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THE PEDIATRIC JOURNEY

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MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN FOLLOWING CORONAVIRUS-19 INFECTION

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For children and their families, and the pediatricians who care for them, the revelation that acute infection with SARS-CoV-2, the virus that causes COVID-19, is generally well tolerated in children has been one of the few positive points of 2020 and the global COVID-19 pandemic [1]. While this finding about primary COVID-19 infection remains true six months into the pandemic, over the last two months it has become increasingly clear that a small subset of previously healthy children who have experienced COVID-19 can develop a post-infectious syndrome of severe inflammation.

This phenomenon was first noticed by physicians in the United Kingdom [2], who noticed an increase in critically ill children presenting to their referral hospital approximately a month after the peak of adult infections in that region. It is now understood that some children, who were typically asymptomatic or minimally symptomatic of their actual COVID-19 infection, will develop significant fever and other signs of illness, as described below, about four weeks later. This condition has been termed Multisystem Inflammatory Syndrome in Children (MIS-C), and is thought to be the result of the immune system response to the virus, although the pathophysiology of the disease is not currently understood.

A case definition for MIS-C (Figure 1) was released in May 2020 by the Centers for Disease Control and Prevention (CDC). The CDC has suggested to consider MISC in patients less than 21 years of age requiring hospitalization for fever and inflammation in the setting of involvement of illness in two or more organ systems when no other explanation could be found, but when there was evidence of current or recent coronavirus infection. That evidence could be a positive PCR, serology, or antigen test for SARS-CoV-2. However, some children (up to 25% in different cohorts) with MIS-C do not have any positive test, but do have a known exposure to a COVID-19 infected individual within four weeks of symptom onset, which is an acceptable criterion. The kinetics of viral shedding and antibody development against SARS-CoV-2 are actively being investigated around the globe. A better understanding of the time course of these findings and the sensitivities of different methods of antibody testing will ultimately help shed light on why some MIS-C patients have positive PCR and antibody testing and others do not.

In one cohort of patients in an early epicenter (New York), only 2/100,000 children had MIS-C, compared to 322/100,000 who had primary COVID-19 [3]. A subset of the more than 500 children with MIS-C now reported in the literature present with clinical features suggestive of Kawasaki Disease (KD) including rash, conjunctivitis, and oro-mucosal changes. Is this a clue to the pathophysiology of the disease? It is not clear, as the entity of MIS-C has been around only for a short time and the pathophysiology of KD has never been fully elucidated itself. The similarities may simply be the result of a stereotyped response to an immune stimulus, so the diseases appear clinically the same or similar.

Notably, there have been some distinctions revealed between MIS-C and classic KD [4], made in a cohort comparison study. MIS-C patients tend to be older and have lower platelets and lymphopenia than historical patients with KD. Another notable clinical difference is GI symptoms. While abdominal pain, nausea/vomiting, and diarrhea are not common features of KD, they appear to be present in most MIS-C patients.

Two large case series of children in the United States with MIS-C were recently published [3,5]. Based on the growing available reports, the "classic" presentation of a patient with MIS-C (if that term can even be used for a condition that has only existed since April 2020), would be a child with fever for 4-5 days and significant GI symptoms, who has lymphopenia, significant elevations of ESR, CRP, and LDH and also neutrophilia with high fibrinogen, ferritin, and D-dimer.

The "classic" MIS-C patient would also have evidence of myocardial inflammation such as an elevated BNP or troponin, or echo showing decreased myocardial function. Around 10% of MIS-C patients have coronary artery dilation [4,5]. Importantly, approximately three-quarters of MIS-C patients required ICU care [4] for shock presentations with requirements for respiratory support and even use of ECMO. Further, rapid deterioration has been frequently reported in MIS-C patients, underscoring the need for early recognition of this clinical condition. Most patients with MISC have presented to medical care on day 4-5 of fever. While the differential for a febrile child is wide-ranging, pediatricians now need to be aware of and consider MIS-C in these patients so appropriate evaluation can be considered. It is now important to screen febrile patients for a personal history or exposure to an individual with COVID-19.

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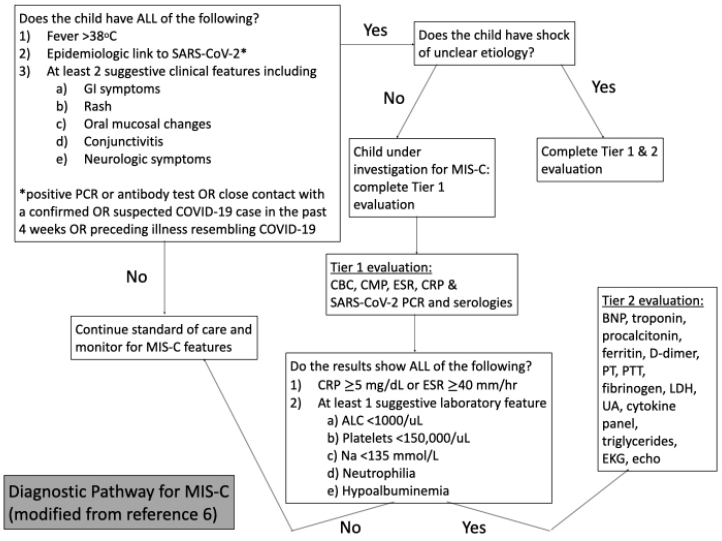
The American College of Rheumatology has created a guideline [6] for tiered evaluation of suspected MIS-C cases (Figure 2).

Fortunately, with proper recognition MIS-C is a treatable disease. Due to the similarities with KD, about three-quarters of children with MIS-C have been given IVIG. Around half of MIS-C patients have been reported to get corticosteroids. In some severe cases, treatment has also required anti-cytokine therapies using anti-interleukin-1 or anti-interleukin-6 pathway inhibitors. However, not all patients need treatment and some recover to baseline with only supportive care. The mortality of this disease from these early cohorts is ~2%.

One of the current difficulties for Texas pediatricians is that, unlike our European and northeastern colleagues, we are currently seeing concurrent presentations of primary COVID-19 and MIS-C in children, which can be difficult to distinguish from each other. The rheumatology service at Texas Children's Hospital is available for consultation on suspected cases of MIS-C in west Texas and reachable through the Provider Connect program (832-TCH-CARE).



Diagnostic Pathway for MIS-C (modified from reference 6)

References for this article will be available upon request, email: thepediatricjourney@elpasochildrens.org

FIGURE 1. Definition of Multisystem Inflammatory Syndrome in Children (MIS-C)*

An individual aged <21 years presenting with fever1, inflammation2, and clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
no alternative plausible diagnoses; AND
positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.

1Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours.
2Such as elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), or neutrophils OR reduced lymphocytes or low albumin.

Note:
Some individuals may fulfill full or partial criteria for Kawasaki disease.

**Source: CDC Health Advisory distributed via the Health Alert Network May 14,2020*

THE UNCERTAINTY OF BACK TO SCHOOL

BY: DR. RICARDO REYNA *Community Pediatrician*

COVID-19, not as easy as ABC -123! The Uncertainty of Back to School?

The back-to-school chatter has begun! But this years chatter sounds a whole lot different than any other year that I have ever heard! The chatter of where did you do over the summer, where did you go for vacation, or the latest back to school fashions, are replaced with should I even send my kids back to school, what about my child with underlying medical issues, and how will I be able to do this online schooling thing again. This summer might have looked a lot different than what you and your family had originally planned and going back to school will also not be the same as we have always expected and known.

There's so much uncertainty. To say that parents are stressed and overwhelmed right now is an understatement. We've been sheltering-in-place and managing our lives around the new coronavirus, COVID-19, for quite some time now. Like a lot of parents, I am also concerned about many aspects of COVID-19 for my patients.

Our world has drastically changed in the last several months, and we're needing to do things that we never imagined and expected. As providers and healthcare professionals, we have to continue monitor and update our knowledge on the daily changes and requirements in beating this virus. There is not a one size fits all approach in addressing this question. Each and every child and family have their unique challenges that they may have to deal with. As providers, we each have to consider each situation and be a resource to our families.

According to the recent stance of the Academy of Pediatrics is, "that reentry policies for back to school should have the goal of students being physically present in school." The AAP laid out its key principles including "being flexible and nimble in responding to

new information" and accommodating disadvantaged students.

I want families to know that they're not alone. Each families may need to handle it differently, based upon their unique situation. Please talk to your doctor about the steps your family should be taking and guidance in dealing with Covid-19 and back to school.

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2020 PEDIATRIC GRAND ROUNDS

The First & Third Wednesday of Every Month

GRAND ROUNDS: 8-9 A.M. Academic Education Center (AEC), 2nd Floor, 4800 Alberta Avenue

PLEASE CONTACT Erika Silvas Erika.Silvas@ttuhsc.edu or Natalie Campa Natalie.Campa@ttuhsc.edu for virtual access to Grand Rounds

SEPTEMBER 2, 2020	Evidence for the role of children in COVID-19 transmission during the swell of the first epidemic wave in the Americas	Dr. Glenn Fennelly, MD, Professor and Chair, Dept. Of Pediatrics, TTTUHSC El Paso
SEPTEMBER 16, 2020	Chronic Kidney Disease Cardiovascular Health Introduction: Dr. Khin	Dr. Lucas Prolacta Bioscience
NOVEMBER 4, 2020	TBD	Ryan Butts, MD UT Southwestern Medical Center
NOVEMBER 18, 2020	Racism in Health care	UNM Pediatrics

TO PROTECT PATIENTS, PHYSICIANS, STAFF, AND THE COMMUNITY,

El Paso Children's Hospital is limiting visitation to one parent/legal guardian as COVID-19 continues to spread. Everyone must pass previously established health-screening criteria before entering the facility. No additional visitors will be allowed to wait in the lobby or waiting rooms. Anyone entering the facility will be asked if they have symptoms of illness and exposure risks upon arrival. Those who have non-severe symptoms such as a fever or cough will be asked to not enter to stop the spread of illness and to seek care from their physician.

While we understand the importance of having the support of loved ones during a hospital visit or stay, we must prioritize the health and safety of our patients and caregivers during this unprecedented pandemic. We encourage support persons to use alternate methods of communication to stay in contact with loved ones, such as phone calls, video chats or texting.

We will continue to modify our response protocols as the needs within our community evolve.

EVERYONE SHOULD CONTINUE TAKING THE FOLLOWING PRECAUTIONS:

- *Wash your hands frequently for at least 20 seconds*
- *Avoid touching your face with unwashed hands*
- *Cover your mouth when you cough or sneeze*
- *Avoid contact with sick people*
- *Avoid large crowds*
- *Practice social distancing*

Everyone entering any El Paso County Hospital District facility, University Medical Center of El Paso, El Paso Children's Hospital, El Paso Health, and UMC/EPCH Foundations MUST wear a surgical mask or cloth facial covering at all times. NO EXCEPTIONS.

El Paso Children's HOSPITAL

TIME 4 CARE