ABSTRACT# 24

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Title: Immunopathology in MIS-C: elevated alarmin and cytotoxicity signatures and autoreactivity that correlates with severity

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Background: Multisystem inflammatory syndrome in children (MIS-C) has emerged as a life-threatening post-infectious complication occurring unpredictably four to six weeks after mild or asymptomatic SARS-CoV-2 infection in predominantly healthy children across the world.

Methods: We define immune abnormalities in 23 MIS-C patients compared to adult COVID-19 and pediatric/adult healthy controls using single-cell RNA sequencing, flow cytometry, antigen receptor repertoire analysis, unbiased serum proteomics, and in vitro assays.

Results: Although we find no evidence of active infection, we discover elevated S100A-family alarmins in myeloid cells and enrichment of serum proteins that map to myeloid cells and pathways including cytokines, complement/coagulation, and fluid shear stress in MIS-C patients. Moreover, NK and CD8 T cell cytotoxicity genes are elevated, and plasmablasts harboring IgG1 and IgG3 are expanded. Furthermore, we detect elevated binding of serum IgG from severe MIS-C patients to activated human cardiac microvascular endothelial cells in culture.

Conclusions: Thus, we define immunopathology features of MIS-C with implications for predicting and managing this syndrome in children and better understanding age-related control of the immune response.

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(data provided below)
Schematic model of immunopathology drivers in MIS-C. Figure generated with Biorender.com.