now start standardizing our approach so we can continue to learn more about this condition together.

And thankfully, it seems that this -- and I'm not going to review the CDC definition per se, however I will say that our definition of the patients that we've included that I'll be reporting on do all fit these definitions. So at least we can move forward with that. So we'll go to the next slide, please. So, overall, like I mentioned, we've had 43 kids as of yesterday (I think it's 44 today) who have met these criteria. I'm going to report on 33 of them to limit the timeframe when we have data available to complete this definition, so from mid-April through this past week.

Of those 33 children, you're going to see a lot of similarities or hear a lot of similarities between what we've experienced here at Cohen's as compared to what we just heard from the UK description that was eloquently described by Dr. Levin. So, our children, the median age range was 8 1/2 years. And you can see the wide range though of two to 17 years of age. There was a male predominance as well.

And racially, we see that about a quarter were black and only about 10% were Asian or white. That may potentially just reflect our particular demographic of where we are in New York. However, as we collect more and share more data throughout the country, we'll get a better sense of any kind of racial disposition. And 27% of our children were Hispanic. Next slide, please.

As we've also seen and we're becoming more understanding of is that most of these children were previously normal healthy children with no underlying comorbidities. We only had, I believe, two children who had a comorbidity that were not very significant -- an unrepaired DST I believe in a child with a renal tubular acidosis. Half of the children are normal weight and about 40% or so were obese. And as we're all familiar with with the acute COVID infections, obesity is clearly a risk factor, particularly in the adult population that we've been seeing. Only about 15% of our children have had underlying reactive airways disease or asthma.

So again, just to reemphasize, this seems to be a condition that does not seem to be associated any known predisposition, predisposing conditions. Next slide, please. So what are these children presenting with at least in our experience here in this institution? The children had a median duration of fever for four days prior to arriving in our hospital. About two-thirds, a little more than half, had neurocognitive symptoms, which were similar to what we heard earlier -- headache, some lethargy, things of that nature. Almost all children presenting with gastrointestinal symptoms -- either abdominal pain, vomiting, diarrhea.

But that is almost universal. Only a few have had some type of either radiograph, CAT scan of the abdomen. And of those that we do have results on, they were very nonspecific or rather normal. A few children have had evidence of some ileitis or some bowel wall thickening, but nothing -- as we heard earlier -- nothing that was surgical or that were the cause of the presentation. About half of the children did have respiratory symptoms.

And I'll speak a little bit more coming up related to their respiratory support needs. Interestingly though, I think we've all seen that these children, their respiratory symptoms are clear to be secondary to

cardiovascular disease rather than primary lung infections. And we'll get back to that. About two-thirds of the children have presented with shock, where they either required fluid resuscitation -- and the majority of whom also required some type of inotrope or vasopressor and care in the intensive care unit. If we were to breakdown the presenting signs and symptoms and try to categorize these children into meeting criteria for Kawasaki disease or not, about two-thirds met complete Kawasaki disease criteria.

And of those patients, actually about three-quarters of them had shock -- which is obviously, as we're familiar, very uncharacteristic of typical Kawasaki disease, where usually it's only about 5% of those children develop shock. Next slide, please. About 80% of our children in our cohort have required ICU care. And overall, the length of stay for these children has been about four days. Next slide, please.

So the lab results are quite striking and really illustrative of the inflammatory disease that we think is going on here. Our children all had a fairly normal white counts in general. These are medians of 9.1. With, important, lymphopenia, as we heard previously as well -- 80% had lymphopenia, in fact.

Mild anemias were fairly common, with normal platelet count in general. The C-reactive protein levels were exceptionally elevated, as you see here, the median was 206, which is quite high. The D-dimers were also quite elevated at 1,700. Fibrinogens were elevated. And we've seen much higher than this, I'm just reporting the medians.

Ferritins as well were elevated significantly, as we are getting familiar with. Lactate dehydrogenase levels were elevated. Mild elevation in INR. The Pro-BNP levels were remarkably elevated. Again, really putting emphasis on the incidence of the cardiovascular system involvement right from the early presentation.

And again, speaking to the amount of shock that we noticed and were treating. We also saw again, significant increase in troponin T -- which on our scale here, I think less than 14 is normal. So 31 being quite elevated already. The procalcitonin levels were elevated. Which is interesting, knowing that these children did not have bacterial infections.

And so I guess we'll still learn as to the relevance and the utility of procalcitonins in managing these patients. There were significant incidence of hyponatremia. Our median was 133. There were mild levels of hepatopathy identified in these children. As you see, some mild elevations of the ALT and AST.

And as well there were, as expected, also some mild decreases of albumin. So lab results that really reflect a very active inflammatory system, leading to other markers that we do see in vasculopathies. Next slide, please. So if we look at the population of patients who were either PCR positive or PCR negative for an acute SARS-CoV-2 infection, we see that the vast majority were negative. They did not show any evidence at the time of presentation of acute SARS-CoV-2.

However, the vast majority if not I believe all of our patients were positive for the IgG immunoglobulin for SARS-CoV-2. Again, indicating the previous infection. Next slide, please. As we're describing this syndrome, we are including clearly multiple organ involvement as part of the definition. And many of our children did have various organ involvement.

21% had some degree of acute liver injury. Almost three-quarters had evidence of acute kidney injury. I don't believe any have required renal replacement therapy. However, based on AKI criteria, they met --

a significant proportion met AKI definition. About half the children required some type of respiratory support, either supplemental oxygen or positive pressure ventilation, but only a few.

I believe it was six patients actually required intubation. And again, what was striking was that these intubations were not primarily for lung disease that may indicate a direct injury to the lung from the virus, rather they were -- these children were intubated for hemodynamic support and severe cardiac dysfunction. And those who were intubated remained such for approximately three days. Next slide, please. A striking finding here and what I would put into my category of alarming finding with this group of children is that about half the children already had coronary artery abnormalities.

And you can see them described in front of you, where looking at specifically with Z-scores, there was significant involvement of -- or significant findings of coronary enlargement and coronary aneurysms. Which, as we know, is quite early if compared to typical Kawasaki. And is also a significant higher burden of coronary involvement compared to typical Kawasaki. Again, illustrating perhaps a different disease process altogether. Many of the children already had or developed myocardial dysfunction.

And that's in about almost a little more than half of those children. Again, speaking to the need for critical care for the majority of these kids. Next slide, please. And so what have we been using for our therapies for these children? And I really break it down to almost a two-pronged approach. The first one -- which is not up here -- which is we like to consider good old-fashioned critical care.

These children all need care for the shock that they're in. And so the therapies including inotropes or vasopressors, mechanical ventilation. That is one of the two areas that we are using to treat these children. But specific to this inflammatory disease, every one of our children received intravenous immunoglobulin. About a third actually required a second dose.

Which is usually indicated for a persistent fever after 24 hours of termination of the first dose of IVIG. We also use a much more aggressive approach, the intensified strategy for Kawasaki disease. We've extrapolated from there, and so most of the children received some type of corticosteroid, generally methylprednisolone as well, and aspirin. You see that there were a few children, particularly earlier in the course -- in the timeframe here -- that required other types of immune modulation, which was generally indicated after persistence of ongoing inflammation or either fever or blood tests after the IVIG and the steroids were being used. And then, related to enoxaparin or blood thinning would be -- really we are collaborating very closely with our pediatric hematologists just to individualize the therapy based on some of the coagulation profiles.

And so that's still very much an area of interest of trying to understand how to best manage these children. You know, we do know very clearly from both the adult population and even earlier pediatric experience with acute COVID that there seems to be associated that all needs some type of anticoagulation. Next slide, please. Thankfully, of our 33 reported and 43 that we've had, or 44 now, there have been no mortalities. Children are responding well to these therapies; 82% of our children in this cohort have already been discharged alive and there are a few still hospitalized but also seem to be responding.

Interestingly, there are still a significant number of children who are leaving the hospital with some mild or some depressed cardiac function or some cardiac involvement and close follow-up with a pediatric cardiologist or infectious diseases is going to be imperative. Next slide, please. Thank you very much for allowing me to share our data with you. Again, it's just one single center and I'm sure we all are going to continue to learn together. And the collaboration associated with this has just been fantastic.

So, I think at this point, I'll pass the baton, if you will, to Dr. Marconi.

Great. Wonderful talk. Thank you so much, Dr. Schneider and also Dr. Levin.

And I want to thank the organizers from the CDC for the opportunity to also participate in this discussion. For slightly a bit of a different take on COVID-19, I've been asked to talk a little bit about the adult perspective in terms of what the inflammatory syndrome looks like for adults, as well as talk a little bit about some of the therapies that you've heard discussed already by Dr. Levin and Dr. Schneider and what has been looked at so far in clinical trials and mostly single arm studies. Next slide.

Nothing major to disclose. Next slide. So just to start off, first with what a standard -- you've heard some of the descriptions in children, but what is a usual presentation for an adult look like? And this is for individuals who have gone on to have severe or critical COVID-19 disease at this point. And this is an actual patient that we saw fairly early on, presented around mid-March to one of our hospitals here in Atlanta. And this individual was in their mid-50s at presentation and did have some underlying hypertension, was overweight but not obese, and also had underlying diabetes but no emphysema of note.

And was his usual state of health, but actually presented initially with fever, cough, and shortness of breath. Though did not have earlier symptoms predating this but presented acutely with shortness of breath in conjunction with the fever and cough. And also had significant diarrhea. And just sort of showing on the slides here the colored bars running horizontally, giving the time course of presentation onward. And over time, the patient who had an oxygen requirement initially then progressed after a couple of days of being moved into the ICU and requiring intubation.

As you can follow in the gray figure -- the gray square, the part of the upper half of the figure -- the temperature maximum in red and minimum in blue. So remained febrile throughout that initial period of presentation and was intubated and brought into the ICU really on hospital day two. So this is after being in the hospital for a couple of days. And required significant amount of ventilation and oxygenation, as you can see, requiring FIO₂s of 80, even up to 100%. Also, the patient continued in this course for many days.

As you can see, was intubated for the better part of more than almost two weeks, three weeks time period. And throughout this time, required vasopressors for shock -- because blood pressure dropped on day seven. That was also predated by a bacterial pneumonia, as well as acute kidney injury. And while all this was happening -- if you could view the top half of the figure, you'll see that all of the biomarkers that were described earlier were also elevated for this individual. So CRP was very high, SED rate as well.

D-dimers, you can see, was in the 15,000 range, so quite high. IL-6 well above the upper limit of normal. And so all of these sort of inflammatory markers being elevated despite receiving some therapy -- this patient got hydroxychloroquine, Azithromycin -- remained febrile and remained intubated and even had experienced deep venous thrombosis on day 10, that did not progress into the lungs but had remained in the lower extremities. And continued on in this course, as I said, for many days, still requiring oxygen and slow to recover both from the inflammatory markers as well as oxygenation. Fever curve did decrease by hospital day 11 and I had a few low-grade fevers thereafter, but again, was extubated on day 21 or so and moved out of the ICU.

So very prolonged course, and as you can see, requiring a significant amount of hospital support at the time. Next slide. So as was described earlier on by Dr. Bamrah and others that there is sort of several phases to this disease that we've seen in adults and perhaps what we're seeing in children, some of these presentations are fitting part of this paradigm, where others are not. But at the very beginning, there's typically a viral response phase that's characterized by constitutional symptoms -- influenza-like illness, dry cough, fever, headache, kind of thing, and can have some diarrhea.

And it's during this time that there is significant amounts of viral replication, especially occurring in the lungs as well as other parts of body. And what can be seen traditionally is lymphopenia, sometimes profound, and some of the elevations of these biomarkers as well. Now, the vast majority of individuals will recover at this point and not progress onward to what's described as sort of a pulmonary phase, or what often in severity is described as kind of moderate presentation of COVID at this point. And now you're starting to see significant shortness of breath, hypoxia at this point, and significant elevation of those same inflammatory biomarkers, sometimes going into the several thousands -- so ferritin, LDH, and the like. And it's at this point where patients will tend to progress very rapidly if they're going to go on into the hyperinflammatory phase or this sort of stage three.

Where biomarkers go extremely high and illness severity, often requiring again intubation and ICU stay. Often seeing a shock syndrome and ARDS and the microthrombotic events that we've described. Next slide. And next slide. And what we have come to understand as the pathogenesis, especially of this sort of microthrombotic phase, is worth looking at to some extent in some detail.

The first aspect that's unique to this virus as opposed to other influenza or other syndrome similar to these viral syndromes we're seeing here is that SARS-CoV-2 binds to the ACE2 receptor that's found significantly in the lungs and also in the hypopharynx, kidney, the gut, as well as testes and brain and cardiac tissue. Once binding, it becomes internalized into the cell. And as a result of that, much of the ACE2 receptor that we have seen in this disease becomes down modulated, down expressed on the surface of these cells. And as a result of that, there's a decrease in conversion of antigens in II antigens and 1-7. And because of this decrease in antigens in 1-7 and increase in antigens II, we see an increase in reactive oxygen species and a decrease in vasodilators.

And this is a perfect setup for thrombosis and vascular vasoconstriction. Next slide. And combining that with the inflammatory process and platelet activation that's set off by the complement cascade -- next slide -- we have a sort of terrible mix of thrombosis, inflammation, and this complement deposition that leads to the really terrible presentation of microthrombosis throughout the body. Next slide. And so in understanding the therapies that may be useful here, it's worth looking at what happens immunologically to sort of set all of this off.

Well, we believe that initially in the viral replication phase that the innate immune system responds with the sort of host antiviral campaign. And that's largely made up of type I interferons. These are alpha and beta interferons that are released to target cells that are infected and eliminate the infection. And macrophage is also responding, which trigger some involvement as the infection progresses unabated, helper T-cell involvement in the adaptive immune system. And from this, if the virus hasn't been contained and cleared, results in a large elaboration of cytokines at this point, including IL-1 and TH-17 cells releasing IL-17.

As well as now at this stage, interferon and gamma. So type II interferon release, which is much more destructive especially into the lungs and causes a lot more of that inflammation that we're seeing. And throughout this time, there's a large depletion in natural killer cells with a very significant expansion in

plasma cells at this point. And whether or not this expanse of inflammatory syndrome is because of an ineffective, neutralizing antibody and an initial innate immunity still remains unclear, or if it can happen even in that setting. But without effective clearance, nonetheless, there is this large expansion again of these inflammatory cytokines that seem to be responsible for a lot of the pathological consequences.

And as you can see on the right half of this figure, there are a number of areas in cytokines that have been targeted over many years for various different diseases -- which we'll review -- that are being repurposed and leveraged for COVID-19 and may be useful not only for adult therapy but, as you heard today from our two earlier speakers, have been used in sort of the Kawasaki presentation and MISC presentation we see in children. Next slide. So to start off with, probably the one that has been out earliest in studies and use is IL-6 receptor and IL-6 cytokine antagonists have been probably the most commonly studied so far. The ones that you've seen in the news and in the literature, including sarilumab recently, siltuximab, sirukumab also being studied. Those are cytokine antagonists, whereas sarilumab and tocilizumab are receptor blockade monoclonal antibodies.

They've been used across the spectrum in many different diseases, including Multicentric Castleman disease and cancers, rheumatoid arthritis, as well as systemic-onset juvenile idiopathic arthritis, and even for the treatment of CAR-T cytokine release syndrome and giant cell arthritis, which is a vasculitis somewhat similar -- similar overlap with Kawasaki's disease as well. Some of the downsides that you can see with monoclonal antibodies includes hypersensitivity reactions. There's been hyperlipidemia described, as well as some respiratory tract infections, some upper and some lower, resulting in even black box warnings. There's been also, again, with the hypersensitivity, rashes described and peripheral edema. These are all given either IV or subcutaneously and can have some liver effects.

This is just an initial look at some of the first three studies that were done, two of them out of China, one of them from New York. These were small, single-arm studies that looked at patient populations and their hospital that were given, various modalities. Most of these were also given methylprednisolone in combination. The vast majority were considered either serious or critical, as you can see here, across the board. The majority were male, although the US population was closer to being balanced between the two.

And that population, again, the Pereira lowest study at the bottom was out of patients who had already been transplanted an average of six years prior to. Doses varied depending on the study, although most received a 400-mg dose, either a single time or repeated doses, depending on initial response. And for the first China study by Luo et al, 67% that showed a decrease in IL-6, as would be expected; 20% of these patients died and 80% remained inpatient at the time of publication. The second study from PNAS, which is shown in the bottom four figures describing sort of decreases in CRP, temperature, and FiO2 requirements with increases in PaO2. None of their patients died; 90% were discharged at the time of submission.

And then the New York study showed about the same percentage died as the first Chinese study, about 24%. And 54% of those were discharged. Again, this study of the US population was amongst many other drugs that were studied, but just pulling out the 14 patients who had received IL-6. Next slide. The next target that has been looked at, and you heard anakinra being mentioned.

This is an IL-1 blockade, and anakinra in particular has uses in diseases including periodic fever syndromes, and systemic-onset juvenile idiopathic arthritis, as well as the macrophage-activating syndrome which has been described in some of these children as well. Anakinra blocks both aspects of IL-6, both the beta and the alpha aspect because it's an antagonist. Whereas the canakinumab only

blocks IL-1 beta. Both of these are being studied now in COVID, have clinical trials ongoing -- canakinumab and the CAN-corona trial that's being given as a subcutaneous injection every 26 days, as needed. And the anakinra is being given in different studies depending on the study, either in COVID -- or another study emapalumab, which is an interferon gamma blockade, as IV, QID, or subcutaneously.

Some of the side effects include headache. There's injection reactions, again, similar to lipids, and infection risks, as well as cytopenias. There's some question that potentially could be some cancer risk, although that hasn't been fully borne out at this time. But I wanted to show you one study looking at anakinra so far that has been published, showing some, again, of the cytokine reductions that we're seeing here. So this is across the top -- a C-reactive protein, procalcitonin, ferritin, and then troponin elevations, which as was described in children, seeing some declines as well as in D-dimer, and then oxygenation changes and clinical scores.

Next slide. So the next marker or the next blockade is GM-CSF. This is upstream from a lot of the inflammatory processes. Next slide. As you can see, can block a lot of the downstream inflammatory biomarkers, including IL-1 and IL-6, etc.

So this is an attractive monoclonal to be used and there's been several, actually almost half a dozen, that are in trials currently, including gimsilumab, lenzilumab, and otilimab, all being studied currently for COVID. They have previous a good track record in ankylosing spondylosis and CAR-T syndrome or CAR-T cytokine storm, as well as rheumatoid arthritis, etc. Some of the adverse effects seen with this blockade includes hypertension, again hypersensitivity, and there's also been shown in alveolar proteinosis syndrome for some of these markers but not all, as well as some shortness of breath. It's also given IV. And as you can see here, in particular, this is lenzilumab, showing marked reduction in levels of GM-CSF in human and mouse models.

Next slide. And also significant across the board inflammatory marker reduction. Next slide. And consequent improvements in wait, at least in the xenografts that have been studied in vitro, but waiting to see how this looks in human studies. Next slide.

The other large number of trials that are looking at JAK inhibitors, both baricitnib and ruxolitinib around the world. This drug has an advantage of being able to block multiple cytokine signaling pathways, including IL-6. Next slide. As well as GM-CSF and IL-2, etcetera. It doesn't seem to have as much of a significant reduction in tumor necrosis factor in IL-17, but does have an impact on interferon gamma, less so than the interferon alpha and beta reduction.

So it may give you some protection in the antiviral campaign. So it has been looked out across the board in multiple different disease states for this class, including rheumatoid arthritis, myelofibrosis, polycythemia vera, etcetera. The baricitnib and ruxolitinib, in particular, are orally delivered medications. Baricitnib clears renally, whereas ruxolitinib is through the liver. There are some adverse effects described in the previous studies, including infections primarily in endemic fungi, tuberculosis, and herpes virus diseases, as well as a black box warning for thrombotic processes that can occur in long-term use, as well as cytopenia.

Next slide. There was an interesting finding from Lancet in February this year, showing that baricitnib may actually have antiviral activity above and beyond its anti-inflammatory effects. Next slide. Where it appears that several entry points for the virus internalizing into the cell and being released are blocked in a JAK independent process. Next slide.

And in fact, one single-arm study comparing to Kaletra, a standard of care in sequential historical comparison, showed remarkable improvement in ICU admissions and discharges in the baricitinib bar. Next slide. And also showing in another study, also out of Italy, patients showing not only the remarkable reductions in cytokines here IL-6 in blue, but also significant reductions in nasopharyngeal and oropharyngeal swabs of the virus during concomitant treatment. Next slide. And for those of you who are participating in the ACTT 2 trial now -- if you were in the ACTT 1 trial which was Remdesivir versus placebo.

ACTT 2 trial will be adjunctive therapy of Remdesivir plus baricitinib versus Remdesivir alone. About 100 sites will be participating between 800 and 1,000 patients. And we look forward -- that started rolling about 10 days ago and we look forward to seeing the outcome of that study. Next slide. And finally, tumor necrosis factor blockade, multiple agents also being explored, as you can see here, and being describe for these children being used already -- like infliximab and etanercept.

This is used in rheumatoid arthritis and inflammatory bowel disease, as you can see here is a chart from the Secure IBD database. Which showed patients who were on some of these therapies at the time of acquiring COVID-19 -- you can see 877 patients at the time of this publication at Lancet had been receiving some of these agents. Next slide. And you can see those who had been given a tumor necrosis factor either with or without 6MP, AZA, and methotrexate, only 1 to 2% of those ultimately died. Next slide.

And that compared to patients receiving parenteral steroids, where there were 11% of those individuals. Again, this is not a controlled study but just observational data. Next slide. And also we do know these drugs have been used for treating Kawasaki disease. Again, may in studies bear out to be useful in this condition MISC being described in children.

Some of the adverse effects, including cytopenias, infections. There is some anaphylaxis described and demyelination as well and questions about cancers arising as well. Next slide. So in conclusion, what's really impressive is this is the first large-scale testing of anti-inflammatories for a deadly viral disease. And again, we caution off-label use outside of studies if possible, but recognize limitations of being able to participate in studies at some sites.

They do appear to reduce the fever and cytokine storm. But the time to recovery and mortality data are really lacking. So we're looking for randomized controlled trials to look at this. And again, unclear impact of virus control, also secondary infections, thromboses and cytopenias in the short-term use compared to what we've seen in rheumatologic conditions, more long-term use. There are really more classes that can fit in 15 minutes here.

There's many other trials that are underway. We don't have time to discuss them but I encourage you to look further into these. Next slide. Next slide. Oh, sorry.

Steroids -- I forgot that animation. So steroids have not been recommended by IDSA or by the NIH at this point unless in a clinical trial for treatment of COVID-19 in adults. I recognize the MISC and Kawasaki syndrome may have different recommendations, but this is for adults. Next slide. And finally, a tremendous thanks to so many people who've been a part of the studies that we've participated in here and the helping of putting together these slides.

And I'll stop there.

Thank you so much, Dr. Marconi. And before we move into the Q&A session, I've been informed that we have the honor of being joined by Admiral Giroir, the assistant secretary for health at the US Department of Health and Human Services. Welcome, Admiral Giroir. Would you like to share some brief remarks at this time? Trying again to get if Admiral Giroir is on the line and if he's able to unmute this phone.

Okay, while we wait for the Admiral to join, we'll continue our webinar. Presenters, thank you for providing our audience with such a wealth of useful information on this rapidly-evolving pandemic. We will now go into our Q&A session. Please remember, you may submit questions to the webinar system by clicking the Q&A button at the bottom of your screen and then typing your question.

So our first question is: Can the presenters please discuss similarities and differences in the epidemiology of this syndrome versus Kawasaki disease? Versus any adult?

Thank you. It's Mike Lavin from London, tempting to answer that question. I think the Kawasaki disease that pediatricians have been familiar with for the last 30 or so years does have some very distinct differences from the Kawasaki disease that appears to have had an upsurge in the numbers of cases associated with the COVID-19 pandemic. The perhaps most striking feature is that Kawasaki disease prior to COVID was a disease of young children. And the comparison that we did comparing the patients with post-COVID Kawasaki disease is that they tend to be older.

I think I tried to show in my talk the laboratory differences in which certainly for the shock patients, there was a much higher level of many inflammatory markers, particularly lower albumins and lower hemoglobins and in particular higher proportion of patients with indicators of myocardial injury. So I think that while COVID -- and we are assuming that the upsurge of Kawasaki cases that we're seeing is a response to COVID. COVID must be triggering an immunological response, which has enough similarities to the Kawasaki disease as we knew it before COVID to result in the rash, the conjunctival injection, some mucous membrane changes in some patients. But the pathophysiology does appear to be different, as indicated by the age of the children and these spectrum of laboratory results. We've also had a striking understanding of the ethnic propensity to Kawasaki disease.

So that patients from China and Japan and Asia generally have increased incidence of Kawasaki disease as we knew it before COVID. Whereas COVID, so far from what information we've had from Japan and my colleague Jane Burns has been in contact with Japanese colleagues. And there doesn't appear to have been an upsurge of Kawasaki disease in Japan. So it does look like COVID is triggering a response that has many features in common with Kawasaki disease, but also important differences. So I'll stop there and see if Dr. Schneider has some comments on the same question.

Thank you. There are a couple of other I guess general differences that this multisystem inflammatory syndrome presents with compared to Kawasaki. In that we generally think of Kawasaki disease -- and as a pediatric intensivist, I generally think of it as a group of patients I don't get to see that frequently. Where we only think of about 5% of typical Kawasaki disease develops some type of shock syndrome where they end up in our intensive care unit. However, what we're seeing with this newer syndrome that seems to be related to COVID is that, at least in our institution, the majority of children are ending up requiring critical care where they present in shock, where they need fluid resuscitation, where they need inotropes or vasopressors and some ventilatory support.

So to me, that's a clear characteristic difference between the two. And also, shockingly, where we think of I guess the classic have been about 23 to 25% of classic Kawasaki children untreated would lead to

coronary anomalies. And treated with a current regimen of intravenous immunoglobulin, that's down to only about 3 to 4%. However, again, in our current cohort of children we've seen, close to half have had coronary abnormalities and at a very early stage of the illness. So that, again, speaks to this really inflamed state that they're in and the vasculopathy that's developing with this syndrome.

So I think those are two really important characteristics. And the last one I'll say is in terms of how these children are presenting. The typical presentation that we're noticing is the fever -- which clearly overrides or goes along with Kawasaki. But almost all of our children are really presenting with abdominal symptoms. And we know that that can be part of the Kawasaki spectrum.

However, it's almost universal in this group of patients that we've seen. So this would be some of the other characteristics that I think I'd like to highlight. And I will leave it to one of my other colleagues if they'd like to add in as well.

Yeah, this is Ermias Belay from CDC. If I might add, clinically, more patients with MIS seem to have respiratory symptoms. Which is very uncommon in KD. As Dr. Schneider said, they have GI symptoms, specifically diarrhea and vomiting, particularly diarrhea in MIS patients.

Which, again, is uncommon in KD, in addition to all the other features that previous speakers described. Thanks.

Thank you, everyone, for your insight on that discussion. Before we move on to our next question, I want to try and see if Admiral Giroir is on -- the assistant secretary of health at the US Department of Health and Human Services. Admiral Giroir, are you able to unmute yourself? Okay, we will try again in a few moments.

Our next question is regarding testing. **Can our presenters please discuss what kind of testing is recommended for a child or adult who presents with concerns for this syndrome?**

Hi, this is James Schneider, I'll be happy to take the first attempt at this one. I think the key to this syndrome is the hyperactive inflammatory response. And so getting evidence of inflammation is really key to differentiating this from other syndromes. And so when children show up with signs of fever and then some of the other clinical findings -- whether it's abdominal pain, vomiting, diarrhea, the rash, oral, or eye changes -- those kids generally should be getting a full spectrum of a complete blood count, a complete metabolic panel, a CRP. We like to look at evidence of myocardial involvement, looking at peptide levels, neutrophilins.

We also look at other inflammatory markers such as ferritin, D-dimer, procalcitonin, full coagulation panel, lactate dehydrogenase. And of course, we also want to look for evidence of either current or previous SARS-CoV-2 infection. So we do get a PCR, as well as now we have the capacity to do serology testing for antibodies -- which we should get right away. The other important I think aspect is to not forget that children with bacterial sepsis or other forms of sepsis are still out there and may be missed if we're not being vigilant. So getting blood cultures and full respiratory viral panels is still I think really important.

And then because of the very high incidence of important cardiovascular involvement from the early onset, a screening ECG is really helpful. And then based on some of those results, will determine the next phase of management. I'll ask one of my other colleagues to see if they'd like to add on to that.

This is Dr. Matthew Oser. That's I think a great summary. And one thing that many institutions are doing now as well with some of the cardiac manifestations that you mentioned, are getting an echocardiogram in any kids that they suspect this syndrome. Obviously if they see any abnormalities on that, they can follow that up during a hospitalization or beyond, or at the very least, a conservative baseline.

For those who have a normal echocardiogram, from there, many places are just trending the troponins and BNP's, as you mentioned, and then just giving follow-ups as indicated for clinical deterioration or changes in any of the biomarkers.

Yeah. And I can say -- this is Vince Marconi -- just for adults, again, a slightly overlapping syndrome. We would get the same set of tests that were described in terms of, you know, procalcitonin, troponin, D-dimers, CRP, ferritin, etcetera. And usually what prompts us is either cardiovascular instability or signs of troponin elevation, EKG changes, that would prompt us to get echocardiograms at that point.

Thank you for that. Another question we have is: **Do children with underlying medical conditions have a higher risk for this syndrome?**

Hi. This is Matthew Oser. I'll attempt that one. Based on what we've seen in our cohort of those three I described earlier, there really do not seem to be any definitive underlying medical conditions that predispose children to this syndrome. I think obviously as we continue to collaborate and pool our data, we may be able to find some other trends.

As we know, in the adult acute COVID population, having obesity, hypertension, diabetes, these are things we know classify an adult as higher risk, and so perhaps, as we gain more knowledge and experience with this syndrome, we'll be able to identify some other underlying conditions that predispose kids. Thank you.

Thank you for that. Another question we have is: **For those who are PCR-positive and IgG-positive, how do we distinguish between acute COVID-19 and MIS?**

Let me take this one. This is Ermias Belay from CDC. That's obviously very, very tricky. But one thing that could potentially be helpful is among MIS patients, there has been a delay of about two to six weeks between the initial COVID-19 infection and the onset of MIS, which has been reported in many patients. That could potentially halt more very clear information.

In patients with milder or even asymptomatic antecedent COVID-19 infection, distinguishing the acute infection from MIS can be tricky. Although as discussed previously, the picture of the cytokine storm and increasing inflammatory markers can be very suggestive of MIS, and that can probably help favor the diagnosis of MIS as opposed to acute COVID-19 infection. Dr. Levin, would you like to add anything?

Thank you. I agree. It's been a very difficult situation to distinguish. There is clearly an inflammatory response but there is evidence of the virus. Certainly, when we have patients that are both positive for virus on PCR and have the inflammatory syndrome, it raises the concern of will immunosuppression be harmful? And maybe makes one a bit more cautious on thinking about using steroids.

Obviously, immunoglobulin, we are comfortable in using with PCR-positive patients. I really don't know how to answer that question because the PCR-positive patients are probably resembling closer to

the adult patients who have COVID and then develop an inflammatory syndrome. And that should be interesting to hear from the physicians treating adults whether the combination of PCR-positive for the virus and the development of inflammatory features is what they are seeing in adults.

So this is Vince Marconi. So, just to understand, the question is whether or not both having a positive swab and biomarkers being elevated at the same time is concurrent with the inflammatory syndrome?

Yes. I think what I was raising is that when we see children who are PCR-positive for the virus and also have the inflammatory features, this seems more similar to what adults are seeing where patients evolve from being virally infected to developing an inflammatory problem. Whereas most of the children with the inflammatory syndrome don't have the acute viral type illness and come in with the inflammation being the only presenting feature.

Yeah, that's exactly right. So none of the patients we've seen and really largely what has been described in the literature has had SARS-CoV-2 negative. There may be a few exceptions, but almost always. And in fact, severe disease, if you're going to see it in the bloodstream as well, which is not commonly done, routinely done in the clinical setting but it's done in research settings. If you're going to see SARS-CoV-2 presence, PCR-positive presence in the blood, it's usually with severe or critical disease.

Thank you for that. Before we move on, let me do one more check and see if we have Admiral Brett Giroir, the assistant secretary for health at the US Department of Health and Human Services on the line. Admiral Giroir, are you available to share some brief remarks? Okay. We'll keep moving on with our questions.

Our next question is: Providers are seeing various presentations in younger kids, more like Kawasaki, versus older kids, more like abdominal pain or headache or myocarditis.

Can you comment about what kind of presentation you're seeing in young adults?

Yes, this is James Schneider. I think, just from our experience here, in general what we've noticed in the acute COVID infections -- and we've treated many now at our institution -- the presentation is quite varied and there's no obvious pattern. But related to MIS, I think the pattern continues that it is slightly varied. You know, what we have seen in some of the older kids, there is a teen in the unit right now, and it was more of the general fever, abdominal pain and chills and myalgia were the presentations. But I think we've seen those in younger kids too, so at least in our experience here, there hasn't been an obvious pattern here.

Clearly again, as we've gain more knowledge and more experience and more numbers, we may be able to sort out the patterns. I don't know if Dr. Marconi has any other experience.

This is Dr. Morris. Dr. Marconi had to exit to a next meeting. Commander Khan, can we go to the next question? Thank you.

Certainly. Let's see. Another question that has come in is: Given the progression to shock in so many of these patients, when should a provider send a child to the ER? Similarly, should children who would typically be sent home from the ER with some of these symptoms instead be admitted and observed?

This is James Schneider again. I'm going to try to tackle this one in simplified fashion. In general, right, we know that children who have classic Kawasaki disease need inpatient therapies. They need IVIG. They need aspirin.

We know this helps to protect their coronaries -- at the very minimum. It depends on the severity. And we also know that with this current syndrome that there is a very high incidence of cardiovascular involvement, even early on in the course of the illness. So I would think that any child at home who has a persistent fever, abdominal pain or abdominal symptoms, as well as a rash or conjunctivitis eyes, they should be seen by a pediatrician right away. And I think, as a pediatrician evaluates a child, if there are any signs or symptoms of Kawasaki disease, the child should be referred for additional evaluation and a cardiologist needs to see this child.

Clearly, if a child is otherwise looking unwell, has any evidence of respiratory illness, respiratory distress, or has evidence of tachycardia in the office, then I think the child deserves further evaluation. We are seeing kids that do not fit classic Kawasaki criteria in terms of the outward appearance related to the rash, the eyes, the hands, etc. So I think we need to have a low threshold for at least evaluation, because we're finding a remarkable number of kids with both myocardial and coronary abnormalities, even early on. I hope that's helpful.

It's Mike Levin in London. I can maybe add to that from some of the experience in the UK. I think we had an impression with the earlier patients when we first recognized the syndrome that patients were arriving critically ill from the moment they arrived in hospital. And one of the reasons for this may have been because of lockdown and because of fear of coming to hospitals. The public health message in the UK was that patients should try and stay at home and not attend hospital because hospitals were under pressure.

And so children were remaining at home with fevers for longer than they might have normally and arriving in a very seriously ill state. And now that we've become more familiar with this problem, there's been a very clear public health message that if children have persistent fever they do need to be evaluated. And the laboratory tests, the CRP and the white count, will very quickly point to a group of patients that have elevated inflammatory markers. And I think we would very much agree that if you have got inflammatory markers that are elevated, even if there are no features of typical Kawasaki disease, that warrants the child being investigated and bacterial infection excluded and watched very closely, generally as an inpatient. And certainly, if there's any of the suggestion that the CRP is rising or there's lymphopenia, the ferritins are rising.

And certainly, any markers suggestive of myocardial involvement with the troponins going up or the BNP's going up, those patients definitely need inpatient assessment and very careful evaluation.

I would agree with everything that was just said. Well said.

Thank you so much. Next question: **If a patient is admitted for the syndrome yet is PCR-negative, do they need enhanced precautions? Can family members visit? Can you please elaborate on that?**

This is Ermias Belay from CDC. We do not know a lot about the dynamics of the virus shedding in these patients, even if PCR-positive, whether or not that translates into positive shedding of the virus -- may not be true all the time. And in those patients who are PCR-negative, I would think that it's ok to allow visitors some precautions. But I would like to know what others think from the panel.

This is James Schneider from Cohen's. We have noticed that during this era the PCR testing has not always been 100% accurate. We have a fairly important false negative rate. And so all children with this syndrome, we actually are testing at least twice, minimum 12 hours apart. So we presume when these children are first admitted to the hospital that they are infection.

I would treat them as a PUI until the second PCR becomes negative. We have the luxury, at least in our intensive care unit, that every room is single-patient and negative pressure, so every patient is treated the same. We do allow one family member to visit all patients in the intensive care unit and in the hospital. But any patient who is PCR-positive, then the family member is not allowed to leave the room other than using the specified restroom. So yes, we do two tests and they are treated as PUI because we do not know -- as Dr.

Belay just said, it's hard to know for sure whether they are infectious. Even though we think that this is a noninfectious entity, it's just too -- we're not quite sure yet.

Thank you for that. Our next question is asking: **Are hospitalizations a certainty in all cases?**

Let me try to take that one also. We've heard a lot about the illness from the presentations. I think it's possible that there may be a spectrum for the illness and we're just catching the most severe cases who are hospitalized and wind up in the ICU. That has happened in Kawasaki disease. There are severe forms of the disease and there's also a milder presentation or atypical or incomplete presentation of Kawasaki disease.

So it's possible that that could also happen with MIS. This is one of the reasons that we need to conduct more data to better understand the clinical phenotype of the illness. But as currently stands, not all of these cases are hospitalized and most of them end up in the ICU.

Mike Levin again. I agree completely with that. We are certainly seeing children with mild illness with just fever, no other features, no organ failure, not needing to go to the intensive care, but surprising elevation of C-reactive protein, ferritin, and other markers for which there is no other explanation. And while those patients don't look so ill when you see them, what we don't know is the direction of travel. So if we don't observe them or if we don't undertake echoes, if we don't follow them up as we would for a Kawasaki, will they progress to the more severe phenotype? So, until we know more about it, in the UK we are hospitalizing them, doing the complete set of investigations, including echocardiography and ECG, and only thinking of home management if we're sure that the CRP and the other inflammatory markers aren't progressively worsening on a daily basis.

Thank you for that. **Can you talk about the information or knowledge we have so far about the chances of death from this syndrome if the child receives appropriate care at a healthcare facility?**

Let me try to tackle that one also. This is Ermias Belay from CDC. There have been deaths that are reported among patients who meet the case definition for MIS. Fortunately, it appears to be rare. And we still need to understand more about this disease.

In one series that I reviewed, from over 80 suspected cases there have been two deaths that have been reported -- specifically cases meeting the definition for MIS. But again, as I say, fortunately it's rare. But having said that, as we've heard, the illness causes significant morbidity, with most children ending up in the ICU. Anyone who would like to add to that?

Yeah. I think the experience from the UK is very similar. So far, we know of, I think, three deaths, one of them in a child with typical Kawasaki disease and thrombosis and aneurysm rupture and two others. But we have had very severe illness and patients requiring extracorporeal membrane oxygenation in a few cases. So it can be very severe but the mortality rate seems similar to your experience in the States.

Great. Thank you so much for that information. We have time for one last question. The question states: **If this syndrome can follow even the mildest or asymptomatic of an acute illness, what are the implications of this syndrome for vaccine development, testing, or safety?**

It's Mike Levin again. Again, it's just speculation, but the timing of this illness does seem that it coincides with when acquired immunity would be developing. And there is quite an extensive literature from SARS-CoV-1 that antibodies may enhance the illness, either by the same mechanism as in Dengue where antibodies actually enhance viral replication. That's probably less likely for the syndrome we're seeing because PCR is negative. But in SARS-CoV-1, there were reports that anti-spike protein antibodies caused macrophage activation and a similar inflammatory process, both in primates and human tissues.

So I think there's a concern that we are seeing a dysregulated immune response. And for that reason, I think understanding if this is an immune response rather than the protective response that we want from a vaccine. I think it's really quite an important area for research that we define exactly what is the antibody and T cell recognition in this disease and is it different? What is underlying it? Is it genetically determined? And I think that information would be very important in ensuring safe introduction of vaccines.

Yeah, this is Ermias Belay from CDC again. I completely agree. I understand the antigen or the protein or the group of proteins that are triggering the immune system to go into overdrive. If we could identify those and avoid it in the vaccine production process, that could potentially solve the problem. In addition, I'm carefully monitoring and collection of safety data during the vaccine trials will be very, very critical.

Thank you very much. Before we conclude our call, would Dr. Morris like to make any closing comments please?

Hi. Thank you, Commander. I just wanted to first of all apologize. We were trying to get our assistant secretary of health on and just were having technical difficulties with being able to add him on the speaker line. So I apologize to him and his office for that.

We were really working behind the scenes and we just couldn't get it to work. We wanted to thank all of the speakers for their time today and just comment that CDC is working with our other federal partners, including NIH and the Office of the Assistant Secretary of Health in a collaboration to, as Dr. Belay described, better describe this syndrome and to kind of work towards understanding what kind of care and treatment is real successful. So we hope to have future calls to share what we've learned. And we, again, just want to thank all of our speakers today for spending all of this time this afternoon with us.

Thank you, Dr. Morris. And a closed captioned video for this COCA call will be posted on COCA's webpage shortly after the live call at emergency.cdc.gov/coca.

Please continue to visit emergency.cdc.gov/coca over the next several days, as we intend to host COCA calls to keep you informed of the latest guidance and updates for COVID-19. In addition to our

webpage, COCA call announcements for upcoming COCA calls will also be sent via email. So please remember to subscribe to receive these notifications by going to emergency.cdc.gov/coca/subscribe.asp.

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Thank you.