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DOI: 10.1542/peds.2020-1550

Journal: *Pediatrics*

Article Type: Case Report

Citation: McLaren SH, Dayan PS, Fenster DB, et al. Novel coronavirus infection in febrile infants aged 60 days and younger. *Pediatrics.* 2020; doi: 10.1542/peds.2020-1550

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Novel Coronavirus Infection in Febrile Infants Aged 60 Days and Younger

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Financial Disclosure: None of the authors have financial relationships relevant to this article to disclose.

Funding Source: No funding was secured for this study.

Conflict of Interest: None of the authors have conflicts of interest to disclose.

Abbreviations: Emergency department (ED), intensive care unit (ICU), urinary tract infection (UTI)

Contributors' Statement Page
Drs. McLaren and Lubell conceptualized and designed the study, designed the data collection instruments, coordinated and supervised data collection, carried out the analysis, and reviewed and revised the manuscript.

Dr. Dayan conceptualized and designed the study, coordinated and supervised data collection, carried out the analysis, and reviewed and revised the manuscript.

Dr. Fenster coordinated and supervised data collection, and reviewed and revised the manuscript.

Ms. Bugaighis, Ms. Gonzalez, Ms. Ochs, and Mr. Vindas performed data collection and reviewed and revised the manuscript.

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

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Abstract

In this case series, we describe the clinical course and outcomes of 7 febrile infants aged ≤60 days with confirmed SARS-CoV-2 infection. No infant had severe outcomes, including the need for mechanical ventilation or intensive care unit level of care, during hospitalization or at 7-day follow up. Two infants had concurrent urinary tract infections which were treated with antibiotics. While a small sample, our data suggest that febrile infants with SARS-CoV-2 infection often have mild illness.

Introduction

The rapid spread and severity of SARS-CoV-2 infection has led to the publication of several studies characterizing the illness in children, including potential factors associated with prognosis.[1–6] A recently published case series from China suggests that younger children, especially those less than 1 year of age, may be more likely than older children to experience severe outcomes, such as acute respiratory distress syndrome and organ failure.[1] These data regarding the prognosis in specific groups of children have largely come from hospitalized patients with potentially biased samples, as broad surveillance and follow-up have not been feasible.[7]

One population of vulnerable patients who are uniformly hospitalized, irrespective of SARS-CoV-2 status, are febrile infants aged 28 days and younger.[8] This uniform hospitalization practice and our institutional standard to obtain SARS-CoV-2 testing for admitted patients afforded us the opportunity to report on the prognosis of this group. Additionally, febrile infants 29 to 60 days of age are frequently hospitalized and represent a population of concern to clinicians. Limited data regarding the clinical course and illness severity exist that focus on febrile infants aged ≤60 days with SARS-CoV-2 infection. As a tertiary pediatric hospital in the epicenter of the COVID-19 pandemic, our aim was to describe the clinical course and likelihood of severe illness for a series of febrile infants with confirmed SARS-CoV-2 infection. Although the prospective aspect of this study is ongoing, we hoped this case series would provide insights of clinical use during the ongoing outbreak.

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Methods

We conducted a mixed retrospective and prospective study of infants evaluated at our hospital from March 1, 2020 to April 15, 2020 who (1) were 60 days and younger, (2) had documented temperature ≥38.0°C at home or in the emergency department (ED) within the prior 24 hours, and (3) tested positive for SARS-CoV-2, the virus that causes COVID-19 infection. As of April 4, 2020, all admitted infants had in-house nasopharyngeal SARS-CoV-2 Real-Time Polymerase Chain Reaction test (Roche™) performed regardless of symptoms or exposure.

The retrospective sample includes infants who: a) presented to the hospital between March 1, 2020 and March 30, 2020, when the prospective study component started; b) presented to the hospital but were missed for prospective enrollment (e.g. study team unavailable), or c) declined participation in the telephone follow-up. We included eligible infants who either presented to our ED or were transferred directly to our inpatient service from one of our six affiliated hospitals, which transferred all pediatric admissions to our hospital from March 25, 2020 forward. During the prospective study time period, we enrolled infants either from the ED or the inpatient service. The institutional review board approved this study, with requirement for verbal consent for prospectively enrolled infants and a waiver of consent to retrospectively review the medical records of all eligible infants.

For infants enrolled prospectively, we obtained the physical examination findings from discussion with the initial treating clinician using a standardized data form. For the retrospective cohort, one of two experienced physician investigators (SM, TL) conducted the medical record review to determine the presence or absence of patient history and physical examination findings. For the medical record review, we recorded “unknown” when a finding was not explicitly documented and used restrictive key words to

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determine the level of hydration, clinical appearance, and respiratory status (keywords available on request).

We assessed clinical course by reviewing the medical record and conducting telephone follow-up. We evaluated the medical record for use of respiratory support, as well as requirement for fluid resuscitation and/or inotropic medications. We defined severe illness as any of the following: 1) acute respiratory distress syndrome as documented by the intensive care unit physician; 2) respiratory failure, defined as requiring mechanical ventilation, (3) presence of sepsis or shock, as specifically identified in the medical record documentation, (4) requirement for intensive care unit (ICU) level of care, and (5) death. During the 7-day follow-up, we inquired about any unscheduled visits to a medical provider, re-hospitalization, and ICU admission.

Results

Twenty infants were potentially eligible based on age and presence of fever during the screening period; 7 (35%) and 13 (65%) were 0-28 and 29-60 days of age, respectively. Of these 20 infants, 13 had SARS-CoV-2 test completed, including 6/7 (86%) infants aged 0-28 days old and 7/13 (54%) infants aged 29-60 days old. Of the 13 infants tested, 7 (54%) were positive for SARS-CoV-2. Four of the 7 infants were initially evaluated in our ED, while 3 were transferred from our affiliate hospitals. Five of the 7 infants with SARS-CoV-2 were enrolled prospectively, either in the ED or upon hospitalization.

Table 1 describes the characteristics of the infants who tested positive for SARS-CoV-2, with ages ranging from 11 to 56 days. Maternal SARS-CoV-2 status at the time of delivery was not available for any of the infants. One infant had a confirmed SARS-CoV-2 positive contact at home. Fever was the only

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presenting symptom for 3 (43%) infants, and no infant was ill-appearing or in respiratory distress at the time of presentation.

Table 2 details the diagnostic testing results and outcomes of the study infants. No infant had severe outcomes (95% confidence interval 0-35%). Two infants had *Escherichia coli* urinary tract infections (UTIs), both of whom had procalcitonin levels >0.5 ng/mL. Among the 5 infants without chronic medical illness, median length of hospitalization was 2 days (interquartile range 1, 2 days). None of the 7 infants required supplemental oxygen or non-invasive positive pressure ventilation during their hospital course. On 7-day follow-up, none had been re-hospitalized. One infant was known to be re-hospitalized at 14 days for fever; the SARS-CoV-2 test was again positive, no bacterial source was noted, and the clinical course was uneventful. Additionally, none of the febrile infants aged ≤60 days who were not tested for SARS-CoV-2 during the period of this case series were subsequently hospitalized in our center upon medical record review.

Discussion

In our study of 7 febrile infants aged ≤60 days with confirmed SARS-CoV-2 infection, none had severe outcomes. Our result, while based on small numbers, suggests that infants with SARS-CoV-2 generally have mild presentations, similar to typical viral illness with other coronaviruses.[3] This benign clinical course was also observed for the two infants in our study with underlying medical illnesses. As in prior studies of febrile infants, bacterial co-infections, specifically UTIs in our sample, were also concomitantly diagnosed in infants with positive viral respiratory specimen tests (in this case, SARS-CoV-2). In these infants with co-infection, it is unclear if the source of the fever was due to the UTI, with SARS-CoV-2 asymptomatic carriage.

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It is difficult to directly compare our results to prior literature as specific data on the clinical course of SARS-CoV-2 in young infants is lacking. Most case series have either combined the results of all infants under one year of age[1,2] or excluded infants altogether.[6] In three case reports that included infants under 60 days of age (one infant in each study), only one had fever.[4,5,9] In one report, a 55-day-old afebrile infant was described as having multi-organ damage, though this damage was seemingly limited to mild elevations in transaminases and troponin, and no severe outcomes as defined in this case series were reported.[5] The other two infants had benign clinical courses.

Our study had limitations. First, we present a small sample from a single institution, which limits the precision and generalizability of our findings. Second, we are unable to ensure completeness and accuracy of clinical and outcome data for infants identified retrospectively. Third, at our institution, SARS-CoV-2 testing was reserved for children requiring hospitalization; as such, some febrile infants did not undergo testing. Fourth, while data from China suggest that 44-85% of children with COVID-19 develop fever at some point during their illness,[2,4,6] it is unclear what proportion of infants ≤60 days develop fever, and we did not enroll afebrile infants. Additionally, we did not have information regarding maternal SARS-CoV-2 status at the time of delivery as widespread screening was not yet being performed at our institution. As such, we cannot comment on the possibility of vertical transmission or infection through early post-natal contact. Finally, we were unable to complete comprehensive respiratory pathogen panel testing due to a supply shortage; thus, we are unable to comment on the prevalence or impact of viral co-infections.

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References

1. Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics*. March 2020.

2. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. *N Engl J Med*. March 2020.

3. Petra Z, Nigel C. Coronavirus infections in children including COVID-19. *Pediatr Infect Dis J*. March 2020.

4. Wei M, Yuan J, Liu Y, et al. Novel coronavirus infection in hospitalized infants under 1 year of age in China. *JAMA*. February 2020.

5. Cui Y, Tian M, Huang D, et al. A 55-day-old female infant infected with COVID 19: presenting with pneumonia, liver injury, and heart damage. *J Infect Dis*. March 2020.

6. Cai J, Xu J, Lin D, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis*. February 2020.

7. Xie Z. Pay attention to SARS-CoV-2 infection in children. *Pediatr Investig*. 2020;4(1):1-4.

8. Aronson PL, Thurm C, Alpern ER, et al. Variation in care of the febrile young infant <90 days in US pediatric emergency departments. *Pediatrics*. 2014;134(4):667-677.

9. Robbins E, Ilahi Z, Roth P. Febrile Infant: COVID-19 in addition to the usual suspects. *Pediatr Infect Dis J*. April 2020.

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Table 1. Characteristics on presentation of febrile infants with SARS-CoV-2 (N=7)

	All Patients[a]	Patient[b]						
Demographic	No. (%)	1P	2P	3P	4P	5P	6R	7R
Age, median (days)[c]	39 (16, 50)	11	39	56	48	50	16	16
Male	6 (86)	Yes	No	Yes	Yes	Yes	Yes	Yes
Chronic medical illness[d]	2 (29)	No	No	Yes	No	Yes	No	No
Presenting symptoms								
Highest temperature (Celsius)[e]	38.7 (38.3, 38.9)	38.0	38.4	38.9	38.3	38.3	38.6	38.9
Cough	2 (29)	Yes	No	No	Yes	No	No	No
Rhinorrhea	0 (0)	No	No	No	No	No	No	No
Nasal congestion	1 (14)	No	No	No	Yes	No	No	No
Difficulty breathing	1 (14)	No	No	No	Yes	No	No	No
Cyanosis	0 (0)	No	No	No	No	No	Unknown	Unknown
Apnea	0 (0)	No	No	No	No	No	Unknown	Unknown
New feeding difficulties	1 (14)	No	No	No	Yes	No	No	No
Vomiting	1 (14)	No	No	No	Yes	No	No	No
Diarrhea	0 (0)	No	No	No	No	No	No	No
Abnormal activity level	3 (43)	No	No	No	Yes	Yes	No	Yes
Decreased urine output	0 (0)	No	No	No	No	No	No	No
Conjunctivitis	0 (0)	No	No	No	No	No	Unknown	Unknown
Initial emergency department examination								
Ill-appearing	0 (0)	No	No	No	No	No	No	No
In respiratory distress	0 (0)	No	No	No	No	No	No	No
Dehydrated	0 (0)	No	No	No	No	No	No	No

[a] Denotes number (%) except where noted otherwise.
[b] Infants enrolled prospectively are denoted with letter P, while infants identified retrospectively are denoted with letter R.
[c] Age shown in days for individual infants and as median age in days with interquartile range for infants in total.
[d] Infant 3P had a complex congenital heart disease, while infant 5P had a syndrome consisting of imperforate anus, inguinal hernia, Meckel's diverticulum, sacral hypoplasia, spinal dysraphism, tethered spinal cord, and multicystic dysplastic kidney.
[e] Temperature measured at home or in the emergency department. For infants in total, median with interquartile range provided.

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Table 2. Clinical management, testing results, and outcomes for infants with SARS-CoV-2 (N=7)

	All Patients[a]	Patient[b]						
Diagnostic testing[c]		1P	2P	3P	4P	5P	6R	7R
Chest radiograph obtained	4/7 (57)	No	No	Yes	Yes	Yes	Yes	No
New abnormal findings	0/4 (0)	N/A	N/A	No	No	No	No	N/A
Serum								
WBC count (x10^3 cells /μL)	7.0 (4.3, 8.9)	9.3	4.3	7.0	3.9	6.6	8.0	8.9
Lymphocyte %	40.0 (28.6, 56.0)	56.0	52.8	28.6	63.0	17.9	32.0	40.0
Neutrophil %	30.0 (20.6, 51.0)	21.0	20.6	40.3	19.0	75.9	51.0	30.0
Absolute neutrophil count (x10^3/μL)	2.66 (0.87, 4.07)	1.94	0.87	2.81	0.86	5.02	4.07	2.66
C-reactive protein (mg/L)	1.2 (0.8, 3.6)	1.2	0.4	3.6	3.8	0.9	0.8	2.6
Procalcitonin (ng/mL)	0.15 (0.12, 4.91)	N/A	0.14	0.10	N/A	9.30	0.15	0.51
Blood culture positive[d]	0/7 (0)	No	No	No	No	No	No	No
Urine culture positive[e]	2/7 (29)	No	No	No	No	Yes	No	Yes
Cerebrospinal fluid								
Meningitis / encephalitis panel positive[f]	0/4 (0)	No	No	N/A	N/A	N/A	No	No
Culture positive[g]	0/5 (0)	No	No	N/A	No	N/A	No	No
Emergency department disposition								
Admitted	6/7 (86)	Yes	Yes	No	Yes	Yes	Yes	Yes
Length of hospitalization (days)	2.0 (1.0, 2.0)	1	1	N/A	2	2	2	2
Severe outcomes[h]	0/7 (0)	No	No	No	No	No	No	No

[a] Denotes number over total tested (%) for categorical variables and median (interquartile range) for continuous variables.
[b] Infants enrolled prospectively are denoted with letter P, while infants identified retrospectively are denoted with letter R.
[c] N/A: results of tests not obtained or not available
[d] Positive blood culture defined as isolation of a bacterial pathogen from the blood culture

[e] Positive urine culture defined as the growth of a single uropathogen at ≥100,000 colony forming units per mL from a catheterized specimen.

[f] Meningitis / encephalitis PCR panel assesses for presence of *Escherichia coli K1, Haemophilus influenzae, Listeria meningitidis, Streptococcus agalactiae, Cryptococcus neoformans / gattii,* enterovirus, human herpes virus 6, herpes simplex virus (1 and 2), human parechovirus, and varicella-zoster virus.

[g] Positive cerebrospinal fluid culture defined as the isolation of a bacterial pathogen from the cerebrospinal fluid culture

[h] Severe outcomes defined as 1) acute respiratory distress syndrome as documented by the intensive care unit physician, 2) respiratory failure, defined as requiring mechanical ventilation, 3) presence of sepsis or shock, as specifically identified in the medical record documentation, 4) requirement for intensive care unit level of care, or 5) death.

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Pediatrics originally published online June 11, 2020;

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