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Biphasic Variation Over Time in Presenting Features of Patients With COVID-19

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Contributors’ Statement Page

Dr. Philip Zachariah and Dr. R. Colin Carter conceived of the presented concept, reviewed the collected data, contributed to the data analysis, interpretation, development of figures and writing and critical review of this manuscript.

Dr. Nazreen Jamal collected the data, contributed to the data analysis, interpretation, development of figures and writing and critical review of this manuscript.

Dr. Susan Whittier provided the viral load data, contributed to the data analysis, interpretation, development of figures and review of this manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Introduction

Current data suggest lower rates of severe coronavirus disease 2019 (COVID-19) in children compared with adults.\textsuperscript{1,2} While severe respiratory disease has rarely been described,\textsuperscript{3} new data suggest the emergence of a COVID-19-related multi-system inflammatory syndrome in children (MIS-C).\textsuperscript{4,5} Describing the temporal variation of pediatric COVID-19 presentations across the course of a high-prevalence outbreak may help elucidate the epidemiology and biology of these manifestations in children.

Methods

We conducted a retrospective chart review of children (age ≤20 years) presenting to the New York-Presbyterian Morgan Stanley Children’s Hospital Pediatric Emergency Department (PED) from March 13\textsuperscript{th} (date of first known case) to May 19\textsuperscript{th}, 2020 who tested positive for SARS-CoV-2. SARS-CoV-2 testing included reverse transcriptase polymerase chain reaction done on nasopharyngeal swabs (Roche 6800 or Cepheid Infinity platform) or serology (a NY State Department of Health-approved combined IgG/IgM immune assay against SARS-CoV-2 spike trimer or nucleocapsid protein). Serology was only performed when there was clinical suspicion for SARS-CoV-2-related disease and negative PCR results. Only presentations at the time of initial test positivity were assessed.

Across each week of the study period, we calculated: i) mean viral load; ii) mean initial C-reactive protein (the inflammatory marker routinely used at our center); iii) proportions of cases with specific presenting symptomatology.

Viral load in positive nasopharyngeal samples was measured using the inverse of Cycle threshold (Ct) values of the envelope protein, the most consistently amplified viral target.
Hypoxemia was defined as oxygen saturation \( \leq 94\% \) at presentation. Presenting symptomatology was classified by review of initial admission records as recorded by the treating physician. Symptoms were classified into four distinct groups: respiratory (dyspnea, chest pain, cough, nasal congestion), gastrointestinal (abdominal pain, vomiting, diarrhea), mucocutaneous (sore throat, lip redness, rash, conjunctivitis) and neurologic (headache, seizure, altered mental status, cranial nerve VI palsy). Symptom duration was not assessed. Mantel-Haenszel linear-by-linear associations were examined to examine changes in presentation over time. All study activities were approved by the Columbia University Medical Center Institutional Review Board.

**Results**

106 children with COVID-19 presented in two distinct, five-week phases. (Fig. 1A). Hospitalization rates remained stable (Fig. 1A). Although mean age was stable over the study period, the proportion of cases under age 12 months decreased over time \((p = .001)\) from 22.2-71.4\% over phase 1 to 4.5-16.7\% in phase 2. Mean nasopharyngeal viral loads \((n=88)\) decreased over time, while mean initial C-reactive protein concentrations \((n=83)\) increased in the second phase (Fig. 1B). Positive serology was only seen in phase two, during which 25 children had positive serology testing and 29 had positive PCRs.

Fever was prevalent throughout but more common in phase two (Fig. 1C). Hypoxemia and dyspnea predominated early, followed by a striking increase in gastrointestinal and mucocutaneous symptoms (Figs.1C, 1D). In phase one, mucocutaneous complaints were limited to sore throat, while rash and conjunctivitis were present exclusively in phase two. Neurologic symptoms increased over time, with headache presenting throughout but altered mental status and cranial nerve VI palsy exclusively in phase two.
Discussion

These data demonstrate a biphasic nature of disease presentation in a high prevalence SARS-CoV-2 outbreak in susceptible children. The first phase is consistent with uncontrolled community spread followed by a drop in new infections after local non-pharmaceutical interventions (school closures and shelter-in-place orders) were instituted. The second phase reflected a resurgence of disease while non-pharmaceutical intervention measures were still in place and local new infection rates had markedly dropped. Notably, viral load measures in our cohort decreased in the second phase to levels more consistent with remote rather than active infection, while mean inflammatory markers were higher, indicating more severe systemic inflammation. Our findings suggest two phases of immune response to initial SARS-CoV-2 infection in susceptible children: acute COVID-19 with predominantly respiratory symptoms and a delayed post-infectious hyper-inflammatory phenomenon with gastrointestinal, mucocutaneous, and neurologic symptoms, recently described as MIS-C.

While both of these presentations have been previously described, our data demonstrate a distinct epidemiologic time course with clear trends in presenting symptomatology, inflammatory markers, and viral load. These presentations occurred in different children as no patients diagnosed in phase one returned with MIS-C symptoms.

Although recognition of MIS-C may have increased over the study period, per state requirements, we reviewed all ED visits and hospitalizations for presentations compatible with possible MIS-C and found only one case in phase one who had Kawasaki Disease and negative SARS-CoV-2 testing. Surveillance for these distinct acute vs. delayed COVID-19-related disease phenotypes may help epidemiologists assess onset and intensity of ongoing community transmission and may have implications for emergency preparedness for recurrent waves of
SARS-CoV-2 in terms of ensuring supply of relevant medications (e.g. remdesivir vs. IVIG) and supportive interventions (e.g. ventilators vs. circulatory support). Furthermore, in geographic regions where infection trends may be less distinct, presenting symptomatology, inflammatory markers, and viral loads could help clinicians to distinguish between these pediatric manifestations of COVID-19.

References


A. Case numbers (bars) and proportion hospitalized (line)

B. Initial inflammatory markers ($n=83$) and viral load ($n=88$) by week$^1$

C. Presentation vital sign abnormalities by week$^2$

D. Presenting symptomatology by week$^2$

*p $\leq .05$; **p $\leq .01$; ***p $\leq .001$.

$^1$p values for week from A.N.O.V.A.

$^2$p values from Mantel-Haenszel linear-by-linear association term.

Ct = cycle threshold
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