Neonatal Fever in the COVID-19 Pandemic
Odds of a Serious Bacterial Infection

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OBJECTIVES: A sepsis workup is recommended in young infants 56 days or younger with fever to rule out a serious bacterial infection (SBI). Given the reduction in non–severe acute respiratory syndrome - coronavirus 2 viral infections observed in multiple studies during the coronavirus diseases 2019 (COVID-19) pandemic, we sought to determine if the reduction in viral infections led to a change in the incidence of SBI in this vulnerable patient population.

METHODS: We performed a multicenter, retrospective study of infants 56 days or younger presenting with fever to emergency departments of 6 community hospitals. We compared the incidence of SBIs, viral meningitis, and viral bronchiolitis during March 2020 to February 2021 (pandemic year) with the same calendar months in the 2 preceding years (prepandemic years).

RESULTS: From March 2018 to February 2021, 543 febrile infants presented to the emergency departments, 95 during the pandemic year (March 2020 to February 2021) compared with 231 and 217 in the prepandemic years (March 2018 to February 2019 and March 2019 to February 2020, respectively).

During the pandemic year, 28.4% of infants (27 of 95) were diagnosed with an SBI compared with 11.7% and 6.9% (P < 0.001) in the prepandemic years (27 of 231 and 15 of 217, respectively). Five patients were diagnosed with bacterial meningitis over the 3-year period, 4 of them during the pandemic year (4 of 95 [4.2%]). Positivity for viral cerebrospinal fluid polymerase chain reaction during the pandemic year was 6.4% (3 of 47) compared with 20.8% (25 of 120) and 20.4% (23 of 113) in prepandemic years (P = 0.070). During the pandemic year, 2.1% (2 of 95) febrile young infants were admitted with a comorbid diagnosis of bronchiolitis compared with 4.3% and 6.0% in the prepandemic years (P = 0.310).

CONCLUSIONS: The COVID-19 pandemic led to an increase in the incidence of SBIs in febrile infants 56 days or younger, likely a result of reduction in non–severe acute respiratory syndrome - coronavirus 2 viral infections. Greater vigilance is thus warranted in the evaluation of febrile infants during the COVID-19 pandemic.

KEY WORDS: infant, newborn, COVID-19, fever, bacterial infections

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METHODS

This was a retrospective, multicenter study involving all infants 56 days or younger presenting with fever to the EDs of 6 community hospitals located across 2 states in the Mid-Atlantic Region of the United States, all affiliated with the same academic children's hospital. The study was approved by all involved institutional review boards. Reporting of study design and results follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for observational research.

Fever was defined as a documented rectal temperature of ≥38.0°C either at home, at the primary care physician office, or in the ED. All sites follow a common clinical pathway for the evaluation and management of febrile infants younger than 56 days. Infants 28 days or younger and those 29 to 56 days old meeting...
The primary outcome was the presence of an SBI, which was defined as the growth of a true bacterial pathogen in blood, urine, or CSF. A UTI was defined as ≥50,000 colony-forming units (cfu)/mL or greater than 10,000 cfu/mL with a positive urinalysis. The urinalysis was considered positive if there were leukocyte esterase and/or nitrites, or greater than 10 white blood cells/high-power field in an uncentrifuged specimen. Investigators at each study site collected data from electronic medical records of infants seen from March 2018 to February 2021 and entered it into a REDCap database. Data collected included age, sex, race, ethnicity, and results of all laboratory tests pertaining to the infectious workup. We looked at the number of infants presenting across the periods and compared the incidence of SBI during March 2020 to February 2021 (pandemic year) with the previous 2 years between the same calendar months, March 2018 to February 2019 and March 2019 to February 2020 (pre-pandemic years 1 and 2, respectively). We also compared the incidence of viral meningitis and the proportion of patients with a comorbid diagnosis of viral bronchiolitis over the 3 years. Of the 6 participating centers, 4 centers performed a comprehensive meningitis pathogen PCR on all CSF studies. The other 2 centers assessed only enterovirus PCR on CSF samples.

Descriptive summaries of all demographic and clinical variables were tabulated, and to assess the association with the 3 years (March 2018 to February 2019, March 2019 to February 2020, and March 2020 to February 2021), a χ² statistic was calculated. Cases where expected cell counts for calculation of the χ² statistic were <5 are noted. For the primary outcome, SBI, risk differences, and ratios along with the 95% confidence intervals (CIs) were calculated as well as a Bonferroni corrected P value to account for the 3 yearly comparisons. We constructed a mixed effects logistic regression model to assess if the coefficients across the 3 years changed after accounting for the clustering within sites. P values of <0.05 were considered significant, and all analyses were conducted using Stata version 16.1 (College Station, TX).

### RESULTS

Between March 2018 and February 2021, 543 infants 56 days or younger were evaluated for fever across all sites. This included 95 infants in the pandemic year, which was 41% and 44% of the volume of the 2 prepandemic years (231 and 217 in 2018–2019 and 2019–2020), respectively. There were no significant differences in age, sex, race or ethnicity of the patients between the pandemic and prepandemic year cohorts (Table 1).

### TABLE 1. Demographics and Clinical Findings for Total Study Group and by Year

| Total | Prepandemic Year 1 | Prepandemic Year 2 | Pandemic Year |
|-------|--------------------|--------------------|---------------|
|       | March 2018–February 2021, % (n) | March 2018–February 2019, % (n) | March 2019–February 2020, % (n) | March 2020–February 2021, % (n) |
| n     | 543                | 42.5 (231)         | 40.0 (217)          | 17.5 (95)          |
| Age, d |                    |                    |                    |                 |
| 0–8   | 5.9 (32)           | 6.1 (14)           | 6.5 (14)           | 4.2 (4)           | 0.186 |
| 9–28  | 28.2 (153)         | 26.0 (60)          | 33.2 (72)          | 22.1 (21)         |
| 29–56 | 65.9 (358)         | 68.0 (157)         | 60.4 (131)         | 73.7 (70)         |
| Race  |                    |                    |                    |                 |
| White | 72.6 (394)         | 75.8 (175)         | 71.4 (155)         | 67.4 (64)         | 0.362 |
| Black | 11.6 (63)          | 9.1 (21)           | 13.4 (29)          | 13.7 (13)         |
| Asian | 5.9 (32)           | 6.1 (14)           | 9 (4.2)            | 9.5 (9)           |
| Other or unknown | 9.9 (54) | 9.1 (21) | 11.1 (24) | 9.5 (9) |
| Ethnicity |                    |                    |                    |                 |
| Non-Hispanic | 78.1 (424) | 76.2 (176) | 78.8 (171) | 81.1 (77) | 0.688 |
| Hispanic | 14.9 (81)         | 16.5 (38)          | 13.4 (29)          | 14.7 (14)         |
| Unknown | 7.0 (38)          | 7.4 (17)           | 7.8 (17)           | 4.2 (4)           |
| Sex    |                    |                    |                    |                 |
| Female | 44.0 (239)         | 45.5 (105)         | 43.8 (95)          | 41.1 (39)         | 0.764 |
| Male | 56.0 (304)         | 54.6 (126)         | 56.2 (122)         | 59.0 (56)         |
| SBI    | 12.7 (69)          | 11.7 (27)          | 6.9 (15)           | 28.4 (27)         | <0.001 |
| Bacteremia | 3.9 (21) | 2.2 (5) | 1.4 (3) | 13.7 (13) | <0.001 |
| UTI    | 10.7 (58)          | 11.3 (26)          | 6.5 (14)           | 19.0 (18)         | 0.004 |
| Bacterial meningitis | 0.9 (5) | 0.0 (0) | 0.5 (1) | 4.2 (4) | 0.001* |
| Viral CSF PCR viral meningitis† | 18.2 (51) | 20.8 (25) | 20.4 (23) | 6.4 (3) | 0.070 |
| Bronchiolitis | 4.6 (25) | 4.3 (10) | 6.0 (13) | 2.1 (2) | 0.310* |

*P value should be interpreted with caution due to low (<5) expected count values in cells.
†Restricted to 4 study sites where a full PCR panel is done.
There were 84 true positive bacterial cultures (blood, urine, or CSF) in 69 patients over the 3 years (blood only, 6; urine only, 46; CSF only, 2; blood and urine, 12; blood and CSF, 3). The proportion of patients with positive cultures was 28.4% (27 of 95 patients) in the pandemic year compared with 11.7% (27 of 231) and 6.9% (15 of 217) in the prepandemic years (P < 0.001; Table 1). The risk ratio for SBI (Fig. 1) for March 2018 to February 2019 (referred) compared with March 2020 to February 2021 was 2.43 (95% CI, 1.51–3.92; Bonferroni adjusted P = 0.001), and that for March 2019 to February 2020 (referred) compared with March 2020 to February 2021 was 4.11 (95% CI, 2.29–7.37; Bonferroni adjusted P < 0.001). Application of the mixed effects model to account for clustering within the 6 sites did not reveal significant variance at the site level. The incidence of bacteremia was 13.7% (13 of 95) during the pandemic year compared with 2.2% (5 of 231) and 1.4% (3 of 217) in the prepandemic years (March 2018 to February 2019 and March 2019 to February 2020, respectively; Tables 1, 2). The incidence of UTI during the pandemic year was 19.0% (18 of 95) compared with 11.3% and 6.5% in the prepandemic years (26 of 231 and 14 of 217; March 2018 to February 2019 and March 2019 to February 2020, respectively; Table 1). Five patients were diagnosed with bacterial meningitis over the 3-year period, of them during the pandemic year, a rate of 4.2% (4 of 95). A summary of the specific SBI and microbiological etiology by year can be found in Figure 2 and Table 3.

The rate of positivity for viral CSF PCR during the pandemic year was 6.4% (3 of 47) compared with 20.8% (25 of 120) and 20.4% (23 of 113) in the prepandemic years (March 2018 to February 2019 and March 2019 to February 2020, respectively; P = 0.070). The sites that did not have the ability to check for viral CSF PCR were excluded from this calculation. There was no statistical difference in the proportion of infants who underwent a lumbar puncture and CSF studies based on meeting criteria during the pandemic year 49.5% (47 of 95) in comparison with the 2 previous years when the proportions were 52.0% and 52.1% (120 of 231 and 113 of 217; March 2018 to February 2019 and March 2019 to February 2020, respectively; P = 0.904). Of the infants, 2.1% (2 of 95) were admitted with a comorbid diagnosis of bronchiolitis during the pandemic year compared with 4.3% and 6.0% in the prepandemic years (10 of 231 and 13 of 217; March 2018 to February 2019 and March 2019 to February 2020, respectively; P = 0.310). SARS-CoV-2 PCR test was positive in 21 of 95 patients (22.1%) during the pandemic year. The rate of SBI in the COVID-19 positive cohort was 9.5% (2 of 21 patients) compared with 33.8% (25 of 74) in the COVID-19 negative cohort during the same period, which is a risk ratio of 0.28 (95% CI, 0.07–1.09) with COVID-19 positive as the referent group (P = 0.030). One COVID-positive patient had Enterococcus faecalis bacteremia, and the other had Escherichia coli UTI. There were no missed cases of SBI among low-risk infants discharged from the ED, as ascertained by lack of revisits.

**DISCUSSION**

In response to the COVID-19 pandemic, multiple layers of community mitigation strategies, including stay-at-home orders and school closures, took effect in the United States, which changed the landscape of acute pediatric emergency care abruptly. As reported elsewhere,4,6 our pediatric ED volumes also declined steeply. Mirroring the overall decline, we found a reduction in the number of febrile infants presenting to the EDs of 6 academically affiliated community hospitals during the COVID-19 pandemic year compared with the same calendar months in the 2 previous years. In addition, we found a significantly higher incidence of true SBIs during the pandemic compared with the 2 prepandemic years during the same 12 calendar months, with a simultaneous reduction of the number of viral CSF PCR positivity and viral bronchiolitis.

Similar to our findings, Wilder et al10 reported a decline in pediatric hospitalizations for acute medical conditions associated with viral infections (asthma, bronchiolitis, and pneumonia) but no decline in admission for conditions not associated with viral infections (cellulitis, gastroesophageal reflux disease, and UTI). In a large multicenter study of pediatric ED visits and hospital admissions in France, Angoulvant et al11 observed a >70% decline in pediatric cases of viral infections but no decline in UTIs during the pandemic. Other studies have also reported a marked reduction in respiratory illnesses12,14 during the pandemic but no significant decline in rates for nonrespiratory illnesses like UTIs and skin/soft tissue infections.13,14 They hypothesized that social distancing measures decreased the transmission of viral illnesses but had no impact on the rate of UTIs and skin/soft tissue infections. Our findings strongly support this previous hypothesis, and along with a decline in non-COVID viral infections, the proportion of SBI seems to have increased compared with the prepandemic years. A few single-center studies have recently reported low rates of non–SARS-CoV-2 viral infections among young febrile infants during the pandemic.7,15 Our multicenter study also found similar lower rates of viral infections during the pandemic.

Serious bacterial infection rates are lower in febrile infants with respiratory syncytial virus compared with their negative counterparts.16 A single-site retrospective cohort study from March to November 2020 tested a hypothesis of reduced SBI confection with COVID-19 and demonstrated an 8% rate of SBI in the SARS-CoV-2–positive febrile infants 90 days or younger in contrast to a 34% rate in a matched COVID-19–negative control group.16 Although our study included infants 56 days or younger, we report similar incidence rates to that reported by Payson et al15 (9.5% SBI among COVID-19 positive vs 33.8% SBI among COVID-19 negative, P = 0.03). The higher incidence of SBI may adversely affect the negative predictive value of the current algorithm for workup of young febrile infants. It is reassuring that we did not have any missed cases of SBI, showing that our algorithm was equally applicable under pandemic and nonpandemic conditions.

A strength of our study is that it is a multicenter study conducted across 2 states, which minimizes the chance that an observed effect would be due to local variations like local community mitigation measures, proportion with immunity, risk-taking
behaviors, and socioeconomic status. Another strength is that all sites are affiliated with the same academic children’s hospital and follow the same protocol for management of febrile infants 56 days or younger, which minimizes impact of variations in clinical practice. In addition, comparing data for 12 months during the COVID-19 pandemic with the same calendar months in the 2 previous years minimizes any effect due to seasonal variations in infections causing fever.

This study has potential limitations. The total number of infants with SBI and its subtypes was small and may limit our ability to make definitive assertions or interpretations on the observed incidence of bacteremia, UTI, and meningitis. Also, our findings may not be generalizable to all geographic regions. In addition, whereas some institutional protocols consider 90 days or younger as young infants, in our protocol, young infants are defined as 56 days or younger, which must be considered when comparing different studies. Furthermore, our study does not evaluate specific laboratory values or other components of the clinical decision support tools used to stratify higher- and lower-risk infants. Finally, as comprehensive respiratory viral testing is not typically recommended and was not performed on all infants, we are consequently unable to accurately estimate the burden of SBI in patients without a viral etiology.

**CONCLUSIONS**

The social distancing practices instituted during the COVID-19 pandemic markedly changed the landscape of pediatric emergency care. We observed a reduction in the number of febrile young infants presenting to the ED during the pandemic year but a significant increase in the incidence of SBI. We also observed a reduction in the number of non–SARS-CoV-2 viral infections, particularly viral meningitis and bronchiolitis in this patient population. Higher vigilance for SBI is necessary during the evaluation of these infants during the COVID-19 pandemic. More studies are needed to further corroborate or add insights to this observation. Although our study is not powered or designed to provide rationale for any change to existing guidelines for screening and evaluation of these infants, with the evolution of the pandemic and possible change in infectious etiology of febrile infants, it provides data that may be valuable for any such future considerations.

**TABLE 2.** Risk Ratios and 95% CIs for SBI Type and Year Comparison (Year Listed First Is the Referent Value)

| SBI Type            | Year Comparison                  | Risk Ratio | 95% CI          | Bonferroni Adj. P |
|---------------------|----------------------------------|------------|-----------------|-------------------|
| Bacteremia          | Prepandemic year 1 vs prepandemic year 2 | 0.64       | 0.15–2.64       | 1.000             |
|                     | Prepandemic year 1 vs pandemic year | 6.32       | 2.32–17.24      | <0.001            |
|                     | Prepandemic year 2 vs pandemic year | 9.90       | 2.89–33.93      | <0.001            |
| UTI                 | Prepandemic year 1 vs prepandemic year 2 | 0.57       | 0.31–1.07       | 0.224             |
|                     | Prepandemic year 1 vs pandemic year | 1.68       | 0.97–2.92       | 0.194             |
|                     | Prepandemic year 2 vs pandemic year | 2.94       | 1.52–5.66       | 0.002             |
| Bacterial meningitis| Prepandemic year 1 vs prepandemic year 2 | *          | *               | *                 |
|                     | Prepandemic year 1 vs pandemic year | *          | *               | *                 |
|                     | Prepandemic year 2 vs pandemic year | 9.14       | 1.03–80.67      | 0.046             |

*Calculations are not applicable because there are no cases.
Adj. indicates adjusted.

**FIGURE 2.** Summary of culture results by year (percent within year).
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TABLE 3. Detailed Summary of Culture Results

| Organism                  | March 2018–February 2021, % (n) | March 2018–February 2019, % (n) | March 2019–February 2020, % (n) | March 2020–February 2021, % (n) |
|---------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| *Escherichia coli*        | 62.3 (43)                       | 70.4 (19)                       | 73.3 (11)                       | 48.2 (13)                       |
| Group B                   |                                 |                                 |                                 |                                 |
| *Streptococcus*           |                                 |                                 |                                 |                                 |
| *Enterobacter cloacae*    | 5.8 (4)                         | 3.7 (1)                         | 20.0 (3)                        | 4.0 (0)                         |
| *Klebsiella* species      | 7.3 (5)                         | 14.8 (4)                        | 0.0 (0)                         | 3.7 (1)                         |
| *Enterococcus* species    | 5.8 (4)                         | 3.7 (1)                         | 0.0 (0)                         | 11.1 (3)                        |
| *Listeria monocytogenes*  | 2.9 (2)                         | 0.0 (0)                         | 6.7 (1)                         | 3.7 (1)                         |
| *Streptococcus anginosus* | 1.5 (1)                         | 0.0 (0)                         | 0.0 (0)                         | 3.7 (1)                         |
| *Staphylococcus aureus*   | 1.5 (1)                         | 0.0 (0)                         | 0.0 (0)                         | 3.7 (1)                         |

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