CASE REPORT

Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Febrile Neonates

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Most severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in pediatric patients are mild or asymptomatic. However, infants have emerged at higher risk of hospitalization and severe outcomes in pediatric coronavirus disease 2019 (COVID-19). We report a case series of 4 full-term neonates hospitalized with fever and found to have SARS-CoV-2 infection with a spectrum of illness severities. Two neonates required admission to the intensive care unit for respiratory insufficiency and end organ involvement. Half of the patients were found to have a coinfection. One neonate received antiviral therapy with remdesivir and is, to our knowledge, the youngest patient to receive this drug for COVID-19. All neonates had favorable outcomes.

Key words. COVID-19; infant; neonatal sepsis; remdesivir; SARS-CoV-2.

The majority of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in children are mild or asymptomatic. However, infants have been observed to have a higher risk of hospitalization and severe outcomes in pediatric coronavirus disease 2019 (COVID-19). Herein we present a case series of 4 full-term neonates who were hospitalized with fever and found to be infected with SARS-CoV-2.

CASE 1

A 19-day-old full-term previously healthy male infant presented with 1 day of fever and fussiness. He was born via normal spontaneous vaginal delivery at 41 weeks' gestation following an uncomplicated pregnancy. His mother had a history of genital infection with herpes simplex virus (HSV) for which she received prophylactic valacyclovir throughout pregnancy. He resides with his mother, father, 4 siblings, and maternal grandmother and her partner. The latter 2 had recently been diagnosed with COVID-19 1 week prior to his presentation, and the grandmother required hospitalization. The mother also reported upper respiratory symptoms concurrently but had not been tested. Upon presentation, his vital signs were notable for lack of fever (37.4°C, rectal), with normal heart rate (134 beats per minute [bpm]), respiratory rate (30 breaths per minute), blood pressure (95/39 mm Hg), and oxygen saturation (97% in room air). His physical examination was normal, notable for an open, soft, and flat anterior fontanelle, good tone, and nonlabored breathing with lungs clear to auscultation bilaterally. He underwent a full neonatal sepsis evaluation, with laboratory evaluation significant for elevated procalcitonin but otherwise unremarkable (Table 1). SARS-CoV-2 by reverse-transcription polymerase chain reaction (RT-PCR) from a nasopharyngeal (NP) swab was positive. A chest radiograph was normal. He was initiated on empiric therapy with ampicillin, gentamicin, and acyclovir.

Empiric antimicrobials were discontinued when blood, urine, and cerebrospinal fluid (CSF) cultures and HSV PCR from CSF resulted negative at 48 hours. However, just prior to discharge the patient developed respiratory distress with tachypnea, suprasternal and subcostal retractions, and tracheal tugging. He was not hypoxemic but was placed on 0.25 L supplemental oxygen via nasal cannula for comfort. A chest radiograph showed new increased bilateral opacities without focal consolidation and a prominent cardiac silhouette. An electrocardiogram (EGG) was obtained and demonstrated normal sinus rhythm with a right axis deviation. Laboratory evaluation was significant for an elevated high-sensitivity troponin T (58 ng/L [ref: 0–14 ng/L]) and N-terminal portion of pro–brain natriuretic peptide (BNP) (1260 pg/mL [ref: 0–450 pg/mL]). Due to concern for evolving myocardial injury, he was transferred to our hospital for further management on inpatient day 3. On arrival, he was admitted to the step-down intensive care unit (ICU) where he was noted to be afebrile with normal vital signs including oxygen saturation of 98% on 0.25 L via nasal cannula. Physical examination was significant for intermittent mottling while crying, but overall well appearance with good distal

Table 1. Patient Characteristics and Clinical Information

Characteristic	Patient 1	2	3	4
Demographics				
Age, day of life	19 days	24 days	21 days	21 days
Gestational age, wk	41 + 3/7	39	39 + 1/7	41 + 0/7
Sex	Male	Male	Male	Male
Presentation				
Presenting symptoms	Fever	Fever, lethargy, tachycardia	Fussiness, decreased PO intake	Fever, cough, congestion
Duration since symptom onset, days	1	2	4	2
Sick contacts within the home	Maternal grandmother with confirmed COVID-19	Father with fever, myalgias (untested)	Maternal aunt with confirmed COVID-19	2-year-old sibling with URI symptoms (untested)
Laboratory				
Viral PCR (NP)	SARS-CoV-2	SARS-CoV-2, hMPV	SARS-CoV-2	SARS-CoV-2
Blood culture	Negative	Negative	Negative	Negative
Urine culture	Negative	Negative	50 000–100 000 CFUs Escherichia coli	Negative
CSF culture	Negative	Negative	Negative	Negative
Urinalysis	Normal	Normal	Large leukocyte, 6–10 WBCs	Normal
WBC (ref: 8.9–16.7 ×10^3 cells/µL)	9.7	4.63	6	7.82
ALC (ref: 1.68–5.23 ×10^3 cells/µL)	4.11	1.32	3.02	4.14
Hemoglobin, g/dL	15	16	10.4	12.7
Platelets (ref: 214–503 ×10^3 cells/µL)	499	271	279	271
C-reactive protein (ref: <0.5 mg/dL)	0.07	0.5	–	–
Procalcitonin (ref: <0.09 ng/mL)	0.18	0.15	0.06	0.16
AST (ref: 10–65 U/L)	47	74	–	–
ALT (ref: 3–54 U/L)	24	33	–	–
CSF WBC	2	2	5	6
CSF RBC	1100	<1000	24	<1000
CSF protein (ref: 15–45 mg/dL)	37	41	101	30
CSF glucose (ref: 60–80 mg/dL)	52	54	48	45
High-sensitivity troponin T (ref: 0–14 ng/L)	58	–	–	–
Troponin T (ref: <0.01 ng/mL)	0.04	0.05	–	–
NT-proBNP (ref: 0–450 pg/mL)	1260	–	–	–
BNP (ref: 0–100 pg/mL)	105	359	–	–
Ferritin (ref: 10–450 ng/mL)	345	128	–	–
D-dimer (ref: ≤0.5 µg/mL)	0.99	1.03	–	–
Diagnostics				
Chest radiograph	Initially normal, later increased bilateral perihilar opacities with prominent cardiac silhouette	Perihilar opacification	–	–
ECG	Normal sinus rhythm, right axis deviation	Sinus tachycardia	–	–
Echocardiogram	Mild global systolic dysfunction, EF 48%	Normal, EF 58%	–	–

Table 1. Continued

Characteristic	Patient 1	2	3	4
Maximum respiratory support	Nasal cannula (1.5 L)	Nasal cannula (1 L)	Room air	Room air
Management				
Antibiotics	Ampicillin + gentamicin × 48 hours	Ampicillin + ceftazidime × 48 hours, amoxicillin-clavulanate × 7 days	Ceftriaxone, cephalexin × 10 days	Ceftriaxone × 48 hours
Antivirals	Acyclovir × 2 doses; Remdesivir × 7 days	None	None	None
Anti-inflammatory	None	None	None	None
Anticoagulation	Enoxaparin + Aspirin	None	None	None
Length of stay, calendar days	9	3 + 2	3 + 1	2

Abbreviations: ALC, absolute leukocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CFU, colony-forming units; COVID-19, coronavirus disease 2019; CSF, cerebrospinal fluid; ECG, electrocardiogram; EF, ejection fraction; hMPV, human metapneumovirus; NP, nasopharyngeal; NT, N-terminal; PCR, polymerase chain reaction; PO, per oral; RBC, red blood cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; URI, upper respiratory infection; WBC, white blood cell.

perfusion, strong pulses, and a normal cardiac examination. An echocardiogram exhibited normal anatomy with mildly depressed left ventricular function, estimating an ejection fraction of 49% (z score −2.8). Laboratory evaluation was delayed secondary to persistent clot formation of all peripheral blood draws, requiring placement of a peripherally inserted central catheter.

Laboratory studies ultimately demonstrated down-trending troponin T (0.04 ng/mL) and BNP (105 pg/mL), elevated D-dimer (0.8 µg/mL), with normal prothrombin time, partial thromboplastin time, and fibrinogen. RT-PCR from an NP swab was negative for influenza A/B, respiratory syncytial virus, rhinovirus, adenovirus, human metapneumovirus, and parainfluenza viruses 1–4. Multidisciplinary evaluation commenced and he was felt not to meet criteria for multisystem inflammatory syndrome in children potentially associated with COVID-19 [1]. Due to the concern for end-organ involvement with possibly evolving acute myocardial injury as well as a supplemental oxygen requirement, the patient was initiated on therapy with remdesivir on inpatient day 4 via an expanded-access program from the manufacturer after approval from the US Food and Drug Administration and local institutional review board, with informed consent. He received an initial loading dose of 5 mg/kg via intravenous administration, followed by 2.5 mg/kg daily.

Inflammatory and coagulation studies were initially trended daily, and on hospital day 5 D-dimer continued to rise (0.99 µg/mL) prompting initiation of enoxaparin (0.8 mg/kg daily) for thromboprophylaxis. Further evaluation by thromboelastography with platelet mapping was consistent with hypercoagulability, with an elevated clot strength (74.5 mm [ref: 50–70 mm]) and G-parameter (14.6 kg/sec [ref: <11 kg/sec]), for which he was started on low-dose aspirin (20.25 mg daily) on hospital day 6. He subsequently tolerated discontinuation of supplemental oxygen. Two follow-up echocardiograms remained stable, with unchanged mildly depressed left ventricular systolic function. Cardiac markers normalized, and D-dimer declined although remained elevated. The patient received a total of 7 doses of remdesivir, which he tolerated well, with stable creatinine and liver function tests throughout therapy. Enoxaparin was discontinued on the final day of hospitalization, and he was discharged home on inpatient day 9 to continue daily low-dose aspirin.

At 3 weeks postdischarge, an echocardiogram demonstrated normal systolic function and ejection fraction (z score −1.4). Laboratory evaluation was normal aside from persistently elevated D-dimer (0.6 µg/mL) and clot strength (80 mm). He remains on aspirin with close monitoring. Notably all 3 of the patient's siblings have tested positive for SARS-CoV-2 infection since his hospitalization.

CASE 2

A 24-day-old full-term male infant presented with fever, lethargy, and decreased oral intake. He was born via scheduled

repeat cesarean delivery and briefly required phototherapy for neonatal hyperbilirubinemia following birth, but was otherwise healthy. He lives with both parents. Several days before his presentation, his father developed fever, muscle aches, and malaise, but had not undergone SARS-CoV-2 testing. Upon developing symptoms, the infant presented to the emergency department (ED) where he was found to be lethargic, febrile (temperature 38.3°C), and tachycardic (heart rate 180–200 bpm) with normal respiratory rate and oxygen saturation. A full sepsis evaluation was initiated, with laboratory evaluation significant for mild leukopenia and lymphopenia, elevated procalcitonin, and unconjugated hyperbilirubinemia (total bilirubin 8.6 mg/dL), but otherwise unremarkable (Table 1). NP respiratory viral PCR testing demonstrated coinfection with human metapneumovirus and SARS-CoV-2. Due to tachycardia and signs of dehydration, he received intravenous fluid resuscitation and was admitted to a general pediatrics floor on empiric therapy with ampicillin and ceftazidime.

Shortly after admission, the patient demonstrated persistent tachycardia despite fluid resuscitation, as well as desaturations requiring initiation of oxygen therapy delivered by nasal cannula. A chest radiograph showed perihilar opacification but no focal consolidations. An electrocardiogram showed sinus tachycardia with diminished left ventricular forces. Laboratory testing demonstrated an elevated BNP and D-dimer, with normal troponin T (Table 1). Due to clinical concern for evolving myocarditis, he was transferred to the ICU for close monitoring. An echocardiogram was normal, with no evidence of ventricular dysfunction. He remained on a maximum supplemental oxygen support of 1L via nasal cannula during his ICU stay. Notably, he remained febrile through the first 24 hours of his hospitalization. Immunophenotyping, obtained per our hospital's protocol for patients admitted to an ICU with SARS-CoV-2 infection, demonstrated slightly elevated interleukin 10 (20 pg/mL; upper limit of normal [ULN], 18 pg/mL) but an otherwise normal interleukin profile and normal T-cell subsets, with mildly decreased thymic immigrants (50.7%). Immunoglobulin analysis showed borderline low immunoglobulin G (599 mg/dL; ULN, 700 mg/dL). After 24 hours in the ICU, tachycardia had improved and BNP decreased, and he was ultimately discharged home on hospital day 3.

Approximately 4 hours after discharge, he became febrile and drowsy at home. He was brought back to the ED where he was again febrile (temperature 38.9°C), but the remainder of his vital signs were normal. During observation in the ED, he experienced sustained oxygen desaturations to as low as 88% in room air. Repeat laboratory testing was obtained and showed normal white blood cell count (9.07 K cells/μL) with elevated lymphocyte count (7.26 K cells/μL) but marked neutropenia (0.18 K cells/μL), elevated procalcitonin (0.18 ng/mL), and ferritin (487.7 ng/mL). A repeated chest radiograph was remarkable for persistent mild bilateral perihilar peribronchial thickening and increased asymmetric bibasilar opacities. He was restarted on 1 L of supplemental oxygen by nasal cannula and readmitted to the general pediatrics floor. Cefepime was initiated due to concern for potential bacterial superinfection of a viral pneumonia. His drowsiness and oxygenation improved over 24 hours of hospitalization, and he remained afebrile following admission. Antibiotics were transitioned to amoxicillin-clavulanate, with a plan to complete a 7-day course of antibiotics for pneumonia. He was discharged home on hospital day 2. Blood, urine, and CSF cultures remained negative from both his first and second hospitalizations. Notably, his mother began to experience fever and respiratory symptoms while with him in the hospital; she was advised to obtain SARS-CoV-2 testing in coordination with her primary care provider.

CASE 3

A 21-day-old full-term previously healthy male infant presented with fussiness and decreased oral intake for 4 days. He resides in a multigenerational home that includes a maternal aunt who was diagnosed with SARS-CoV-2 infection 1 week prior to his presentation. In the ED, he was febrile (temperature 38.3°C) and tachycardic (heart rate 172 bpm) with otherwise normal vital signs and physical examination. He underwent a full neonatal sepsis evaluation, significant for a urinalysis with 6 to 10 white blood cells and positive leukocyte esterase as well as positive SARS-CoV-2 RT-PCR (Table 1). In the absence of respiratory symptoms, chest imaging was not obtained. He was initiated on empiric therapy with ceftriaxone and admitted to our hospital.

The patient defervesced, remained hemodynamically stable, and did not require supplemental oxygen. He received intravenous fluids for 1 day due to decreased oral intake. Blood and CSF cultures remained negative. Urine culture ultimately grew 50 000–100 000 colony-forming units of *Escherichia coli*, and on hospital day 3 he was discharged home to complete a 10-day course of cephalexin. Over a period of 4 weeks postdischarge, he returned to the ED on 5 occasions for recurrent fever and was readmitted once for observation following a brief resolved unexplained event. Notably, SARS-CoV-2 PCR from an NP swab remained positive when retested 20 days after his initial test.

CASE 4

A 21-day-old full-term male infant presented with fever, cough, and congestion for 2 days. He was born via normal spontaneous vaginal delivery to a Group B *Streptococcus*–positive mother who received inadequate peripartum antibiotic prophylaxis. He lives with his parents and sibling who reportedly had recent upper respiratory symptoms, but did not seek medical care nor SARS-CoV-2 testing. Upon presentation he was found to be febrile

(rectal temperature 38°C) and mildly tachycardic (heart rate 162 bpm), with otherwise normal vital signs and physical examination. He underwent a complete neonatal sepsis evaluation, with laboratory results significant for elevated procalcitonin but otherwise unremarkable (Table 1). SARS-CoV-2 PCR from an NP swab showed positive results. He was initiated on empiric therapy with ceftriaxone and admitted to our hospital. Throughout his 2-day hospitalization he remained afebrile without respiratory distress and did not require supplemental oxygen. Ceftriaxone was discontinued when blood, urine, and CSF cultures were negative at 48 hours, and he was discharged home.

DISCUSSION

These cases illustrate a common pediatric condition—neonatal fever—reevaluated within the paradigm of the COVID-19 pandemic. SARS-CoV-2 has emerged as a significant cause of morbidity and mortality in adults, while most infections in pediatric patients are mild or asymptomatic [2–7]. Infants are noted to be a higher-risk group within pediatric COVID-19 [2, 5, 7]. Yet, to date few neonatal cases have been described [8–12]. Similarly, at present there is very little known about the outcomes of neonates born to mothers with COVID-19 or those infected during this vulnerable neonatal period. In this report, we present 4 febrile neonates hospitalized with SARS-CoV-2 infection with favorable outcomes.

Our patients were admitted between April 17 and May 6, 2020, a period that aligned with peak incidence of SARS-CoV-2 infection in our state. It is likely that our patients were infected postnatally given their ages and the presence of symptomatic individuals in their households. Indeed, the incidence of transmission through familial exposure in pediatric COVID-19 infections has been estimated between 45% and 91% [3, 5, 7]. However, we cannot definitively exclude perinatal transmission from asymptomatic mothers since they were not tested at the time of delivery.

Since all febrile neonates require hospitalization for evaluation of serious bacterial infections, even mild symptoms carry significant repercussions. Half of the neonates in our series were found to have a coinfection, possibly providing an alternative explanation for fever: patient 2 had another respiratory viral infection (human metapneumovirus) and patient 3 had a urinary tract infection. Notably, both of these patients experienced relatively protracted illness courses, including readmission for recurrent fever following initial hospitalization. One patient demonstrated prolonged viral shedding. It remains unclear whether SARS-CoV-2 was responsible for recurrent symptoms. Historical studies have shown that the occurrence of serious bacterial infections is lower in infants with an identified viral infection than in those without a viral infection, but not low enough to obviate the need for sepsis evaluation [13, 14]. Equally, as our series suggests, the identification of

SARS-CoV-2 infection in an infant should not preclude evaluation for invasive bacterial infection.

Myocardial involvement in adults with COVID-19 has been shown to be associated with worse outcomes [15]. Myocardial involvement during acute infection appears to be rare in children [16]. Patient 1 developed elevated cardiac biomarkers, elevated D-dimer, elevated clot strength, and mild systolic dysfunction, initially concerning for early viral myocarditis. Antiviral therapy with remdesivir was promptly initiated and he fortunately did not progress to acute myocarditis. It is unknown whether lack of progression was secondary to the antiviral activity of remdesivir or the natural course of his systemic viral infection. Direct SARS-CoV-2 myocardial injury was felt to be unlikely. A previously suggested pulmonary immunovascular coagulopathy model [17] provides another possible explanation of his abnormal cardiac laboratory and imaging findings. In this model, circulating D-dimer reflects pulmonary microvascular thrombosis, and elevated cardiac enzymes reflect ventricular stress induced by pulmonary hypertension.

Epidemiologic studies of COVID-19 in adults have highlighted the disproportionate effect on populations already at risk of health inequity [18, 19]. We note the presence of at least 2 significant socioeconomic risk factors in each of our patients, also noted by Mithal et al [12]. These include Latinx ethnicity, children of recent immigrants, housing and food insecurity, residence in multigenerational homes, and children of adolescent parents. In developing strategies to protect this vulnerable neonatal population, guidance and management must take into account the neonate as part of the larger family unit to address those risk factors that may make them more susceptible to infection and adverse outcomes.

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