Dr. Ruth Adewuya:

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Dr. Ruth Adewuya:

This episode is part of the COVID-19 mini series addressing up-to-date insights on COVID-19. In today's conversation, I am joined by Dr. Alan Schroeder. Dr. Schroeder is the Associate Chief for Research in the Division of Pediatric Hospital Medicine at Lucile Packard Children's Hospital Stanford. And a Clinical Professor in the Division of Hospital Medicine and the Division of Critical Care. Alan, thanks for chatting with me today.

Dr. Alan Schroeder:

Thank you very much for having me. It's an honor.

Dr. Ruth Adewuya:

I'm pleased to chat with you today about multisystem inflammatory syndrome that has emerged over the past couple of weeks and is being discussed both in the media and in different scientific communities. I wanted to maybe start by asking you what is multisystem inflammatory syndrome in children or MIS-C?And is that still the correct terminology?

Dr. Alan Schroeder:

That is the CDC terminology. They came up with that term after actually the folks in Europe had come up with another term, pediatric inflammatory multisystem syndrome. There've been a number of acronyms, but that was the CDC definition. And happy to tell you lots about it. I will qualify all of this with the notion though, that in part, because the Bay Area still has been reasonably spared mercifully by COVID-19 at least in contrast to many other geographic regions.

Dr. Alan Schroeder:

We still at Lucile Packard Children's Hospital where I practice in the ICU in the pediatric wards, we still really haven't seen a genuine case of, or at least a more severe case of this syndrome. And so, although I have spent a lot of my intellectual bandwidth over the past few months thinking about it and talking about it a little bit, maybe even writing about it a little bit, we really have not had much in the way of patients. And so that's good.

Dr. Alan Schroeder:

What many centers are seeing is that they're seeing an influx of this syndrome, usually about four, maybe even six weeks after they're really getting hit hard with acute infections largely in adults. And so it's possible with the number of cases we saw here in sort of late July, early August, that we may start seeing a few more cases over the next few weeks, but so far, really not much at all.

Dr. Alan Schroeder:

So that being said, and I'm going get to what it is, but I just wanted to give that prequel. We did have a case in March of a baby. This is actually our first baby who was positive for COVID and this baby had a syndrome called Kawasaki disease and Kawasaki disease has a lot of similarities to what is now being

described as MIS-C. That baby had classic Kawasaki disease, happened to test positive for COVID. A test came back right as a baby was about to be discharged from the hospital.

Dr. Alan Schroeder:

And so that was interesting and actually led to that case being written up by the folks who took care of the baby as a case report for a journal where I'm an editor called Hospital Pediatrics. And it laid dormant for a couple of weeks after it was published until people started talking about this multisystem inflammatory syndrome, similar to Kawasaki disease. And then all of a sudden this "first described case" at Stanford at Lucille Packard wound up really being front and center in the news.

Dr. Alan Schroeder:

And so even though we did have that one case of sort of classic Kawasaki disease, I would say that really was just true Kawasaki and not as much of this syndrome that we're seeing. So what is this syndrome? It seems to be an inflammatory response that follows a COVID-19 infection. Most of the patients who have it test negative for the PCR, but are positive for antibodies, which is why folks have concluded that this is really kind of an almost an autoimmune type response to the acute infection rather than an acute manifestation of coronavirus.

Dr. Alan Schroeder:

It tends to be characterized by fever, oftentimes GI complaints, elevated inflammatory markers. And a number of patients have gotten quite sick with cardiovascular collapse, coronary artery abnormalities. In some cases, evidence of myocardial inflammation in some cases, and in a very small fraction of kids, unfortunately, death. So that's a quick synopsis.

Dr. Ruth Adewuya:

Great. So if I'm hearing you correctly, the criteria or the case definition is fever, GI issues, inflammatory and potentially some cardiovascular complications or issues. Is there a defined criteria right now or are we still kind of learning as we go along, or did the CDC come up with something?

Dr. Alan Schroeder:

Yeah, the CDC does have discrete criteria although they should put discreet maybe in quotes and this isn't a knock on the CDC at all. They needed to come up with something, but it's still as it stands fairly vague, but the criteria that you need to be [inaudible 00:05:52], you need to have fever. You need to have laboratory evidence of inflammation. You need to have evidence of illness that is severe enough to require hospitalization. And that's really interesting and maybe something we can talk about later because people are entertaining this in the outpatient world. But at least according to the CDC, the idea is you should be sick enough to be in the hospital to be diagnosed with this.

Dr. Alan Schroeder:

There should be no alternative plausible diagnoses. And maybe we'll talk about that a little bit, but because this is a fairly nonspecific, there are a bunch of things that mimic this, and then you need to have some evidence of SARS-CoV-2 infection either by the PCR or by serology or, and this is where I think it gets a little bit tricky as well.

Dr. Alan Schroeder:

There needs to be exposure to either a suspected or a confirmed COVID case within the four weeks prior to the onset of symptoms. And the reason why that's challenging of course, is that how do you define exposure? And I think in high prevalent areas, you could argue that many people are exposed to people with suspected COVID-19. So that gets to be a little challenging.

Dr. Ruth Adewuya:

Yeah. That's a really great point. And thank you for providing those definitions. So in the course of describing what MIS-C is, you mentioned Kawasaki's and you mentioned some potential similarities to maybe other diseases. And you mentioned the fact that there should be no alternative option per se. So can we talk about Kawasaki's. And then I've also read about toxic shock. Let's talk about Kawasaki's and maybe let's talk about also the other similar diseases that could be maybe mistaken for it. So what is Kawasaki's? What does that look like?

Dr. Alan Schroeder:

What is Kawasaki is kind of a million dollar question because people have been trying to figure that out for decades really. And truthfully it's a disease that folks in the inpatient side and outpatient side get pretty excited about because it's fascinating and it kind of comes together as this story, but it is still not known exactly what causes it. So briefly it's a constellation of physical findings in conjunction with having to have fever for at least five days.

Dr. Alan Schroeder:

And those findings can be red eyes or conjunctivitis, a lymph node, mucous membrane changes, skin rash, sometimes swollen hands and feet. Usually there's elevated inflammatory markers. The reason why it matters is because kids do get coronary artery aneurysms as a sequelae of Kawasaki disease. And IVIG intravenous immunoglobulin has been proven in randomized trials to actually prevent the development of these coronary artery aneurysms. So it's important to diagnose because there's an effective treatment.

Dr. Alan Schroeder:

We also will use aspirin. Some people use steroids. And so a lot of those are similar to what we're seeing with MIS-C. A couple of differences most notably, most kids with Kawasaki are under five. They tend to be infants and toddlers. The median age of diagnosis for MIS-C has been eight. So older kids. Another important distinction is that kids with MIS-C, there's been this real predominance of abdominal pain. So kids present with a lot of abdominal pain, sometimes diarrhea, sometimes vomiting.

Dr. Alan Schroeder:

And abdominal complaints can certainly happen in classic Kawasaki disease, but not as common. So some overlapping features probably Kawasaki disease is like MIS-C, a response to viral infections. Viruses have been isolated in about a third of kids with Kawasaki disease, but that means that two-thirds of the time they're not. But if it's a delayed response like it is in MIS-C, then maybe we're not testing the right way. We should be testing for antibodies and not for PCR evidence of infection in the nasal pharynx. So that's how KD overlaps.

Dr. Alan Schroeder:

You mentioned toxic shock and toxic shock also quite similar to what we're seeing with MIS-C, mostly more of the shock part of this. With Kawasaki disease, shock is not particularly common. When it does happen, some people even call it [Kawashocki 00:10:30] disease, but it's not very common. I think in my career, I've probably managed a hundred kids or more with Kawasaki disease. And I can remember maybe two where we've had to provide blood pressure support or inotropic support. And I don't think I've ever had to intubate anybody and I've never had anybody die. Whereas in toxic shock, very common to need lots and lots of fluids to need inotropic support. Oftentimes patients need to be intubated and will have multisystem organ failure.

Dr. Alan Schroeder:

So that's where toxic shock has some similarities. Toxic shock is largely thought to be due to a toxin released by bacteria, oftentimes either strep or staph. And so different here that we're talking about a response to a virus, an immune response to a virus rather than a toxin released from a bacteria. But we are seeing that these cases do look a lot like toxic shock as well. And the challenge with toxic shock is that it's not always certain that you'll get a positive blood culture.

Dr. Alan Schroeder:

So toxic shock is sort of a clinical diagnosis that we make. So maybe that some of these cases of MIS-C that we're seeing now are just in fact good old-fashioned toxic shock that looks like it fits the criteria for MIS-C and has negative blood cultures. So that's where there's some overlap and then HLH or hemophagocytic lymphohistiocytosis is another condition, particularly with some of the hematologic abnormalities that we've seen with MIS-C where there've been some overlap as well.

Dr. Alan Schroeder:

There was a colleague from Texas Children's who was telling us about probably nine or 10 cases in a row that they had of something called murine typhus, which is flea rickettsial disease that's transmitted by fleas. And it looked very, very similar to MIS-C. I've never seen it. And I think it's endemic to certain areas, but rickettsial diseases, other vector-borne illnesses, malignancies, other autoimmune conditions, such as lupus. All of these things can look like this.

Dr. Alan Schroeder:

And as the prevalence of COVID increases, then your probability of having a positive antibody test goes up. So you could have a positive antibody tests to COVID, but still have murine typhus or Lyme disease or cancer. And so I think just being cautious about anchoring on COVID as a cause of nonspecific array of symptoms and doing as we should generally do doing your workup in a thoughtful and step-wise fashion.

Dr. Ruth Adewuya:

So let's go back to MIS-C. We talked about the signs and sometimes, and things like that. I'm curious about in terms of clinical presentation, are you seeing children with specific co-morbidities being impacted by MIS-C differently than others? Is there any literature on that yet or at least some anecdotal findings?

Dr. Alan Schroeder:

Yeah. It's another good question. To just reiterate, fortunately, maybe unfortunately in terms of personal expertise for this talk, but fortunately for the children of the Bay Area, we haven't seen this very much yet. But at least across the published studies and in terms of my conversations with colleagues from around the country, what is being described there is with adults and COVID in general, there seems to be a little bit more of morbidity in obese patients. There have been certainly racial and ethnic disparities, quite striking disproportionate infection rates out of the UK and describing New York as well. And patients of Afro or Caribbean descent and also Hispanic patients.

Dr. Alan Schroeder:

And that certainly may simply just be a representation of the more disproportionate overall prevalence in those populations. But others have explored potential biologic mediators of differences, such as vitamin D levels or other things. But interestingly, most of these patients are healthy. They tend to be healthy patients without a large amount of comorbidities. And that's kind of been true of Kawasaki disease originally too. Kawasaki disease is known to have some disproportionate amount of prevalence largely of Asian populations.

Dr. Alan Schroeder:

I mean, it was first described by Dr. Kawasaki in Japan and probably two to three times as many cases in Japan as compared to the US. So we have seen these differences for Kawasaki disease before and not really completely understood the root of those, but we're seeing similar racial and ethnic disparities here. And I think warrants some more investigation, but patients by and large have been reasonably healthy.

Dr. Ruth Adewuya:

Earlier when you talked about the criteria or case definition for MIS-C, you talked about the evidence that kind of warrants hospitalization. And yeah, wanted to come back to that. Can you talk about what you meant by that?

Dr. Alan Schroeder:

Yeah, I bring it up because I think general pediatricians have really been struggling with this entity around the country and even locally, we've been hearing about it a lot. Particularly in May and June when this was kind of front and center in the news, the New York Times had a whole bunch of articles on it when the New York City cases were described. And what this means is that patients with fever and rash, people have been concerned that that may represent MIS-C.

Dr. Alan Schroeder:

And so pediatricians have been asked to evaluate kids. Parents have asked for echocardiograms on their patients with fairly mild illnesses. So I think that's why this criteria that they need to be sick enough to warrant hospitalization is important because it sort of says that if you're well enough to be in the outpatient world and don't really have any criteria to be hospitalized, then we may not need to be considering that diagnosis.

Dr. Alan Schroeder:

It doesn't mean that we should dismiss it. And to be honest with you, sometimes we will hospitalize patients for Kawasaki disease simply because the concern for Kawasaki disease in and of itself is a

reason for hospitalization. So it becomes a little bit cyclical on that front. But in that case, it's because there's a treatment for it. And many would argue there's a treatment for MIS-C as well. And we can talk about that, but I think what it means to me is if a child has had a few of these symptoms, but is generally well, I don't know that we need to be doing a whole lot more exploring for possible MIS-C.

Dr. Alan Schroeder:

That being said, if the patient is sort of on the borderline of needing to be admitted and has a number of these potential signs and symptoms. And I think particularly as we're still in a reasonably early phase of understanding this condition, then I don't think it would be unreasonable to bring them into the hospital. But a fever and say a rash in and of themselves, I don't think would warrant further exploration at that stage.

Dr. Ruth Adewuya:

Just thinking about this condition. One question that I had is why does MIS-C develop in this age group of children? You mentioned over eight versus other age groups, and I'm just curious to get your thoughts here as compared to some patients in other age groups.

Dr. Alan Schroeder:

I'm not positive that we know that similar things aren't happening in adults. Early on in the pandemic, we were certainly hearing about adults who were recovering from acute lung disease getting better, and maybe even getting extubated and then kind of having cardiovascular collapse. So that was described, although I don't know that I've seen much in the way of kind of scientific investigations to prove that, but certainly Kawasaki disease to the extent that maybe this is on a spectrum of Kawasaki disease, we don't see much of that in adults.

Dr. Alan Schroeder:

So there is something about children and the immune response that seems to make them more prone to this inflammatory post-infectious condition. But how that applies to MIS-C I think is still poorly understood. And you might find some theories if you tried to read about it, but I don't know that anybody really knows at this point other than that there really does seem to be evidence that this is a post-infectious inflammatory condition.

Dr. Alan Schroeder:

As you know, post-infectious inflammatory conditions are certainly not new. We see that for lots of conditions and many of them in adults. And so maybe some of these cases of prolonged recoveries after COVID infections in adults, perhaps some of that is the post-infectious inflammatory response as well, but we're living and learning each day on those types of questions.

Dr. Ruth Adewuya:

Alan, before we move on to talking about treatment, you mentioned some laboratory tests. You mentioned the fact that most folks came back with a negative PCR, but positive for antibodies. Are there other tests or indicators that clinicians should be looking at when evaluating a potential patient for MIS-C?

Dr. Alan Schroeder:

That hinges a little bit on the setting. And so to my earlier point, I think in the outpatient world I think of the patients generally doing well I'm not sure that you need to be testing a whole lot, but on the inpatient side and there are protocols that vary a bit by center, but most of them call for a number of acute phase reactants. So ferritin levels, D-dimers, either procalcitonins or CRPS. A lot of people are getting troponins and/or NT-proBNPs to try to assess for cardiac involvement.

Dr. Alan Schroeder:

We're seeing some lymphopenia and some thrombocytopenia. So sort of hard to cross the threshold of a hospital without a CBC anyway, but oftentimes those are obtained. And then some people are getting really fancy with various cytokines, interleukins. And you're seeing that rheumatologists for example are involved in the inpatient side of things. Thinking about that in part, because people are tailoring some of the anti-inflammatory treatment to various interleukins for example.

Dr. Alan Schroeder:

But we at Packard have developed a protocol. It was a multi-disciplinary committee that came up with a protocol for testing and advocates for several of those labs and more labs sort of depending on how sick you are.

Dr. Ruth Adewuya:

And then in terms of published guidelines and recommendations, are we there yet? Do we have anything better from the CDC or is it more just kind of the in-house different institutions are coming up with their different treatment?

Dr. Alan Schroeder:

There are some published guidelines, but as you can imagine completely consensus-based. I think it's unfortunate that we have not rallied as a pediatric community nationally or internationally to launch some randomized trials. To my knowledge, I don't think there are any randomized trials going on, but I could be wrong on that, but I am unaware. There are some national registries that are looking at the treatments delivered and I think we'll try to do some comparative effectiveness work on that front.

Dr. Alan Schroeder:

But as we've learned through much of the adult COVID saga, randomized trials sometimes tell stories that are different than that which is told by the observational data. So I think it's too bad that we don't have any ongoing trials. I think part of that is just the numbers, even though we're talking a lot about MIS-C, CDC published a report earlier this month. They actually asked people to submit cases, all cases of MIS-C and I think there were over about a two-month period about 500 cases reported.

Dr. Alan Schroeder:

So not a small number, but also if you think about the recovery trial out of the UK where they had 6,000 adults for the Dexamethasone trial, hard to put together a really robust RCT when the cases are that few and far between. And also where the uniform case definition is challenging. Probably across the studies, the intervention that has been most common has been IVIG intravenous immunoglobulin. And that I think is largely driven by the similarities to Kawasaki disease and the proven efficacy of IVIG in Kawasaki disease.

Dr. Alan Schroeder:

I think somewhere between 70 to 80% of patients in most published reports have gotten that. Steroids are probably second and then a whole slew of the immune modulators have been used with variable degrees across centers after that. So I think it would be hard to be sick with this like in an ICU sick and not get IVIG. And one question maybe whether there's equipoise for a trial say of IVIG versus placebo at this point. But I would personally think there would at least be equipoise for something like IVIG versus steroids. But again, to my knowledge, that's not going on.

Dr. Alan Schroeder:

So I think each center is coming up with their own protocol and that's driven largely by what little amount has been published thus far, what's really tough is that most kids are recovering from this. There have been I think in the CDC report, there have been 10 total pediatric deaths. So looking at mortality and trying to see if drug X reduces mortality is going to be really, really hard in kids. And I think we're going to be stuck just kind of doing the best we can.

Dr. Ruth Adewuya:

Agreed. When this first hit the news and the media, there was obviously a lot of fear and concern from parents. At the time, folks were looking at what the future of school would look like. And so I'm curious to get your thoughts. And I know it might be a little different because in the Bay Area as you mentioned, we thankfully have not been impacted and have a large number of cases.

Dr. Ruth Adewuya:

But what are your thoughts around the impact or the existence of this disease and the decisions around school reopenings or camps and things like that?

Dr. Alan Schroeder:

I think that it's an incredibly complicated question and one which really smart people will debate for a long time. And the question around school closures recently has really hinged a lot more on the transmissibility of the infection from children to children or children to adults. And I think even with the emergence of MIS-C, I think we are all in reasonable agreement that kids still aren't getting very sick from this. Yes, there are some bad cases. We've had a couple bad cases of acute lung infection at Packard, but like maybe two total where kids have really had lung disease.

Dr. Alan Schroeder:

So it's still not very much at all and no cases of MIS-C of true MIS-C yet, but if you talk to hospitalists or intensivists in New York City, they'll tell you, "I think something very different." They may have a couple of kids in the ICU that are sick at a given time. So I think that whatever we can do to decrease prevalence is great as long as you are taking into account what the collateral damage of that is. And that's where the conversation about school is so challenging, because we know that school closures are causing all sorts of harm.

Dr. Alan Schroeder:

We know that they're widening the education gap that already exists. We know that for kids whose parents work sometimes two or three jobs, that childcare is really, really hard. So I think that it's a really challenging question. And I personally don't think that at least in the Bay Area right now that MIS-C

should impact that discussion very much. Thinking of it more in the context of getting the overall community prevalence of the infection down probably is a better approach to thinking about this, and maybe MIS-C weighs in the back of our mind that as prevalence goes up, the possibility of MIS-C goes up a little bit too.

Dr. Alan Schroeder:

But my best guess at this point is that the proportion of kids who get this infection that wind up having MIS-C is probably one in a thousand. There's a very wide confidence intervals around that guess, but that's just based on sort of how many cases occurred in New York City as compared to what the overall seroprevalence is in New York City. So I think that this is still a very rare phenomenon and the vast majority of children who get infected with coronavirus are going to be minimally impacted acutely and in the long run to the extent that we know that at this point.

Dr. Ruth Adewuya:

Which is fantastic.

Dr. Alan Schroeder:

Yeah. Yeah. Well, it's been one of the tiny silver linings of this infection is that in contrast to flu for example where kids, young kids really get it pretty bad. This has been thankful that it's not been that way in COVID as well.

Dr. Ruth Adewuya:

Great. Alan, any other last thoughts on MIS-C that you think would be pertinent for clinicians across the nation?

Dr. Alan Schroeder:

I guess the one thing that I alluded to a little bit earlier is just remembering that it's a nonspecific entity and that there are other things that can look like it.

Dr. Ruth Adewuya:

Fantastic. Alan, thank you so much for chatting with me today.

Dr. Alan Schroeder:

No, thank you, Ruth for having me. It's been a pleasure.

Dr. Ruth Adewuya:

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