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Steven L. Zeichner, MD, PhD, and Andrea T. Cruz, MD, MPH

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Multisystem Inflammatory Syndrome in Children and SARS-CoV-2 Serology

Steven L. Zeichner, MD, PhD[1] and Andrea T. Cruz, MD, MPH[2]

Affiliations: [1]Departments of Pediatrics & Microbiology, Immunology, and Cancer Biology, University of Virginia, Charlottesville, VA; [2]Department of Pediatrics, Baylor College of Medicine, Houston, TX

Address correspondence to: Steven Zeichner, Department of Pediatrics, University of Virginia, Box 801349, Charlottesville, VA 22908, zeichner@virginia.edu or Andrea Cruz, Department of Pediatrics, 6621 Fannin Street, Suite A2210, Houston, TX 77030, acruz@bcm.edu

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Abbreviations: ACE-2: angiotensin-converting enzyme 2; ADE: antibody-dependent enhancement; ARDS: acute respiratory distress syndrome; COVID-19: coronavirus disease 2019; MIS-C: multisystem inflammatory syndrome in children; RBD: receptor binding domain; S: SARS-CoV-2 spike protein; SARS-Co-V-2: severe acute respiratory syndrome coronavirus 2

COVID-19 is arguably the most socially and economically disruptive pandemic since the 1918 influenza pandemic. While pediatric COVID-19 shares features with the adult disease, there are several differences. Children produce virus in amounts at least equal to adults if not higher, [1] and can transmit the virus, just as adults can. [2] School-age children are generally less severely affected than infants or adults, but some children without significant underlying disease become ill or die in a disease process analogous to the one most commonly seen in adults: severe pulmonary disease and respiratory failure. [3-6] Children and adults appear to have different humoral immune responses to COVID-19. [7]

A small fraction of children with COVID-19 experience a hyperinflammatory process, [8-13] termed multisystem inflammatory syndrome in children (MIS-C) in the US, with features distinct from Kawasaki disease. [14] This case definition includes at least two of these symptoms: rash, conjunctivitis, or mucocutaneous inflammation; hypotension; cardiac disease; coagulopathy; or acute gastrointestinal problems. [15] MIS-C, which is not correlated with viral load levels, typically appears some time after initial infection. [13] MIS-C's incidence is difficult to determine, given the high rate of asymptomatic infection. [12]

Adults with COVID-19 also can experience inflammatory disorders: coagulopathies, vasculitis, cardiomyositis, and neuroinflammatory processes. [16-18] That the most effective therapy to reduce mortality in adults with severe COVID-19 yet established is an immune suppressant, dexamethasone, [19] highlights the importance of inflammatory and immune-mediated pathologies.

In this issue of *Pediatrics,* Rostad et al. [20] showed that children hospitalized with MIS-C have significantly higher concentrations of antibodies against the receptor-binding domain (RBD), a part of the SARS-CoV-2 spike protein (S). RBD is the part of S mediating virus binding to its receptor, angiotensin-converting enzyme 2 (ACE2), on host cells. This finding is reinforced by other research, which showed that anti-RBD antibody concentrations were higher in children with severe MIS-C than in children with mild MIS-C or patients not meeting MIS-C definitions. [1] The children also had high SARS-CoV-2 neutralization titers, consistent with the observations that anti-RBD antibodies can effectively neutralize the virus. [21] The MIS-C patients described in Rostad et al. [20] also tended to have higher antibody levels against the entire spike protein and the viral nucleocapsid (N) protein, which is not exposed on the surface of the virion. The anti-RBD antibody levels correlated with the erythrocyte sedimentation rate, suggesting that higher anti-RBD antibodies are associated with a more proinflammatory state.

The finding that MIS-C patients have higher anti-RBD antibodies is interesting and potentially important because, despite case definitions, MIS-C may be difficult to diagnose. If high levels of anti-RBD antibodies are associated with MIS-C, quantitative assays for anti-RBD antibodies might enable more accurate MIS-C diagnosis or predict patients at higher risk for MIS-C, potentially enabling early interventions.

So far, reports describing associations of high anti-RBD IgG with MIS-C have looked at anti-RBD IgG bulk properties. However, all antibodies may not have equal activity, or equal propensities to be associated with – or to cause – MIS-C. Detailed study of the antibodies,

including mapping binding sites within RBD, may yield improved understanding of pathogenesis. Immune responses to COVID-19 are heterogeneous. Neutralizing antibody concentrations vary widely; some patients do not develop detectable titers. [22] Patients who recover exhibit different antibody responses from those who die. [23] It may be helpful to modulate immune responses to achieve ideal levels of activity generally, such as dexamethasone for severe disease, or specifically, if anti-RBD immune responses prove problematic.

Beyond potential use in diagnosing MIS-C, the findings may have implications for pathogenesis, therapy, and vaccine development. In producing immune responses against COVID-19, there may be a response that optimally addresses threats posed by infection without initiating harmful hyperactive immune responses. The response against RBD may reflect general characteristics of immune responses against SARS-CoV-2, or there may be something particularly problematic about immune responses directed against RBD, per se, an idea reinforced by the finding that RBD antibodies are correlated with inflammatory markers.

Another implication may be that if anti-RBD antibodies are associated with MIS-C, it might be desirable to screen convalescent sera for anti-SARS-CoV-2 neutralizing activity and anti-RBD activity, selecting units with good neutralizing activity, but with lower anti-RBD activity. This may also be a consideration for anti-SARS-CoV-2 therapeutic monoclonal antibody development.

Some investigators have hypothesized that children may have milder COVID-19 disease due to cross-reactive immunity to other coronaviruses, [24, 25] but it is also conceivable that such prior coronavirus exposures might have increased risks of an inflammatory response or worse disease, as seen with dengue hemorrhagic fever. [26, 27]

The findings of Rostad et al. [20] may also have implications for vaccine development. Close attention to vaccines eliciting anti-RBD antibodies may be advisable, if dysregulated or aberrant responses against RBD or parts of RBD contribute to hyperinflammation. Many candidate vaccines aim to elicit responses against the entire S, including RBD. Some aim to specifically elicit antibodies against RBD. [28] While a COVID-19 vaccine is urgently needed, leading vaccinologists have cautioned against deploying vaccines without thorough safety evaluations, recalling unfortunate past tragedies involving candidate vaccines, with vaccination yielding increased morbidity and mortality when vaccinees were later infected with circulating virus. [29-32] If strong anti-RBD responses are associated with an increased risk of inflammatory disorders, it may then be advantageous to develop vaccines that, while eliciting excellent anti-SARS-CoV-2 neutralizing activity, preferentially avoid eliciting strong anti-RDB immune responses.

How could aberrant immune responses promote MIS-C? Hypothetical mechanisms include antibody-dependent enhancement (ADE), direct cytotoxicity, immune complexes, and macrophage hyperinflammatory responses, [33] perhaps enabled by substantial differences in humoral responses. [7] Another theoretical possibility would be innate activities of anti-RBD antibodies. Antibodies with catalytic activity (abzymes) have been described and can be

significant in autoimmune diseases. [34, 35] Antibodies against proteins that bind enzymes can themselves have weak catalytic activity; an antibody against a protein (RBD) that binds an enzyme (ACE2) could plausibly have catalytic activity, with physiologic consequences. [36]

MIS-C and COVID-19 inflammatory disorders in children are relatively uncommon, but can be serious. Better diagnostics and improved management will be important as more children are infected. Greater understanding of MIS-C pathogenesis may help optimize convalescent plasma therapy and inform vaccine development.

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