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**HALENA
GAZELKA:** Welcome, everyone, to Mayo Clinic Q&A. I'm Dr. Halena Gazelka. Multisystem Inflammatory Syndrome in Children, or MIS-C, is a condition where different body parts can become inflamed. These can include the heart, the lungs, the brain, and even the skin, and the eyes. While we don't know the cause of MIS-C, there seems to be an association with COVID-19.

And here to discuss this with us today is Mayo Clinic physician Dr. Emily Levy. Dr. Levy is a pediatric critical care and a pediatric infectious disease specialist. Thanks for being here, Dr. Levy.

Could you give us an overview of exactly what is MIS-C? I haven't heard of this, and I'm sure many of our listeners haven't. And what's happening in the body when this occurs?

EMILY LEVY: Multisystem Inflammatory Syndrome in children, which I will call MIS-C for the rest of the interview, is a pretty rare and serious condition. It has to do with dysregulated inflammation. And what's happening in the body is that parts of the body, such as the heart, blood vessels, kidneys, or digestive system, and even the brain, can become inflamed.

We first heard about MIS-C in the pediatric world in April of 2020 when UK reports of previously healthy children presenting with a severe inflammatory syndrome came out. And initially, it was reported as having some Kawasaki disease-like feature, which I'll talk about a little bit more later in the interview. And all of these children had current or recent infection by SARS coronavirus 2, otherwise known as COVID-19.

As of August 20-- so the most recent reporting date we have before this interview-- there's been more than 600 cases of MIS-C in the United States. The CDC definition includes any individual under 21 years old with a fever, laboratory evidence of inflammation, two or more organ systems involved, lab evidence of COVID-19, and importantly, no other plausible diagnosis. So here in the United States, most of the cases have been between one-year-old and 14 years old. The average age is 8 years old that we're seeing.

More than 70% of our cases have been Hispanic, Latino, children or non-Hispanic black children. So we're seeing this disease disproportionately affect minorities. Most children develop MIS-C two to four weeks at their initial infection with COVID-19. And again, the clinical presentation can vary quite a bit-- but always includes fevers and then may have symptoms that indicate shock-- so decreased heart function, poor blood pressure or perfusion, different organs, and multiorgan or vascular disease. And that can be indicated by something like diarrhea or vomiting, cough, rash, red eyes, swollen hands, and on lab testing, elevated blood inflammatory markers.

**HALENA
GAZELKA:** [INAUDIBLE] do we know why COVID-19 is causing MIS-C in patients.

EMILY LEVY: So we don't really know why this specific virus is triggering this immune or autoinflammatory reaction, and we also don't really know why MIS-C is more common in children than in adults. Those are both things that we'll really need to look into over the next couple years or even decades as we're trying to learn more about this disease. What we do know is that it's been suspected for years that there's a viral trigger for Kawasaki disease, which again is somewhat similar to MIS-C. And that viral trigger has never been discovered. So it may be that COVID-19 is working as a similar viral trigger for this inflammatory condition.

HALENA Well, you mentioned Kawasaki disease, could you tell us how this is different from Kawasaki disease? How do the
GAZELKA: difference?

EMILY LEVY: Initially, there were some major parallels between MIS-C and Kawasaki disease because some of the symptoms, specifically conjunctival injection, or red in the whites of your eyes, rash, and fever, were very similar. And for those who are not as familiar with Kawasaki disease, Kawasaki disease is also an inflammatory condition, which typically will present with multiple days of fever, red eyes, rash, and then may have swollen extremities, a swollen tongue, and some other features that could indicate multiorgan inflammation. However, as we've gathered more data about MIS-C, some major differences have emerged. And so it's no longer thought that this is just another form of Kawasaki disease in these patients.

So in comparison to Kawasaki disease, MIS-C patients are older. They have more prominent gastrointestinal symptoms, so they're more likely to have vomiting or diarrhea. They're more likely to present in shock-- that is with low blood pressure or cardiovascular symptoms. And then on lab testing, they're more likely to have a low lymphocyte count, so a low white blood count, specifically the lymphocyte white blood cells-- and more likely to have higher inflammatory markers.

Unfortunately, like children with Kawasaki disease, children of MIS-C may develop coronary artery aneurysms. And we can talk a bit more about the treatment for those later, but we would similarly follow those coronary artery aneurysms with echocardiograms. And they may need similar treatment to what we do right now with children with Kawasaki disease.

HALENA So you mentioned along the way multiple signs and symptoms of MIS-C, and I'm wondering-- is it safe to say that
GAZELKA: these children appear quite ill? Will parents recognize this, and what do they do if they suspect it?

EMILY LEVY: It's always difficult with an emerging disease or syndrome to capture exactly how children are going to appear with the disease. Because there's some suspicion that what we're catching right now is the tip of the iceberg. So that would be a way of saying, what we're seeing the most of is the sickest group of these children, which makes sense because those are the children that are going to present to medical care. And perhaps, there's many more children out there who actually have some form of this syndrome, but are not ill enough to either require hospitalization or critical care.

That being said, what we are seeing right now in terms of the signs and symptoms of MIS-C have mainly been characterized from inpatient children or children in ICUs, and those children are quite sick when they present. So again, they must have a fever. And right now, the CDC is defining that as a temperature greater than 38.0 for more than 24 hours. And then they must have two organ system involvement.

And so in a child, they're going to look relatively ill to parents. They must have some sort of GI involvement-- that's something like vomiting or diarrhea. They could have problems with their coagulation or blood clotting system. That could manifest as different skin rashes, swollen tongue, a red mouth or red lips. They may have neurologic symptoms that could manifest as a child being too tired to awaken or otherwise confused-- and then a variety of other inflammatory-related organ dysfunction.

HALENA One of the signs that you mentioned earlier was a low lymphocyte count. I'm interested in that. Because
GAZELKA: obviously the inflammatory markers are high because we're talking about an inflammatory disorder. But why would some of the white blood cells be low when there are markers of inflammation?

EMILY LEVY: So it's not uncommon in viral illnesses or sepsis-- so for instance a high inflammatory state in a child triggered by an infection-- for them to have this paradoxical immune response. And we actually see this across all sorts of infections or inflammatory conditions in children, where they paradoxically actually have lower immune cells, in terms of certain cells in the body. Some theories around that are that viruses can suppress the bone marrow or suppress the cells that make immune cells, and other theories around it are that the inflammation cascade itself can suppress mobilization of immune cells. But this isn't unique to MIS-C. It's more that I mentioned it because it differentiates it from Kawasaki syndrome, where children actually tend to have higher white blood cell counts or higher immune cell counts.

HALENA And how do you treat MIS-C, and what happens if you don't?

GAZELKA:

EMILY LEVY: There's no specific evidence proven treatment for MIS-C right now-- that is there's no medicine that cures MIS-C. The hallmark of MIS-C treatment is supportive care. And so at this point, if you don't treat MIS-C with any specific medication, it's expected to eventually resolve. But what's needed is often either inpatient hospitalization or even critical care, hospitalization, supportive care, for children who have MIS-C to support them through the symptoms that are related to the disease.

So in terms of the specifics about the types of supportive care that are typically required, more than 50% of children admitted to hospitals with MIS-C require ICU level support. And typically, that involves cardiac or respiratory support, interventions, even like a ventilator or medications that support the blood pressure. Typically, they should be managed by a multidisciplinary team of doctors. So that would include intensivists and infectious disease doctors, like myself, but also hematologists, rheumatologists, immunologists, and cardiologists are often involved.

If there is a lot of overlap with Kawasaki disease, right now we are sometimes trying some of the therapies that have been proven to help in Kawasaki disease. Most common, that would be immunoglobulin-- so antibodies from other patients in the community and aspirin to help with some of the clotting side effects you can have. And then in many cases, we are trying high-dose steroids, which would suppress the inflammation that's causing many of the problems and the symptoms.

Some centers are using anticoagulation for these patients because they do seem more likely to clot, just like we're seeing in adult patients with COVID. There's no specific antiviral therapy indicated-- unfortunately, unlike an acute COVID infection, where you might try antiviral medication. This isn't actually an infection with COVID. It's a dysregulated inflammatory response after COVID.

And so infections that treat the virus-- excuse me-- medications that treat the virus themselves don't work very well. But we sometimes do consider immunomodulatory agents, and these are a bit outside of the scope of this conversation. But there are specific, targeted biologics that can target certain areas of the inflammatory cascade.

HALENA A little bit ago, you mentioned immunoglobulins. And I'm wondering-- that might provoke some of our listeners to wonder, is that the same as giving someone the convalescent plasma that we've heard so much about in the news?

GAZELKA:

EMILY LEVY: That would be the right thing for them to wonder about and something many physicians actually also ask me about. So in general, from MIS-C, we're giving pooled IVIG, which is a general immunoglobulin from the community. So it would be a normal person who probably has not had COVID-19, who is donating their pooled immunoglobulin, which is used in a variety of different conditions. And it's not clear how IVIG works in Kawasaki disease, but it does seem to decrease inflammation in many autoinflammatory or autoimmune diseases. That's compared to convalescent plasma, which is targeted donation from people who have had COVID-19-- often has titers measured against COVID-19-- and also, at our center, at least has neutralizing titers checked against COVID-19.

Interestingly, there are some theoretical concern about giving convalescent plasma in children with MIS-C. Because people wonder if you gave them COVID-19 antibodies, would that propagate this inflammatory response they're having? But the majority of the children actually already have COVID-19 antibodies, so the majority of them have had COVID-19, developed this inflammatory condition. And when you check, they actually have the COVID-19 antibody already. That's one of the ways we used to diagnose MIS-C.

**HALENA
GAZELKA:** Is it anticipated that children who develop MIS-C will recover fully, and is there any risk of permanent damage or long-term illness?

EMILY LEVY: The vast majority of children will eventually recover. There's overall been a very low death rate reported, so less than 1% in the studies reported in both the United States and in Europe. As you might guess with a new disease, it's only been around for three or four months now.

We don't have very good long-term data, but the long-term data we have is optimistic. And the other thing that we can speculate about is that typically Kawasaki disease long-term outcomes are quite good. The biggest long-term thing we see in our Kawasaki disease patients are coronary artery aneurysms, which can occasionally require long-term monitoring with serial echocardiograms and sometimes even long-term anticoagulation.

What's a bit more difficult to speculate about in MIS-C outcomes is many of the complications are going to be related to how sick the child would be while they were in the hospital and what would be needed for supportive care. And so at this point, it's not really possible to list percentages about long-term outcomes. What we do know is that children seem to be doing pretty well in that medium term, couple months of data we have.

**HALENA
GAZELKA:** Last several months has been frightening and I think anxiety provoking for many. And particularly when you consider your child or your grandchild becoming this ill-- I'm sure that some of our listeners will wonder, is there anything that I can do to prevent my child or my grandchild from developing MIS-C?

EMILY LEVY: Because MIS-C is thought to be a direct sequelae from COVID, so an inflammatory reaction to having had COVID-19 infection, the best way to prevent it is to prevent your child from being exposed or having COVID-19 infection. And that would just be the simple measures that have been recommended to most people in the population at this point to prevent exposure or contracting COVID-19.

And they include simple infection control things, like keeping your hands clean, avoiding people who are sick, whether or not they have a formal diagnosis of COVID-19, practicing social distancing when possible, wearing a face mask when possible, even in a child, cleaning and disinfecting high-touch surfaces, and washing clothing after being around people in public in a very close way where social distancing wasn't possible. So all of the common-sense things you do for your child normally, and particularly in the era of COVID-19, are things that would prevent them to ever develop MIS-C because they would hopefully prevent them to ever develop COVID-19.

HALENA
GAZELKA: Well, I remember in the beginning watching the news and hearing essentially that children weren't developing COVID-19. And clearly, that was not the case. And I think this has been a really informative session for me and for our listeners, and I think a good reminder to use those universal precautions for COVID-19 prevention. Thanks so much for being here with us, Dr. Levy.

EMILY LEVY: Thank you so much for having me.

HALENA
GAZELKA: Our thanks to Mayo Clinic pediatric critical care and infectious disease specialist, Dr. Emily Levy. I hope that you learned as much as I did today. And we wish you a wonderful day.

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