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Compelling evidence of a novel multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 infection

— Sarah S. Long, MD

Two studies totaling 66 previously unreported cases of MIS-C associated with SARS-CoV-2 infection in the US put meat on the bones of news reports and individual case notes. Several aspects of the studies make them clean and comparable, and their messages clear. Each reports 33 pediatric patients with confirmed SARS-CoV-2 infection (predominantly by antibody testing), over the same 4-week period from mid-March through mid-April, 2020 (ie, weeks *following* the peaks of community COVID-19 cases) from children's medical centers in epicenters of COVID-19 in New Hyde Park, Queens (Capone et al) and 3 institutions in New York City (Kaushik et al). Both provide granular detail of patient characteristics, laboratory test results, management, and short-term outcomes. Although the spectrum of severity, especially that documented by precise measurement of cardiac dysfunction, was broad, the clinical manifestations and aberrations of the inflammatory response were unmistakable and similar.

In the 2 studies, median ages were 8.6 and 10 years, males 61%, underlying conditions 21% and 44%, and symptom duration prior to hospitalization 4 and 4.5 days. Fever was universal, gastrointestinal symptomatology (abdominal pain, diarrhea, or vomiting) universal, hypotension 63% (Kaushik et al), and shock requiring vasopressor therapy 76% (Capone et al). Although 64% of patients met criteria for complete Kawasaki disease in the study by Capone et al, for the most part patients did not have laboratory abnormalities or behave like patients with Kawasaki disease. Inflammatory markers were markedly elevated and cardiac function was markedly abnormal while coronary arteries were more likely to be normal or mildly abnormal. Medical therapies were varied in the studies reported herein, most focusing on halting the up-regulated inflammatory cytokines. Median lengths of hospital stay in these studies were remarkably short—4 days in the study by Capone et al that included PICU and non-PICU MIS-C cases and 4.7 days from shock to discharge from the PICU in the study by Kaushik et al. Although most patients with MIS-C have hypotension requiring vasopressor therapy, they are less ill appearing and less irritable than patients with the shock presentation of Kawasaki disease, and less ill and obtunded than patients with shock associated with bacterial infection (Associate Editor's personal observation). Most remarkably, cardiac dysfunction in MIS-C usually is rapidly reversible, which distinguishes patients with MIS-C from patients with viral or post-infectious myocarditis/cardiomyopathy (Associate Editor's personal observation).

MIS-C is a unique clinical entity seemingly of cytokine "toxicity" and thrombosis—an inflammatory syndrome, yes, but *absent tissue inflammation* such as vasculitis or myocarditis. Words matter. To take another opportunity for precision in language, MIS-C should not be referred to as *COVID*-associated since patients characteristically do not have the primary respiratory tract signs, symptoms, or outcomes of patients with COVID-19. MIS-C certainly is related to SARS-CoV-2 infection and it is unique.

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Further reassurance on the safety profile of colchicine

— Philip J. Hashkes, MD, MSc

Colchicine is a potent anti-inflammatory agent (non-immunosuppressive!) with multiple mechanisms of action on the innate immune system and neutrophils. The indications for colchicine are rapidly increasing, with one study showing that low-dose colchicine substantially decreased ischemic cardiovascular events among patients who recently underwent a myocardial infarction (*N Engl J Med* 2019;381:2497-505). This study led some to dub colchicine as the "new aspirin" (Could colchicine be the new aspirin? https://www.medscape.com/viewarticle/923819). There is a large trial underway to treat/prevent the hyperinflammation associated with COVID-19. However, colchicine is potentially fatal when overdosed, with a narrow margin of safety between effective and toxic doses, including bone marrow suppression. Therefore, it is important to study its safety profile.

The main indication of colchicine in children is for familial Mediterranean fever (FMF) in which colchicine needs to be taken lifelong. First discovered as effective for FMF in 1972, the safety profile of colchicine appeared to be excellent, but there are very few reports on the issue of leukopenia. A study by Sag et al reported in this volume of *The Journal* regarding the prevalence and significance of leukopenia was not systemically studied in a prospective cohort. They found an 11% prevalence of leukopenia unexplained by other causes among 213 consecutive children with FMF treated with age-based standard doses of colchicine. None of the patients had severe leukopenia/neutropenia and infection rates were not increased among these patients. Leukopenia resolved after dose adjustments. Although we periodically need to monitor white cell counts in these patients, the results of this study add another layer to the known safety profile of colchicine and should be reassuring to physicians and the increasing number of patients using this medication.

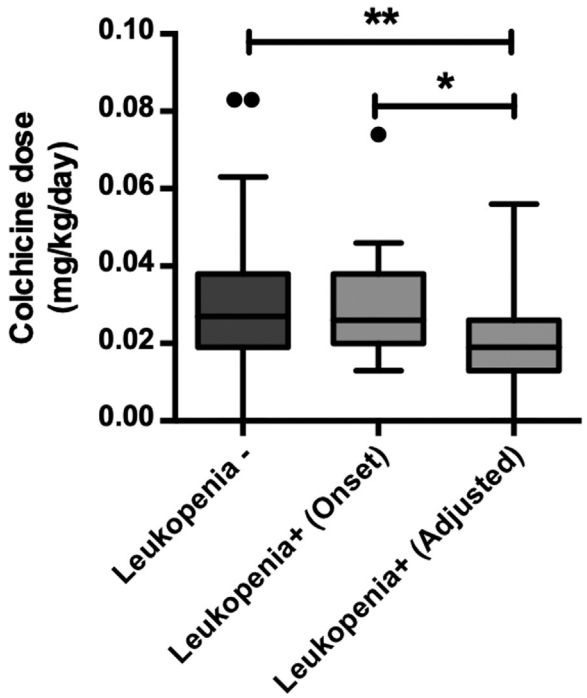

Figure. Colchicine doses were comparable in patients with or without leukopenia at the time of leukopenia onset. Adjusted doses were significantly lower. *$P < .05$, **$P < .01$.

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COVID-19: A teachable moment for vaccines and trust

— Sarah S. Long, MD

The commentary in this volume of *The Journal* by Williams et al validates, through evidence, the trusted role that pediatricians play in advising parents regarding administration of recommended vaccines, especially when parents are hesitant. They also provide a roadmap for forging mutually rewarding, therapeutic relationships with parents who might initially refuse vaccination. They posit proven methods of interaction based on truth, partnership, and persistence that build trust. They hope that this approach will curb the growing trend for dismissals of vaccine-hesitant families from practices, and lead to immunized, safer children and their communities.

The SARS-CoV-2 pandemic may provide a unique "teachable moment" as the tens of thousands of deaths in the US from a rampant infectious disease are an experiential reality rather than a theoretical risk. Only the development of a safe and effective vaccine offers the hope for restoration of life that resembles the one we took for granted just months ago. Poliovirus epidemics in the 1950s were similar national catastrophes "cured" by effective vaccines. The clamor for a SARS-CoV-2 vaccine is appropriate. Should such a vaccine(s) become a reality, the will and wherewithal to implement recommendations must follow. As we are learning from the SARS-CoV-2 pandemic, trust is earned, such as it has been for truth tellers who are public health and infectious diseases experts and for thousands of dedicated healthcare workers, trust in primary providers for implementation of a new vaccine will be pivotal.

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