Novel Coronavirus Infection in Febrile Infants Aged 60 Days and Younger

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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 severe acute respiratory syndrome coronavirus 2 infection. No infant had severe outcomes, including the need for mechanical ventilation or ICU level of care. Two infants had concurrent urinary tract infections, which were treated with antibiotics. Although a small sample, our data suggest that febrile infants with severe acute respiratory syndrome coronavirus 2 infection often have mild illness.

The rapid spread and severity of the novel severe acute respiratory syndrome coronavirus 2 (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 <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 because 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, is 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 are focused on febrile infants aged ≤60 days with SARS-CoV-2 infection. As a tertiary pediatric hospital in the epicenter of the coronavirus disease 2019 (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 hope this case series provides insights of clinical use during the ongoing outbreak.

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 a documented temperature ≥38.0°C at home or in the emergency department (ED) within the previous 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 Diagnostics, Indianapolis, IN) performed regardless of symptoms or exposure.

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Drs McLaren and Lubell conceptualized and designed the study, designed the data collection instruments, coordinated and supervised data collection, and conducted the analysis; Dr Dayan conceptualized and designed the study, coordinated and supervised data collection, and conducted the analysis; Dr Fenster coordinated and supervised data collection; Ms Bugaighis, Ms Gonzalez, Ms Ochs, and Mr Vindas performed data collection; and all authors reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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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 (eg, study team was 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 1 of our 6 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 a requirement for verbal consent for prospectively enrolled infants and 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, 1 of 2 experienced physician investigators (S.M. and T.L.) 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 determine the level of hydration, clinical appearance, and respiratory status (keywords available on request).

We assessed the 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 requirements 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 ICU 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 ICU level of care, and (5) death. During the 7-day follow-up, we inquired about any unscheduled visits to a medical provider, rehospitalization, and ICU admission.

TABLE 1 Characteristics on Presentation of Febrile Infants With SARS-CoV-2 (N = 7)

	All Patients[a]	Patient[b]						
		1P	2P	3P	4P	5P	6R	7R
Demographic								
Age, d[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, °C[c,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 ED 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] Data are expressed as n (%) except where noted otherwise.

[b] Infants enrolled prospectively are denoted with the letter P, whereas infants identified retrospectively are denoted with the letter R.

[c] Denotes median (interquartile range) for infants in total.

[d] Infant 3P had a complex congenital heart disease, whereas infant 5P had a syndrome consisting of imperforate anus, inguinal hernia, Meckel diverticulum, sacral hypoplasia, spinal dysraphism, tethered spinal cord syndrome, and a multicystic dysplastic kidney.

[e] Temperature was measured at home or in the ED.

RESULTS

Twenty infants were potentially eligible on the basis of age and presence of fever during the screening period; 7 (35%) and 13 (65%) were 0-to-28 and 29-to-60 days of age, respectively. Of these 20 infants, 13 had a SARS-CoV-2 test completed, including 6 of 7 (86%) infants aged 0-to-28 days old and 7 of 13 (54%) infants aged 29-to-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, whereas 3 were transferred from our affiliate hospitals. Five of the 7 infants with SARS-CoV-2 were enrolled prospectively, either in the ED or after 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 presenting symptom for 3 (43%) infants, and no infant was ill appearing or in respiratory distress at the time of presentation.

The diagnostic testing results and outcomes of the study infants are detailed in Table 2. No infant had

TABLE 2 Clinical Management, Testing Results, and Outcomes for Infants With SARS-CoV-2 (N = 7)

	All Patients[a]	Patient[b]						
		1P	2P	3P	4P	5P	6R	7R
Diagnostic testing								
Chest radiograph obtained	4 of 7 (57)	No	No	Yes	Yes	Yes	Yes	No
New abnormal findings	0 of 4 (0)	N/A	N/A	No	No	No	No	N/A
Serum								
WBC count, $\times 10^3/\mu L$	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, $\times 10^3/\mu L$	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
Positive blood culture result[c]	0 of 7 (0)	No	No	No	No	No	No	No
Positive urine culture result[d]	2 of 7 (29)	No	No	No	No	Yes	No	Yes
Cerebrospinal fluid								
Positive meningitis/encephalitis panel result[e]	0 of 4 (0)	No	No	N/A	N/A	N/A	No	No
Positive culture result[f]	0 of 5 (0)	No	No	N/A	No	N/A	No	No
ED disposition, admitted	6 of 7 (86)	Yes	Yes	No	Yes	Yes	Yes	Yes
Length of hospitalization, d	2.0 (1.0–2.0)	1	1	N/A	2	2	2	2
Severe outcomes[g]	0 of 7 (0)	No	No	No	No	No	No	No

N/A, not applicable; WBC, white blood cell.

[a] Data are expressed as n of N (%) for categorical variables and median (interquartile range) for continuous variables.

[b] Infants enrolled prospectively are denoted with the letter P, whereas infants identified retrospectively are denoted with the letter R.

[c] Positive blood culture result was defined as isolation of a bacterial pathogen from the blood culture.

[d] Positive urine culture result was defined as the growth of a single uropathogen at ≥100 000 colony forming units per milliliter from a catheterized specimen.

[e] Meningitis and encephalitis polymerase chain reaction panel was used to assess for the presence of *Escherichia coli* K1, *Hemophilus influenzae*, *Listeria* meningitis, *Streptococcus agalactiae*, *Cryptococcus gattii*, *Cryptococcus neoformans*, enterovirus, human herpesvirus 6, herpes simplex virus (1 and 2), human parechovirus, and varicella-zoster virus.

[f] Positive cerebrospinal fluid culture was defined as the isolation of a bacterial pathogen from the cerebrospinal fluid culture.

[g] Severe outcomes were defined as (1) acute respiratory distress syndrome, as documented by the ICU 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 ICU level of care; or (5) death.

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, the median length of hospitalization was 2 days (interquartile range 1–2 days). None of the 7 infants required supplemental oxygen or noninvasive positive pressure ventilation during their hospital course. On 7-day follow-up, none had been rehospitalized. One infant was known to be rehospitalized at 14 days for fever; the SARS-CoV-2 test result 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 at our center.

DISCUSSION

In our study of 7 febrile infants aged ≤60 days with a confirmed SARS-CoV-2 infection, none had severe outcomes. Our result, although 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 2 infants in our study with underlying medical illnesses. As in previous studies of febrile infants, bacterial coinfections, specifically UTIs in our sample, were also concomitantly diagnosed in infants with positive viral respiratory specimen test results (in this case, SARS-CoV-2). In these infants with coinfection, it is unclear if the source of the fever was due to the UTI, with asymptomatic carriage of SARS-CoV-2.

It is difficult to directly compare our results to previous literature because specific data on the clinical course of SARS-CoV-2 in young infants are lacking. Most case series have either combined the results of all infants <1 year of age[1,2] or excluded infants altogether.[6] In 3 case reports that included infants <60 days of age (1 infant in each study), only 1 infant had a fever.[4,5,9] In one report, a 55-day-old afebrile infant was described as having multiorgan damage, although 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 2 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 the completeness and accuracy of the 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, although data from China suggest that 44% to 85% of children with COVID-19 develop a 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 because 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 postnatal contact. Finally, we were unable to complete comprehensive respiratory pathogen panel testing because of a supply shortage; thus, we are unable to comment on the prevalence or impact of viral coinfections.

ABBREVIATIONS

COVID-19: coronavirus disease 2019
ED: emergency department
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
UTI: urinary tract infection

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