

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

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Coronavirus disease 2019 (COVID-19) is arguably the most socially and economically disruptive pandemic since the 1918 influenza pandemic. Although 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-aged 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 United States, with features distinct from Kawasaki disease.¹⁴ This case definition includes ≥ 2 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 reveals the importance of inflammatory and immune-mediated pathologies.

In this issue of *Pediatrics*, Rostad et al²⁰ showed that children hospitalized with MIS-C have significantly higher concentrations of antibodies against the receptor-binding domain (RBD), a part of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein (S). RBD is the part of S mediating virus binding to its receptor, angiotensin-converting enzyme 2, 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 patients with MIS-C described in Rostad et al²⁰ also tended to have higher antibody levels against the entire spike protein and the viral nucleocapsid 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 patients with MIS-C have higher anti-RBD antibodies is interesting and potentially important

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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, authors of 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 to cause, or equal propensities to be associated with, 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 because of cross-reactive immunity to other coronaviruses,^{24,25} but it is also conceivable that such previous coronavirus exposures might have increased risks of an inflammatory response or worse disease, as seen with dengue hemorrhagic fever.^{26,27}

With their findings, Rostad et al²⁰ 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 Although 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 vaccine recipients 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-RBD immune responses.

How could aberrant immune responses promote MIS-C? Hypothetical mechanisms include antibody-dependent enhancement, 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 (angiotensin-converting enzyme 2) 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.

ABBREVIATIONS

COVID-19: coronavirus disease 2019

MIS-C: multisystem inflammatory syndrome in children

RBD: receptor-binding domain

S: severe acute respiratory syndrome coronavirus 2 spike protein

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

REFERENCES

1. Yonker LM, Neilan AM, Bartsch Y, et al. Pediatric SARS-CoV-2: clinical presentation, infectivity, and immune responses. *J Pediatr*. 2020;S0022-3476(20):31023–31024
2. Park YJ, Choe YJ, Park O, et al.; COVID-19 National Emergency Response Center, Epidemiology and Case Management Team. Contact tracing during coronavirus disease outbreak, South Korea, 2020. *Emerg Infect Dis*. 2020; 26(10):2465–2468
3. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145(6):e20200702
4. Cruz AT, Zeichner SL. COVID-19 in children: initial characterization of the pediatric disease. *Pediatrics*. 2020; 145(6):e20200834
5. She J, Liu L, Liu W. COVID-19 epidemic: disease characteristics in children. *J Med Virol*. 2020;92(7):747–754
6. Chao JY, Derespina KR, Herold BC, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 at a tertiary care medical center in New York City. *J Pediatr*. 2020;223:14–19.e2
7. Selva KJ, van de Sandt CE, Lemke MM, et al. Distinct systems serology features in children, elderly and COVID patients. *medRxiv*. Preprint posted online May 18, 2020; doi:10.1101/2020.05.11.20098459; 2020.2005.2011.20098459
8. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239): 1771–1778
9. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094
10. Whittaker E, Bamford A, Kenny J, et al.; PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020;324(3):259–269
11. Cheung EW, Zachariah P, Gorelik M, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York city. *JAMA*. 2020;324(3):294–296
12. Dufort EM, Koumans EH, Chow EJ, et al.; New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York state. *N Engl J Med*. 2020; 383(4):347–358
13. Feldstein LR, Rose EB, Horwitz SM, et al.; Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in U.S. Children and adolescents. *N Engl J Med*. 2020; 383(4):334–346
14. Consiglio C, Cotugno N, Sardh F, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19 [published online ahead of print September 6, 2020]. *Cell*. doi: 10.1016/j.cell.2020.09.016
15. World Health Organization. *Multisystem Inflammatory Syndrome in Children and Adolescents with COVID-19*. Geneva, Switzerland: World Health Organization; 2020. Available at: <https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>
16. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506
17. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with covid-19. *N Engl J Med*. 2020;382(17):e38
18. Hanafi R, Roger PA, Perin B, et al. COVID-19 neurologic complication with CNS vasculitis-like pattern. *AJNR Am J Neuroradiol*. 2020;41(8):1384–1387
19. Horby P, Lim WS, Emberson JR, et al; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with covid-19 - preliminary report [published online July 17, 2020]. *N Engl J Med*. doi:10.1056/NEJMoa2021436
20. Rostad CA, Chahroudi A, Mantus G, et al. Quantitative SARS-CoV-2 serology in children with multisystem inflammatory syndrome (MIS-C). *Pediatrics*. 2020;146(6):e2020018242
21. Shi R, Shan C, Duan X, et al. A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. *Nature*. 2020;584(7819):120–124
22. Wu F, Liu M, Wang A, et al. Evaluating the association of clinical characteristics with neutralizing antibody levels in patients who have recovered from mild COVID-19 in Shanghai, China. *JAMA Intern Med*. 2020;180(10):1356–1362
23. Atyeo C, Fischinger S, Zohar T, et al. Distinct early serological signatures track with SARS-CoV-2 survival. *Immunity*. 2020;53(3):524–532.e4
24. Brodin P. Why is COVID-19 so mild in children? *Acta Paediatr*. 2020;109(6): 1082–1083
25. Devulapalli CS. COVID-19 is milder in children possibly due to cross-immunity [published online ahead of print June 10, 2020]. *Acta Paediatr*. doi: 10.1111/apa.15407
26. Katzelnick LC, Gresh L, Halloran ME, et al. Antibody-dependent enhancement of severe dengue disease in humans. *Science*. 2017;358(6365):929–932
27. Wilder-Smith A, Ooi EE, Horstick O, Wills B. Dengue. *Lancet*. 2019;393(10169): 350–363
28. Thanh Le T, Andreadakis Z, Kumar A, et al. The COVID-19 vaccine development landscape. *Nat Rev Drug Discov*. 2020; 19(5):305–306
29. Graham BS. Rapid COVID-19 vaccine development. *Science*. 2020;368(6494): 945–946
30. Hotez PJ, Corry DB, Bottazzi ME. COVID-19 vaccine design: the Janus face of immune enhancement. *Nat Rev Immunol*. 2020;20(6):347–348
31. Corey L, Mascola JR, Fauci AS, Collins FS. A strategic approach to COVID-19

- vaccine R&D. *Science*. 2020;368(6494): 948–950
32. Iwasaki A, Yang Y. The potential danger of suboptimal antibody responses in COVID-19. *Nat Rev Immunol*. 2020;20(6): 339–341
33. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis*. 2020;S1473-3099(20): 30651–30654
34. Bowen A, Wear M, Casadevall A. Antibody-mediated catalysis in infection and immunity. *Infect Immun*. 2017;85(9): e00202–e00217
35. Nevinsky GA, Buneva VN. Catalytic antibodies in healthy humans and patients with autoimmune and viral diseases. *J Cell Mol Med*. 2003;7(3):265–276
36. Friboulet A, Izadyar L, Avalle B, Roseto A, Thomas D. Abzyme generation using an anti-idiotypic antibody as the “internal image” of an enzyme active site. *Appl Biochem Biotechnol*. 1994;47(2–3):229–237, discussion 237–239

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