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# Risk of Bacterial Coinfections in Febrile Infants 60 Days Old and Younger with Documented Viral Infections

Prashant Mahajan, MD, MPH, MBA[1,*], Lorin R. Browne, DO[2], Deborah A. Levine, MD[3], Daniel M. Cohen, MD[4], Rajender Gattu, MD[5], James G. Linakis, MD, PhD[6], Jennifer Anders, MD[7], Dominic Borgialli, DO, MPH[8], Melissa Vitale, MD[9], Peter S. Dayan, MD, MSc[10], T. Charles Casper, PhD[11], Octavio Ramilo, MD[12], Nathan Kuppermann, MD, MPH[13], and the Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN)[†]

**Objective** To determine the risk of serious bacterial infections (SBIs) in young febrile infants with and without viral infections.

**Study design** Planned secondary analyses of a prospective observational study of febrile infants 60 days of age or younger evaluated at 1 of 26 emergency departments who did not have clinical sepsis or an identifiable site of bacterial infection. We compared patient demographics, clinical, and laboratory findings, and prevalence of SBIs between virus-positive and virus-negative infants.

**Results** Of the 4778 enrolled infants, 2945 (61.6%) had viral testing performed, of whom 1200 (48.1%) were virus positive; 44 of the 1200 had SBIs (3.7%; 95% CI, 2.7%-4.9%). Of the 1745 virus-negative infants, 222 had SBIs (12.7%; 95% CI, 11.2%-14.4%). Rates of specific SBIs in the virus-positive group vs the virus-negative group were: UTIs (33 of 1200 [2.8%; 95% CI, 1.9%-3.8%] vs 186 of 1745 [10.7%; 95% CI, 9.2%-12.2%]) and bacteremia (9 of 1199 [0.8%; 95% CI, 0.3%-1.4%] vs 50 of 1743 [2.9%; 95% CI, 2.1%-3.8%]). The rate of bacterial meningitis tended to be lower in the virus-positive group (0.4%) than in the viral-negative group (0.8%); the difference was not statistically significant. Negative viral status (aOR, 3.2; 95% CI, 2.3-4.6), was significantly associated with SBI in multivariable analysis.

**Conclusions** Febrile infants ≤60 days of age with viral infections are at significantly lower, but non-negligible risk for SBIs, including bacteremia and bacterial meningitis. *(J Pediatr 2018;203:86-91).*

Approximately 500 000 infants 60 days of age and younger are evaluated annually in emergency departments (EDs) in the US because of fever.[1,2] Of these infants, 8.4%-12.9% have confirmed bacterial infections and more than 50% have documented viral infections.[1-3] The relatively immature immune system of these young infants predisposes them to developing invasive bacterial illnesses such as bacteremia and bacterial meningitis, and many also develop urinary tract infections (UTIs). Collectively, these 3 infections are referred to as serious bacterial infections (SBIs). Expert guidance for management includes obtaining blood screening tests, which may include a white blood cell count, absolute neutrophil count (ANC), band count, and serum procalcitonin and C-reactive protein concentrations, in addition to urinalysis and evaluation of the cerebrospinal fluid (CSF), as well as cultures of these fluids. This is primarily because previous

| | |
|---|---|
| ANC | Absolute neutrophil count |
| CSF | Cerebrospinal fluid |
| ED | Emergency department |
| PECARN | Pediatric Emergency Care Applied Research Network |
| RSV | Respiratory syncytial virus |
| SBI | Serious bacterial infection |
| UTI | Urinary tract infection |
| YOS | Yale Observation Scale |

From the [1]Department of Emergency Medicine, University of Michigan, Ann Arbor, MI; [2]Department of Pediatrics and Emergency Medicine, Children's Hospital of Wisconsin, Medical College of Wisconsin, Wauwatosa, WI; [3]Department of Emergency Medicine and Pediatrics, Bellevue Hospital New York University Langone Medical Center, Bellevue Hospital Center, New York, NY; [4]Section of Emergency Medicine, Department of Pediatrics, Nationwide Children's Hospital and The Ohio State University, Columbus, OH; [5]Division of Emergency Medicine, Department of Pediatrics, University of Maryland Medical Center, Baltimore, MD; [6]Department of Emergency Medicine and Pediatrics, Hasbro Children's Hospital and Brown University, Providence, RI; [7]Department of Pediatrics, Johns Hopkins University, Baltimore, MD; [8]Department of Emergency Medicine, Hurley Medical Center and University of Michigan, Flint, MI; [9]Division of Pediatric Emergency Medicine, Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, PA; [10]Division of Emergency Medicine, Department of Pediatrics, Columbia University College of Physicians & Surgeons, New York, NY; [11]Department of Pediatrics, University of Utah, Salt Lake City, UT; [12]Division of Pediatric Infectious Diseases and Center for Vaccines and Immunity, Nationwide Children's Hospital and The Ohio State University, Columbus, OH; and [13]Department of Emergency Medicine and Pediatrics, University of California, Davis, School of Medicine and UC Davis Health, Davis, CA

*Formerly: Division of Emergency Medicine, Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit, MI

†List of additional members of the FIWG PECARN is available at www.jpeds.com (**Appendix**).

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literature has demonstrated that the clinical examination is limited in establishing a precise diagnosis or excluding diagnoses in most febrile infants.[4-10] Blood, urine, and CSF cultures are the reference standards to confirm SBIs and many clinicians treat young febrile infants empirically with antibiotic(s) intravenously and often hospitalize these young infants until bacterial culture results are available.[4-6]

Owing to widespread availability of rapid turnaround and point-of-care testing for viral infections, many clinicians are less likely to perform comprehensive evaluations for SBI in the presence of confirmed viral infections, because the risk of SBI has been shown to be lower among infants who come to attention because of fever and are confirmed to have viral infection.[7,8,11-15] However, most previous studies that have attempted to determine the risk of SBI among young febrile infants with viral infections have been conducted on small cohorts,[8] had retrospective study designs,[11,12] were limited to a single viral infection, and/or were performed more than a decade ago.[8,11,12,14,15]

In this planned subanalysis of a large, multicenter, prospective cohort study of febrile infants 60 days and younger evaluated for SBIs, we compared the risk of SBIs between virus-positive and virus-negative infants.

## Methods

We performed a planned secondary analysis of a prospective observational cohort study on a convenience sample of febrile infants 60 days of age and younger who were evaluated for the presence of SBIs with at least a blood culture at 26 EDs in the Pediatric Emergency Care Applied Research Network (PECARN) from December 2008 to May 2013. The methods for the parent study have been reported previously.[16,17] The institutional review boards at all participating sites approved this study and eligible infants were enrolled only after informed consent was obtained from the parents/guardians of participants. The methods pertinent to this secondary analysis are described herein.

### Selection of Participants

We enrolled febrile infants (defined by ED rectal temperatures of >38°C, or temperatures of a similar degree measured at home or at a referring clinic) evaluated in the ED with laboratory evaluations that included blood, urine, and/or CSF cultures. In addition to testing for SBI, infants evaluated in this secondary analysis had to be tested for the presence of at least 1 viral infection. We excluded infants with clinical signs of sepsis, prematurity, major systemic comorbidities (eg, serious congenital abnormalities, inborn errors of metabolism), or clear evidence of focal bacterial infections (not including otitis media) because the management of these febrile infants is not controversial.

### Measurements

For each patient, clinicians prospectively recorded patient demographics, physical examination findings including the Yale Observation Scale (YOS) score, and laboratory test results. The YOS is a clinical score that provides a quantitative assessment of wellness and clinical risk of SBI in febrile infants and toddlers based on simple clinical and observational findings.[10] A YOS score of 10 or less is considered normal. Tests for the presence of viral infections were performed at the discretion of the individual clinicians. There was variability across sites regarding the type and number of viral studies performed, ranging from testing for individual seasonal viruses (such as respiratory syncytial virus [RSV] and influenza during winter months) to comprehensive respiratory viral panels.

### Outcomes

The main outcome was the diagnosis of SBI, which we defined as the presence of bacterial meningitis, bacteremia, or UTI, or any combination of these 3 infections. Patients were considered not to have an SBI when blood and urine cultures were negative. Patients were excluded from the main SBI analysis if either blood or urine culture results were negative and meningitis status was unknown. However, when any of these cultures was positive, the patient was considered to have an SBI. We defined bacteremia and bacterial meningitis as growth of a known pathogen in the blood or CSF, respectively. Patients who did not have lumbar punctures performed were included in the analysis for bacterial meningitis if they were available for telephone follow-up. We categorized these patients as not having bacterial meningitis if they were well at the time of telephone follow-up. Cultures with growth of multiple bacteria or those not commonly considered pathogens (eg, coagulase-negative *Staphylococcus*, diphtheroids, Bacillus species, viridans streptococci) were categorized as contaminants and considered negative for the analysis of SBI. We defined UTI as the growth of a single pathogen in the urine with colony counts meeting 1 of 3 criteria: (1) greater than 1000 cfu/mL if specimen obtained by suprapubic aspiration, (2) greater than 50 000 cfu/mL from a catheterized specimen, or (3) greater than 10 000 cfu/mL from a catheterized specimen in association with an abnormal urinalysis (positive for leukocyte esterase or nitrites, or >5 white blood cells per high-power field on microscopic examination of unspun urine).[18,19] We also categorized febrile infants for the purpose of analysis on the basis of results of viral tests as virus positive or virus negative.

### Statistical Analyses

We compared patient demographics and histories, physical examination findings, laboratory results, and prevalence of SBIs between virus-positive and virus-negative infants. We also compared the risk of SBI in viral-positive and virus-negative infants stratified by age (≤28 days vs >28 days of age). We analyzed continuous variables using the Student *t* test and categorical data using risk differences. Ordinal variables were compared using the Wilcoxon rank-sum test. We also compared rates of SBI by individual type of virus detected. Finally, we performed a multivariable logistical regression analysis to assess the association of viral infections with SBIs, adjusting for patient age, temperature, YOS, complete blood count and ANC. All statistical tests were 2 tailed. Statistical significance was designated at $P < .05$. Statistical analyses were performed using

SAS software version 9.4 (SAS institute Inc, Cary, North Carolina).

## Results

A total of 4778 febrile infants were enrolled in the parent study. Of these, 3072 (64.3%) had viral testing performed. A total of 578 patients had single viral tests performed on, 2186 had testing for 3 or more viruses, and 1515 had comprehensive respiratory panel testing. We were able to ascertain viral test results and SBI status in 2945 of the 3072 febrile infants (95.9%), and these 2945 infants were included in the analysis. There were 1706 infants who did not have viral testing performed and, among these, we were able to ascertain SBI status in 1637 (nonanalytic cohort). The overall rate of SBI in this virus-not tested cohort was 177 of the 1637 (10.8%; 95% CI, 9.3%-12.4%).

The mean age of the 2945 infants evaluated in this secondary analysis was 34.1 ± 0.3 days. The mean temperature was 38.5°C ± 0.01°C. There were 1092 infants (37.1%) who were 28 days of age or younger. The characteristics of virus-positive and virus-negative infants are described in **Table I**. Virus-negative infants were more likely to be 28 days of age or younger and to have a higher mean white blood cell count and ANC count than viral-positive infants. **Table II** describes the various types of viral tests that were performed on enrolled patients across the participating EDs.

### Rates of Viral Infections and SBIs

Overall, of the 2945 infants analyzed, 266 (9.0%; 95% CI, 8.0%-10.1%) had SBIs. This included 219 (7.4%; 95% CI, 6.5%-8.4%) with UTIs, 59 (2.0%; 95% CI, 1.5%-2.6%) with bacteremia, and 19 (0.6%; 95% CI, 0.4%-1.0%) with bacterial meningitis. In addition, of the 219 infants with UTIs, 21 (9.6%; 95% CI, 6.0%-14.3%) also had bacteremia and 2 of the 219 (0.9%; 95% CI, 0.1%-3.3%) had both bacteremia and

**Table I. Patient demographics and clinical characteristics of febrile infants across viral testing cohorts**

| | Viral positive | Viral negative | Viral testing not performed |
|---|---|---|---|
| | (n = 1200) | (n = 1745) | (n = 1637) |
| Female | 528 (44.0) | 739 (42.3) | 724 (44.2) |
| ≤28 days | 380 (31.7) | 712 (40.8) | 369 (22.5) |
| Temperature in Celsius | 38.5 ± 0.4 | 38.5 ± 0.5 | 38.5 ± 0.4 |
| YOS | 6.0 [6.0-8.0] | 6.0 [6.0-8.0] | 6.0 [6.0-8.0] |
| White blood count ($\times 10^3/\mu L$) | 10.5 ± 4.3 | 11.0 ± 5.2 | 10.3 ± 4.4 |
| ANC ($\times 10^3/\mu L$), including bands if available | 3.9 ± 2.6 | 4.5 ± 3.5 | 4.0 ± 3.0 |
| Urinalysis positive | 115 (9.6) | 313 (17.9) | 292 (17.8) |
| Hospitalized | 1030 (85.8) | 1505 (86.2) | 910 (55.6) |
| Any SBI | 44 (3.7) | 222 (12.7) | 177 (10.8) |
| UTI | 33 (2.8) | 186 (10.7) | 164 (10.0) |
| Bacteremia | 9 (0.8) | 50 (2.9) | 25 (1.5) |
| Bacterial meningitis | 5 (0.4) | 14 (0.8) | 5 (0.3) |

Values are n (%), mean ± SD, or median (IQR).

**Table II. Types of assays and specimen sources for detected viral pathogens**

| | Assay type | | | | | Source | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Viruses | Rapid | Immunofluorescence | Culture | PCR | Blood | CSF | Nasopharyngeal/ Respiratory | Stool | Skin | Urine | Eye | Other |
| Adenovirus | 1/79 (1.3%) | 2/652 (0.3%) | 1/293 (0.3%) | 7/883 (0.8%) | 1/7 (14.3%) | 0/9 (0.0%) | 9/1493 (0.6%) | 1/54 (1.9%) | 0/0 (0.0%) | 0/4 (0.0%) | 0/2 (0.0%) | 0/6 (0.0%) |
| Enterovirus | 0/6 (0.0%) | 0/0 (0.0%) | 11/74 (14.9%) | 275/946 (29.1%) | 29/98 (29.6%) | 260/902 (28.8%) | 9/52 (17.3%) | 5/34 (14.7%) | 0/1 (0.0%) | 12/32 (37.5%) | 0/3 (0.0%) | 35/97 (36.1%) |
| Herpes simplex | 1/4 (25.0%) | 0/9 (0.0%) | 4/67 (6.0%) | 11/930 (1.2%) | 2/112 (1.8%) | 11/888 (1.2%) | 2/57 (3.5%) | 0/8 (0.0%) | 2/18 (11.1%) | 0/1 (0.0%) | 0/29 (0.0%) | 3/63 (4.8%) |
| Influenza A | 60/719 (8.3%) | 25/696 (3.6%) | 14/310 (4.5%) | 79/1273 (6.2%) | 0/4 (0.0%) | 0/19 (0.0%) | 127/2056 (6.2%) | 0/1 (0.0%) | 0/0 (0.0%) | 0/0 (0.0%) | 0/1 (0.0%) | 0/6 (0.0%) |
| Influenza B | 12/711 (1.7%) | 4/696 (0.6%) | 1/307 (0.3%) | 22/1231 (1.8%) | 0/5 (0.0%) | 0/23 (0.0%) | 34/2038 (1.7%) | 0/1 (0.0%) | 0/0 (0.0%) | 0/0 (0.0%) | 0/1 (0.0%) | 0/6 (0.0%) |
| Parainfluenza | 2/59 (3.4%) | 40/651 (6.1%) | 11/308 (3.6%) | 46/902 (5.1%) | 0/1 (0.0%) | 0/19 (0.0%) | 86/1540 (5.6%) | 0/1 (0.0%) | 0/0 (0.0%) | 0/0 (0.0%) | 0/1 (0.0%) | 0/5 (0.0%) |
| Rotavirus | 16/78 (20.5%) | 8/31 (25.8%) | 2/16 (12.5%) | 4/23 (17.4%) | 0/0 (0.0%) | 0/1 (0.0%) | 1/14 (7.1%) | 28/128 (21.9%) | 0/0 (0.0%) | 0/0 (0.0%) | 0/0 (0.0%) | 1/2 (50.0%) |
| RSV | 206/1072 (19.2%) | 64/680 (9.4%) | 26/298 (8.7%) | 163/1172 (13.9%) | 0/2 (0.0%) | 3/11 (27.3%) | 321/2125 (15.1%) | 0/4 (0.0%) | 0/0 (0.0%) | 0/0 (0.0%) | 0/1 (0.0%) | 0/5 (0.0%) |
| Human metapneumovirus | 0/30 (0.0%) | 9/480 (1.9%) | 0/66 (0.0%) | 27/886 (3.0%) | 0/1 (0.0%) | 0/5 (0.0%) | 33/1199 (2.8%) | 0/2 (0.0%) | 0/0 (0.0%) | 0/0 (0.0%) | 0/0 (0.0%) | 0/5 (0.0%) |
| Rhinovirus | 12/28 (42.9%) | 0/3 (0.0%) | 2/12 (16.7%) | 277/777 (35.6%) | 0/0 (0.0%) | 1/5 (20.0%) | 289/810 (35.7%) | 0/1 (0.0%) | 0/0 (0.0%) | 0/0 (0.0%) | 0/0 (0.0%) | 1/1 (100.0%) |
| Other | 4/13 (30.8%) | 2/6 (33.3%) | 18/192 (9.4%) | 30/339 (8.8%) | 6/32 (18.8%) | 6/98 (6.1%) | 39/380 (10.3%) | 3/35 (8.6%) | 0/4 (0.0%) | 1/26 (3.8%) | 1/9 (11.1%) | 0/8 (0.0%) |

*PCR*, polymerase chain reaction.
The numerator is the number of positive studies; the denominator is the total number of studies.

**Table III. Rate of SBI among febrile infants with and without documented viral infections**

| | Virus positive | | Virus negative, n (%) (95% CI) | | Risk Ratio (95% CI) |
|---|---|---|---|---|---|
| | n (%) | 95% CI | n (%) | 95% CI | |
| Any SBI | 44/1200 (3.7%) | 2.7%-4.9% | 222/1745 (12.7%) | 11.2%-14.4% | 3.5 (2.5-4.8) |
| UTIs | 33/1200 (2.8%) | 1.9%-3.8% | 186/1745 (10.7%) | 9.2%-12.2% | 3.9 (2.7-5.6) |
| Bacteremia | 9/1199 (0.8%) | 0.3%-1.4% | 50/1743 (2.9%) | 2.1%-3.8% | 3.8 (1.9-7.7) |
| Meningitis | 5/1200 (0.4%) | 0.1%-1.0% | 14/1745 (0.8%) | 0.4%-1.3% | 1.9 (0.7-5.3) |

bacterial meningitis. Of the 2495 infants tested, 1200 (40.7%; 95% CI, 39.0%-42.5%) had a positive test for at least 1 virus.

Of the 1200 virus-positive infants, 44 (3.7%; 95% CI, 2.7%-4.9%) had SBIs vs 222 of the 1745 virus-negative infants (12.7%; 95% CI, 11.2%-14.4%), yielding an absolute risk difference of 9.0% (95% CI, 7.2%-10.9%). The rates of specific SBIs including UTI and bacteremia were significantly lower in virus-positive infants compared with virus-negative infants (**Table III**). Although the rate of bacterial meningitis tended to be lower in the virus-positive group (0.4%) than in the virus-negative group (0.8%), the difference was not statistically significant (**Table III**).

When stratified by age group, regardless of virus status, the overall rate of SBI was 12.5% (136 of 1092) in febrile infants 28 days of age or younger compared with 7.0% (130 of 1853) among infants older than 28 days of age (difference 5.5%; 95% CI, 3.2%-7.7%). Virus-positive infants 28 days of age or younger had lower rates of SBI than virus-negative infants in the same age cohort (**Table IV**).

The rates of SBI in infants was consistently lower in the virus-positive group regardless of specific viruses identified compared with virus-negative infants (**Table V**; available at www.jpeds.com).

In the multivariable analysis with SBI status as the dependent variable, the variables that were significantly associated with SBI were virus-negative status (aOR, 3.2; 95% CI, 2.3%-4.6), age 28 days or younger (aOR, 1.4; 95% CI, 1.1%-1.9), temperature (aOR, 1.8 for every 1°C increase above 38.0°C; 95% CI, 1.4%-2.4), and ANC (aOR 1.3 for every 1000 cells/mm$^3$ increase; 95% CI, 1.2-1.4). **Table VI** (available at www.jpeds.com) provides the details regarding bacteria and viruses identified in the study cohort.

**Table IV. Rate of SBI stratified by age among febrile infants with and without documented viral infections**

| Variables | Virus positive | Virus negative | Age-specific RR |
|---|---|---|---|
| SBI | | | |
| ≤28 d | 4.2% (2.4%-6.7%) | 16.9% (14.2%-19.8%) | 4.0 (2.4-6.6) |
| >28 d | 3.4% (2.3%-4.9%) | 9.9% (8.1%-11.9%) | 2.9 (1.9-4.3) |
| UTI | | | |
| ≤28 d | 2.6% (1.3%-4.8%) | 13.3% (10.9%-16.1%) | 5.1 (2.7-9.6) |
| >28 d | 2.8% (1.8%-4.2%) | 8.8% (7.2%-10.7%) | 3.1 (2.0-4.9) |
| Bacteremia | | | |
| ≤28 d | 1.1% (0.3%-2.7%) | 4.4% (3.0%-6.1%) | 4.1 (1.5-11.6) |
| >28 d | 0.6% (0.2%-1.4%) | 1.8% (1.1%-2.9%) | 3.0 (1.1-8.1) |
| Meningitis | | | |
| ≤28 d | 0.8% (0.2%-2.3%) | 1.7% (0.9%-2.9%) | 2.1 (0.6-7.5) |
| >28 d | 0.2% (0.0%-0.9%) | 0.2% (0.0%-0.7%) | 0.8 (0.1-5.6) |

The percentages in the columns represent the proportion of infants with the type of SBIs stratified by age category and by individual type of SBI.

## Discussion

In this large multicenter study, we demonstrated that infants 60 days old and younger who come to medical attention with fever and who have confirmed viral infections are at substantially lower risk for SBIs than virus-negative infants. However, the non-negligible 3.7% rate of SBI including the 1.0% rate of invasive bacterial infections (bacteremia and meningitis) in virus-positive febrile infants should be taken into consideration during clinical decision making regarding evaluation, management, and disposition.

Many young febrile infants have viral or presumed viral infections, and several previous studies have similarly revealed lower risks of SBI among febrile infants with documented viral infections.[7,8,11,12,15] Compared with the earlier studies, the current study was large, prospective, and had the statistical power to provide more precise estimates of rates. A previous multicenter, prospective study in febrile infants 60 days old and younger with and without documented RSV infections revealed UTI and bacteremia rates of 7.0% and 1.1%, respectively, in RSV-positive infants compared with 12.5% and 2.3% in RSV-negative infants.[14] In a separate subanalysis of that same cohort, a lower rate of SBI and invasive bacterial infection was also documented when influenza-positive febrile infants were compared with those infants without documented influenza infections,[15] similar to the findings of the current study. Other studies using retrospective cohorts similarly revealed a lower prevalence of SBI among virus-positive febrile infants.[7-9,11]

The substantial practice pattern variation that exists in the evaluation of young febrile infants has been influenced by the increasing availability of multiplex panel, rapid turnaround viral tests.[20-24] Some studies have revealed that providers frequently change their behavior when they are aware of the results of viral tests.[20,25] Furthermore, virus-positive febrile infants are less likely to receive empiric antibiotics or to be hospitalized and are more likely to receive antiviral therapies.[20-22] A recent survey of ED and inpatient clinicians in 16 Canadian pediatric centers using a 3-week-old and a 5-week-old febrile infant case scenarios further highlights the substantial variation in the evaluation and management of febrile infants based on the results of viral tests. Surveyed hospitalization rates for the 3-week-old infant after detection of a respiratory virus decreased from 95% to 83% ($P < .001$) and for the 5-week-old

infant from 52% to 36% ($P < .001$). Treatment with empirical antibiotics also decreased after detection of a respiratory virus for the 3-week-old infant (92% vs 65%; $P < .001$) and the 5-week-old infant (39% vs 25%; $P < .001$).[20]

Despite the lower prevalence of SBI among virus-positive febrile infants documented in the current and earlier studies, the implications for clinicians are not straightforward. Some investigators have suggested that the performance of comprehensive evaluations for SBI, especially lumbar punctures, can be avoided[26] in the presence of a documented viral infection in a well-appearing young febrile infant and the use of empiric antibiotics and hospitalization can be reconsidered.[27] Others have suggested that practices should be based on the age of the infant, with a full evaluation for SBI including lumbar puncture in the first month of life despite the presence of a viral infection, because SBI rates remain non-negligible in this highest risk age group and the ability to determine wellness by the YOS is limited.[14,15,24]

Our study findings add to the current knowledge regarding the epidemiology of SBI as well as the risk of SBI among virus-positive febrile infants. The strengths of the current study include a large, geographically diverse, prospective cohort of febrile infants who were comprehensively evaluated for SBI, and our risk estimates for SBI were therefore more precise and generalizable than in previous studies. Furthermore, we did not limit our study to a single virus or individual viral illnesses, such as bronchiolitis or influenza.

The data identified a non-negligible risk of bacteremia and bacterial meningitis in the first 2 months of life. We suggest that clinicians need to exercise caution, especially in the first month of life, regarding comprehensiveness of evaluation including performance of lumbar punctures, regardless of virus infection status. For both age groups, at a minimum, an evaluation for UTI by collecting samples for urinalysis and urine culture should be strongly considered regardless of viral status. Finally, our study suggests the importance of incorporating the results of viral testing to provide better risk estimates of SBI in these infants and assist the clinician with decisions regarding lumbar puncture, empirical antibiotic treatment, and hospitalization. Formal decision analyses and cost-effectiveness analyses using these data will help to develop recommendations regarding viral testing and its impact as a part of the evaluation and management of these young febrile infants.

Our study has several limitations. First, the parent study cohort consisted of a convenience sample of febrile infants and viral testing was performed at the discretion of the treating clinician during a time in which rapid testing was evolving. Furthermore, the number of viruses detectable and type of tests performed varied between sites (1) by season, (2) by type of test, namely, polymerase chain reaction vs other, (3) whether single viral tests or multiplex viral polymerase chain reaction panel tests were performed, (4) by type of specimen (nasal swab vs throat swab), and (5) by what tissue or fluid was sampled (CSF vs blood vs respiratory secretions). It is possible that the rates of SBI and the prevalence of viral infections detected would be different if comprehensive viral testing was performed on all patients or if higher sensitivity and specificity viral testing was used. Therefore, we cannot comment on the exact prevalence of viral infections in our study cohort. However, if higher, some of the current virus-negative patients with SBIs may have been virus positive with SBIs, and could have increased the rate of coinfection, thus, strengthening our conclusions. In addition, it is possible that the risk of SBI may vary with the type of viral infection and with the number of viral coinfections.[20] Despite these limitations, the rate of SBI in the enrolled population was remarkably similar to that described in previous studies.[28,29] Second, we intentionally excluded febrile infants with obvious sources of bacterial infections (such as cellulitis) and critically ill-appearing infants because those infants represent a less significant diagnostic and therapeutic conundrum. The purpose of our study was to identify the risk of SBI in noncritically ill-appearing febrile infants who have confirmed viral infections to aid clinician decision making. Third, the analysis in which we stratified by type of viral infection did not have sufficient power to detect statistically significant differences in the risk of SBI by virus type; nevertheless, the results are hypothesis generating. Despite the substantial size and multicenter design of the study, we also did not have sufficient statistical power to comment on the risk difference in bacterial meningitis between virus-positive and virus-negative infants. Therefore, we suggest that clinicians retain low thresholds for performing lumbar punctures in young febrile infants with documented viral infections, especially those younger than 1 month of age. In addition, most of the EDs in PECARN are large, tertiary care, academic institutions and practice patterns including testing for viral pathogens as well as evaluation for SBI may not be representative of practice patterns in community EDs or primary care pediatric offices.[27] Finally, the American Academy of Pediatrics has proposed an updated definition of UTI that requires the presence of an abnormal urinalysis and a positive urine culture defined as at least 50 000 cfu/mL of a pathogenic bacterium.[30] We did not use this definition in our study cohort because these guidelines apply to infants older than 2 months of age.

In summary, febrile infants 60 days of age and younger with documented viral infections are at significantly lower risk for SBIs than similarly aged febrile infants who test negative for viral infections. Nevertheless, the risk of SBI was non-negligible in virus-positive infants, particularly UTIs, and approximately 1% of infants with documented virus infections in the first month of life had bacteremia and/or bacterial meningitis. Therefore, we concluded that the presence of a documented viral illness should not affect the initial (ED) evaluation for SBI in febrile infants 28 days of age and younger. In the second month of life, at a minimum, evaluation for UTI would be prudent in febrile infants with documented viral infections, as well as a low threshold maintained for testing for bacteremia and meningitis. ■

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Reprint requests: Prashant Mahajan, MD, MPH, MBA, Department of Emergency Medicine, University of Michigan, 1540 E. Hospital Dr, CW 2-737, Ann Arbor, MI 48109-4260. E-mail: pmahajan@med.umich.edu

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## Appendix

Additional members of the Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN)

1. Ann & Robert H. Lurie Children's Hospital (Elizabeth C. Powell, MD, MPH)
2. Bellevue Hospital Center (Deborah A. Levine, MD; Michael G. Tunik, MD)
3. Boston Children's Hospital (Lise E. Nigrovic, MD, MPH)
4. Children's Hospital of Colorado (Genie Roosevelt, MD)
5. Children's Hospital of Michigan (Prashant Mahajan, MD, MPH, MBA)
6. Children's Hospital of Philadelphia (Elizabeth R. Alpern, MD, MSCE)
7. Children's Hospital of Pittsburgh (Melissa Vitale, MD)
8. Children's Hospital of Wisconsin (Lorin Browne, DO; Mary Saunders, MD)
9. Children's National Medical Center (Shireen M. Atabaki, MD, MPH)
10. Cincinnati Children's Hospital Medical Center (Richard M. Ruddy, MD)
11. Hasbro Children's Hospital (James G. Linakis, MD, PhD)
12. Helen DeVos Children's Hospital (John D. Hoyle, Jr., MD)
13. Hurley Medical Center (Dominic Borgialli, DO, MPH)
14. Jacobi Medical Center (Stephen Blumberg, MD; Ellen F. Crain, MD, PhD)
15. Johns Hopkins Children's Center (Jennifer Anders, MD)
16. Nationwide Children's Hospital (Bema Bonsu, MD; Daniel M. Cohen, MD)
17. Nemours/Alfred I. DuPont Hospital for Children (Jonathan E. Bennett, MD)
18. New York Presbyterian-Morgan Stanley Children's Hospital (Peter S. Dayan, MD, MSc)
19. Primary Children's Medical Center (Richard Greenberg, MD)
20. St. Louis Children's Hospital (David M. Jaffe, MD; Jared Muenzer, MD);
21. Texas Children's Hospital (Andrea T. Cruz, MD, MPH, Charles Macias, MD)
22. University of California Davis Health (Nathan Kuppermann, MD, MPH; Leah Tzimenatos, MD)
23. University of Maryland (Rajender Gattu, MD)
24. University of Michigan (Alexander J. Rogers, MD)
25. University of Rochester (Anne Brayer, MD)
26. Women and Children's Hospital of Buffalo (Kathleen Lillis, MD).

**Table V. Rates of SBI among febrile infants with and without documented viral infections**

| | Number tested | SBI rate in virus-positive infants | SBI rate in virus-negative infants | Risk Ratio (95% CI) |
|---|---|---|---|---|
| Enterovirus | 991 | 3.2% (1.5%-6.0%) | 13.5% (10.7%-16.5%) | 4.2 (2.1-8.2) |
| Influenza | 2089 | 3.1% (1.0%-7.1%) | 13.3% (11.3%-15.4%) | 4.3 (1.8-10.3) |
| RSV | 2142 | 2.2% (0.9%-4.4%) | 12.8% (10.9%-14.8%) | 5.9 (2.8-12.5) |
| Rhinovirus | 817 | 6.5% (4.0%-10.0%) | 14.1% (10.5%-18.4%) | 2.2 (1.3-3.6) |
| Adenovirus | 1537 | 0.0% (0.0%-33.6%) | 15.0% (12.6%-17.7%) | — |
| Herpes | 969 | 9.1% (0.2%-41.3%) | 13.9% (11.4%-16.9%) | 1.5 (0.2-10.0) |
| Parainfluenza | 1565 | 0.0% (0.0%-4.2%) | 14.6% (12.3%-17.3%) | — |
| Rotavirus | 145 | 0.0% (0.0%-11.6%) | 8.6% (3.8%-16.2%) | — |
| Human metapneumovirus | 1211 | 6.1% (0.7%-20.2%) | 15.2% (12.3%-18.5%) | 2.5 (0.6-9.8) |
| Others | 523 | 9.8% (3.3%-21.4%) | 14.9% (10.8%-19.7%) | 1.5 (0.6-3.7) |

Some relative risks were not estimated due to zero cells.

**Table VI. Types and frequency of bacterial and viral pathogens detected**

| Infections | Pathogen | Viral Coinfection |
|---|---|---|
| Bacteremia | *E coli* 19 (32.2%) | Enterovirus 1 (5.3%) |
| | | Influenza A 1 (5.3%) |
| | | Rhinovirus 1 (5.3%) |
| | Group B streptococcus (GBS) 16 (27.1%) | None |
| | *Staphylococcus aureus* 9 (15.3%) | Enterovirus 1 (11.1%) |
| | | Influenza A 1 (11.1%) |
| | *Enterobacter* spp 3 (5.1%) | None |
| | *Neisseria meningitidis* 2 (3.4%) | Other: Coronavirus 1 (50.0%) |
| | Lactose-fermenting gram-negative bacilli 1 (1.7%) | None |
| | *Pseudomonas* spp 1 (1.7%) | RSV 1 (100.0%) |
| | *Listeria monocytogenes* 1 (1.7%) | None |
| | *Flavobacterium* spp 1 (1.7%) | Enterovirus 1 (100.0%) |
| | *Moraxella catarrhalis* 1 (1.7%) | None |
| UTI | *E coli* * 194 (88.6%) | Rhinovirus 14 (7.2%) |
| | | RSV 4 (2.1%) |
| | | Enterovirus 3 (1.5%) |
| | | Human metapneumovirus 2 (1.0%) |
| | | Influenza A 2 (1.0%) |
| | | Enterovirus, Rhinovirus 1 (0.5%), |
| | | Other: |
| | | Coronavirus OC43 RNA 1 (0.5%), |
| | | Coronavirus OC43 RNA, RSV 1 (0.5%) |
| | | Enterovirus, Herpes, Rhinovirus 1 (0.5%) |
| | | Viral culture 1 (0.5%) |
| | *Enterococcus* spp† 9 (4.1%) | Enterovirus 1 (11.1%) |
| | *Klebsiella pneumoniae* 6 (2.7%) | None |
| | *Enterobacter* spp‡ 4 (1.8%) | Rhinovirus 1 (25.0%) |
| | Group B Streptococcus (GBS) 2 (0.9%) | Influenza A 1 (50.0%) |
| | *Citrobacter freundii* 1 (0.5%) | None |
| | *Pseudomonas aeruginosa* 1 (0.5%) | None |
| | *Proteus mirabilis* 1 (0.5%) | None |
| | *Klebsiella oxytoca* 1 (0.5%) | None |
| Meningitis | Group B Streptococcus (GBS) 7 (36.8%) | Other: Coronavirus NL63 1 (14.3%) |
| | *E coli* 3 (15.8%) | None |
| | *Enterococcus* spp 2 (10.5%) | None |
| | *Klebsiella pneumoniae* 1 (5.3%) | None |
| | *Enterobacter* spp 1 (5.3%) | None |
| | *Klebsiella oxytoca* 1 (5.3%) | RSV 1 (100.0%) |
| | *Listeria monocytogenes* 1 (5.3%) | None |
| | *Streptococcus pneumoniae* 1 (5.3%) | Rhinovirus 1 (100.0%) |
| | *Staphylococcus aureus* 1 (5.3%) | Rhinovirus 1 (100.0%) |
| | *Neisseria meningitidis* 1 (5.3%) | Other: Coronavirus 1 (100.0%) |

*Including 10 *E coli* seen in combination with another organisms.
†Including 4 *Enterococcus faecalis* among the UTI organisms and 2 among the bacterial meningitis organisms.
‡Including 1 *Enterobacter* with mixed/multiple flora/organisms.