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Risk of Serious Bacterial Infection in Young Febrile Infants With Respiratory Syncytial Virus Infections

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ABSTRACT. Background. The evaluation of young febrile infants is controversial, in part because it is unclear whether clinical evidence of a viral infection significantly reduces the risk of serious bacterial infections (SBIs). Specifically, it remains unclear whether the risk of SBI is altered in a meaningful way in the presence of respiratory syncytial virus (RSV) infections.

Objective. The objective of this study was to determine the risk of SBI in young febrile infants who are infected with RSV compared with those without RSV infections.

Methods. We conducted a 3-year multicenter, prospective, cross-sectional study. All febrile (≥38°C) infants who were ≤60 days of age and presented to any of 8 pediatric emergency departments from October through March 1998–2001 were eligible. General clinical appearance was evaluated using the Yale Observational Scale. We determined RSV status by antigen testing of nasopharyngeal secretions. We defined bronchiolitis as either wheezing alone or chest retractions in association with an upper respiratory infection. We evaluated infants with blood, urine, cerebrospinal fluid, and stool cultures. Urinary tract infection (UTI) was defined by single pathogen growth of ≥5 × 10⁶ cfu/mL, or ≥10⁷ cfu/mL in association with a positive urinalysis in a catheterized specimen, or ≥10⁶ cfu/mL in a suprapubic aspirate. Bacteremia, bacterial meningitis, and bacterial enteritis were defined by growth of a known bacterial pathogen. SBI was defined as any of the above-mentioned 4 bacterial infections.

Results. We enrolled 1248 patients, including 269 (22%) with RSV infections. The overall SBI status could not be determined in 1169 (94%) of the 1248 patients, and the rate of SBIs was 11.4% (133 of 1169; 95% confidence interval [CI]: 9.6%–13.3%). The rate of SBIs in the RSV-positive infants was 7.0% (17 of 244; 95% CI: 4.1%–9.9%) compared with 12.5% (116 of 925; 95% CI: 10.5%–14.8%) in the RSV-negative infants (risk difference: 5.5%; 95% CI: 1.7%–9.4%). The rate of UTI in the RSV-positive infants was 5.4% (14 of 261; 95% CI: 3.0%–8.8%) compared with 10.1% (98 of 966; 95% CI: 8.3%–12.2%) in the RSV-negative infants (risk difference: 4.7%; 95% CI: 1.4%–8.1%). The RSV-positive infants had a lower rate of bacteremia than the RSV-negative infants (1.1% vs 2.3%; risk difference: 1.2%; 95% CI: −0.4% to 2.7%). No RSV-positive infant had bacterial meningitis (0 of 251; 95% CI: 0%–1.2%); however, the differences between the 2 groups with regard to bacteremia and bacterial meningitis did not achieve statistical significance.

Conclusions. Febrile infants who are ≤60 days of age and have RSV infections are at significantly lower risk of SBI than febrile infants without RSV infection. Nevertheless, the rate of SBIs, particularly as a result of UTI, remains appreciable in febrile RSV-positive infants. Pediatrics 2004;113:1728–1734; fever, infant, RSV, serious bacterial infection, bronchiolitis, bacteremia, urinary tract infection.

ABBREVIATIONS. SBI, serious bacterial infection; UTI, urinary tract infection; RSV, respiratory syncytial virus; ED, emergency department; CSF, cerebrospinal fluid; UA, urinalysis; CXR, chest radiograph; URI, upper respiratory tract infection; WBC, white blood cell; CI, confidence interval; RR, relative risk.

Febrile infants ≤60 days of age are at risk for serious bacterial infections (SBIs), including meningitis, bacteremia, and urinary tract infection (UTI). Several investigators have attempted to create algorithms to identify which febrile infants are at greatest risk for SBI. It remains unclear from these studies, however, whether con-
current viral infections alter the risk of SBI in these febrile infants. Some investigations have demonstrated that young febrile children with recognizable viral infections are at decreased risk of SBI compared with febrile children without recognizable viral infections.\textsuperscript{24–29} However, the youngest infants (≤60 days of age) composed only small numbers in many of these studies.\textsuperscript{24,28} Recent retrospective reviews have demonstrated that young febrile infants with concurrent viral respiratory infections are at a low but nonnegligible risk for SBIs, especially for UTIs.\textsuperscript{26,27,29–31} These studies, however, are limited by the potential biases inherent in retrospective study designs; in this case, the most important of these was whether the initial apparent diagnosis of viral infection was changed to that of the SBI once the latter was discovered. There remains substantial controversy over the evaluation of the young febrile infant despite current published guidelines.\textsuperscript{1–7,13,18,20,22,32}

Few studies have assessed prospectively the specific relationship between respiratory syncytial virus (RSV) infections and SBI in young infants. Typically, children with RSV infections present with signs and symptoms of upper and lower respiratory tract disease. In very young infants, however, fever may be the sole manifestation of this infection.\textsuperscript{33,34} Although concurrent bacterial infection and RSV is uncommon, it has been reported to occur.\textsuperscript{1,24,28,30,35–37}

The objective of this study was to determine the risk of SBIs in young febrile infants who test positive for RSV compared with those who test negative for RSV. We hypothesized that the risk of SBIs would be less in febrile infants with RSV compared with the risk of febrile infants without RSV infections.

**METHODS**

**Patient Selection**

We conducted a prospective cross-sectional study in 8 pediatric emergency departments (EDs) over a 3-year period. Two centers enrolled patients only during the last 2 years of the study period. All infants who were ≤60 days and presented from October through March 1998–2001 with a rectal temperature ≥38°C by history or in the ED were eligible for enrollment. Infants were excluded when they had received antibiotics within 48 hours of ED presentation or when a parent or guardian refused consent. Patients who met enrollment criteria but were not enrolled prospectively were defined as “missed” patients. Patients were defined as having “failed protocol” and excluded from the analysis when either an RSV test was not obtained or no bacterial cultures were obtained. Infants were included in the study analysis when any culture was performed and when they had a known RSV status. The study was approved by the Institutional Review Board at each site.

**Study Design: Clinical Evaluation**

Physicians who evaluated the patients in the ED performed a standard history and physical examination on all enrolled patients. Data collected included patient age, gestational age, gender, race, medical history, history of RSV infections, circumcision status, number of days with fever, and recent history of respiratory signs or symptoms. Physical examination data collected included vital signs; oxygen saturation; and the presence of cough, rhinorrhea, rales or flaring, retractions, wheezing, and any specific infection source. Maximum temperature was defined as the highest rectal temperature recorded either at home or in the ED. Before laboratory evaluation, the examining physician completed a Yale Observation Scale assessment.\textsuperscript{36} After the examining physician completed the history and physical examination, a standardized laboratory evaluation was performed. We obtained nasopharyngeal aspirates for rapid RSV antigen detection via enzyme immunoassay or indirect florescent antibody on each enrolled patient. Analysis of urine, blood, and cerebrospinal fluid (CSF) was part of the standard evaluation for these infants.\textsuperscript{13} This included bladder catheterization or suprapubic aspiration for urinalysis (UA) and urine culture, complete blood count and differential, blood culture, CSF cell count, and CSF culture. Stool cultures and chest radiographs (CXR) were performed at the discretion of the examining physicians. For the purposes of this study, all CXRs were interpreted by one pediatric radiologist blinded to patient data. A second pediatric radiologist reviewed a random sample of 10% of CXRs, and interobserver reliability was measured.

Therapeutic decisions, including those regarding antibiotic therapy and/or hospitalization, were at the discretion of the responsible physician and not determined by study protocol. We considered patients who were discharged to home from the ED 4 to 7 days after the initial ED visit to determine patient status. Patients who were determined at a subsequent visit to have an SBI that was not detected during the initial ED visit were included as having had an SBI in the analysis.

**Definitions and Outcome Measures**

We analyzed infants according to their RSV status, documented as positive or negative on rapid immunoassay. When the result of the RSV immunoassay was indeterminate, the patient was considered to have a negative RSV status. Upper respiratory tract infection (URI) was defined as either history or positive result on examination of cough or rhinorrhea. Bronchiolitis was defined by the presence of either wheezing or chest retractions in association with an URI in the absence of CXR evidence of focal consolidation. We defined pneumonia as a focal consolidation on CXR as interpreted by the study pediatric radiologist.

We defined UTI as a positive test for leukocyte esterase or nitrite or ≥5 white blood cells (WBCs) per high power field on a urine sample.\textsuperscript{39} We defined UTI as the growth of a single known pathogen with colony counts meeting 1 of 3 criteria: 1) ≥1000 cfu/mL for urine cultures obtained by suprapubic aspiration, 2) ≥50 000 cfu/mL from a catheterized specimen, or 3) ≥100 000 cfu/mL from a catheterized specimen in association with a positive UA. The first 2 criteria are based on the reporting of previous research regarding UTIs in infants and have been found to discriminate between true UTI and asymptomatic bacteruria caused by contamination or colonization.\textsuperscript{35,40} The third criterion was established to minimize the risk of misclassifying a child with bacterial colonization of the urine as having a UTI in our analysis. We considered a urine culture to be contaminated and defined it as negative for the analysis when >1 bacterial organism was identified.

Bacteremia and meningitis were defined as any growth of a known bacterial pathogen in the blood or CSF, respectively. We considered blood and CSF cultures to reflect growth of contaminants when the bacterial isolates were not commonly accepted pathogens (eg, Staphylococcus epidermidis, α or γ hemolytic-streptococcus, diphtheroids, bacillus species). Patients who did not have lumbar punctures performed were included in the analysis for bacterial meningitis when they did not receive antibiotics in the ED and were available for follow-up.\textsuperscript{11} We categorized these patients as not having bacterial meningitis if they were well on follow-up. We defined bacterial enteritis as growth of a known bacterial pathogen in the stool.

We defined SBI as the presence of bacterial meningitis, bacteremia, UTI, or bacterial enteritis. We did not consider pneumonia to be an SBI because of the inability to differentiate a viral from bacterial cause on CXR.\textsuperscript{41,42} In the main SBI analysis, patients were considered not to have an SBI when blood and urine cultures and meningitis status all were known and negative. Patients were excluded from the main SBI analysis when either blood or urine cultures or the meningitis status was unknown and the remaining cultures were negative. However, when any culture, including stool cultures, was positive, the patient was considered to have an SBI regardless of whether other cultures were obtained. Patients were not excluded from the main SBI analysis when only stool cultures were missing. In subanalyses, we investigated the rates of specific individual bacterial infections, rates of SBI by age categories (≤28 days vs 28–60 days of age), and the risk of SBI in patients with and without clinical bronchiolitis regardless of RSV status.
Statistical Analysis

We compared the demographics, historical characteristics, physical examination findings, laboratory results, and prevalence of SBI between RSV-positive and RSV-negative infants. We also compared the risk of SBI in infants with and without RSV and bronchiolitis stratified by age (using an age cutoff of 28 days). We analyzed continuous variables using a t test and categorical data using the Fisher exact test. Ordinal variables were compared using the Wilcoxon rank sum test. We evaluated interobserver agreement with regard to CXR interpretations using the κ statistic. To evaluate the possibility of enrollment bias, we compared enrolled and missed patients with regard to culture results. Finally, we performed a multiple logistic regression analysis with SBI as the outcome variable and clinical evaluation data and RSV status as predictor variables to assess the independent effect of RSV status on the risk of SBI. All statistical tests were 2 tailed. Statistical significance was designated at P ≤ .05. Statistical analyses were performed using SPSS 10.1 (SPSS Inc, Chicago, IL) and Stata (Release 7.0; Stata Corp, College Station, TX) statistical software.

Sample Size Calculations

The minimum prevalence that we expected for SBI in febrile infants who were younger than 60 days and had no apparent source for fever was 7%.14 We estimated that the prevalence of SBI in the RSV-positive group would be 1%.30 We considered the least clinically important difference in SBI status between groups to be 5% (the difference between the 7% prevalence of SBI in the RSV-negative group and a 2% prevalence of SBI in the RSV-positive group). To detect this difference with sufficient power (β = 80%, α = .05), we planned to enroll ~300 RSV-positive and 300 RSV-negative patients. Furthermore, if none of 300 RSV-positive febrile infants had bacterial meningitis, then this sample size would provide an upper limit of the 95% confidence interval of 1% for the risk of bacterial meningitis in the RSV-infected infants.

RESULTS

Patient Population

During the study period, 1868 patients were eligible for the study, 1248 (67%) of whom were enrolled (Fig 1). Of the 1868 eligible, 564 (30%) infants were missed and 56 (3%) either failed the enrollment protocol or the parent refused to sign the study consent. Of the 1246 enrolled patients, 269 (22%) tested positive for RSV.

Patient Demographics

The mean age of enrolled patients was 35.5 days (standard deviation [SD]: ±14.4 days). A total of 411 (33%) patients were 28 days or younger, and 55% were male. The mean gestational age was 39 weeks (SD: ±2 weeks), and 7% of all infants were products of gestations lasting <37 weeks. The mean maximum temperature of enrolled patients was 38.6°C (SD: ±0.5°C). The characteristics of infants with and without RSV infections are illustrated in Table 1.

Serious Bacterial Infection

Of the 1248 enrolled infants, lumbar punctures were performed in 1164 (93%), blood cultures were performed in 1235 (99%), and urine cultures were performed in 1227 (98%) of patients. All 3 culture evaluations were performed in 1135 (91%) patients. The overall SBI status could be determined in 1169 (94%) as these patients had a blood and urine culture and a CSF culture or a known meningitis status based on clinical follow-up without antibiotic administration.

The overall rate of SBI in the study population was 11.4% (133 of 1169; 95% confidence interval [CI]: 9.6%–13.3%). Of enrolled patients, 8 (0.7%) of 1189 patients had bacterial meningitis, 25 (2.0%) of 1235 had bacteremia, 112 (9.1%) of 1227 had UTIs, and 2 (1.9%) of 107 had bacterial enteritis. Of all infants with UTIs, 8% (9 of 112) had bacteremia and 1% (1 of 112) had meningitis and bacteremia. The bacterial pathogens isolated are reported in Table 2.

Although pneumonia was not considered an SBI, 29 (5.7%) of 507 patients on whom CXRs were obtained had focal consolidations on CXR. Interobserver agreement between the study radiologists regarding the presence of a focal consolidation was 96%, with a κ statistic of .64 (P < .001).

RSV-positive infants were less likely to have an SBI compared with the RSV-negative infants (7% vs 12.5%; relative risk [RR]: 0.6; 95% CI: 0.3–0.9; Table 3). RSV-positive infants had an appreciable rate of UTI (5.4%; 95% CI: 3.0%–8.8%), although this rate was significantly less than that of RSV-negative infants. RSV-positive patients had a lower rate of bacteremia than RSV-negative patients and had no cases of bacterial meningitis. However, the differences between the 2 groups with regard to these infections did not achieve statistical significance. In a multivariable analysis, RSV infection was associated with a lower risk of SBI (adjusted odds ratio: 0.58; 95% CI: 0.33–0.99) after adjusting for age, temperature, Yale Observation Score, and WBC count.

The 156 infants with clinical bronchiolitis regardless of RSV status had a 7.1% (95% CI: 3.5%–12.7%) rate of SBIs (and no bacteremia or meningitis events), versus a 12.5% (95% CI: 10.5%–14.7%) rate in the 1035 infants without bronchiolitis, although this comparison did not reach statistical significance (P = .07). The rate of UTIs in infants with bronchiolitis who had urine cultures performed was nevertheless 6.5% (95% CI: 3.2%–11.7%).
In a subanalysis comparing SBI rates stratified by age, we found no overall statistical difference in the rate of SBI or RSV positivity between the younger and older infants. Infants who were ≤28 days of age had an overall rate of SBI of 13.3% (95% CI: 10.1%–17.2%), regardless of RSV status. Among the 82 RSV-positive infants who were ≤28 days, 10.1% (95% CI: 4.5%–19.0%) had SBIs, including 5 of 82 (6.1%; 95% CI: 2.0%–13.7%) with UTIs and 3 of 82 (3.7%; 95% CI: 0.8%–10.3%) with bacteremia. The overall rate of SBI in infants who were ≤28 days of age did not differ significantly between those who were and those who were not RSV infected (10.1% vs 14.2%; RR: 0.71; 95% Cl: 0.35–1.5).

The overall rate of SBI in the 187 RSV-positive infants who were 29–60 days of age was 5.5%, all of whom had UTIs and none had bacteremia or meningitis. In these older infants, there was a statistically significant difference in the rate of SBI between those who were and those who were not RSV infected (5.5% vs 11.7%; RR: 0.47; 95% Cl: 0.24–0.91).

Among all 269 RSV-positive infants in this study, those who were ≤28 days of age were more likely to have an SBI than infants who were older than 28 days (10.1% vs 5.5%; RR: 1.9; 95% Cl: 0.74–4.6), although this comparison did not achieve statistical significance. We were unable to compare rates of specific types of SBI between these subgroups, however, because of small numbers.

The 3 patients with RSV infection and bacteremia were 9, 10, and 19 days of age. Enterobacter cloacae, Escherichia coli, and group B streptococcus were isolated from their cultures, respectively.

All 3 patients had fevers documented above 39.2°C. None of the patients, however, had a history or evidence of a URI or wheezing, although the youngest patient was noted to have retractions on examination and a negative CXR. Of note, the 10-day-old patient had a WBC count of 27 700/mm3, and the 19-day-old patient had a Yale Observation Score of 16.

Fourteen infants had concurrent RSV infection and UTI; 11 (79%) were male. Pathogens identified in these 14 patients included Escherichia coli in 10, Enterobacter cloacae in 1, Citrobacter species in 1, Klebsiella pneumoniae in 1, and Proteus mirabilis in 1.

### TABLE 1. Patient Demographics: Comparison by RSV Status

<table>
<thead>
<tr>
<th>Variable (Mean [SD])</th>
<th>RSV Positive (N = 269)</th>
<th>RSV Negative (N = 979)</th>
<th>Difference Between Means or Percentages (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, d</td>
<td>36.4 (14.2)</td>
<td>35.3 (14.4)</td>
<td>1.2 (–0.8 to 3.2)</td>
</tr>
<tr>
<td>Male, %</td>
<td>136/269 (51%)</td>
<td>547/979 (56%)</td>
<td>–5% (–12.1%–1.4%)</td>
</tr>
<tr>
<td>URI symptoms, %</td>
<td>244/268 (91%)</td>
<td>603/977 (62%)</td>
<td>29% (24.7%–33.9%)</td>
</tr>
<tr>
<td>Tmax, ºC</td>
<td>38.5 (0.46)</td>
<td>38.7 (0.52)</td>
<td>–0.12 (–0.19% to 0.06%)</td>
</tr>
<tr>
<td>Median YOS (IQR)</td>
<td>6 (6, 8)</td>
<td>6 (6, 6)</td>
<td>–</td>
</tr>
<tr>
<td>WBC ×1000/mm³ (SD)</td>
<td>12.3 (4.2)</td>
<td>11.7 (5.6)</td>
<td>0.6 (0–1.2)</td>
</tr>
<tr>
<td>ANC ×1000/mm³ (SD)</td>
<td>4.7 (3.1)</td>
<td>4.9 (3.8)</td>
<td>–0.2 (–0.7 to 0.2)</td>
</tr>
<tr>
<td>ABC ×1000/mm³ (SD)</td>
<td>0.78 (1.2)</td>
<td>1.1 (1.2)</td>
<td>–0.32 (–0.45 to –0.1)</td>
</tr>
<tr>
<td>UA Positive, %</td>
<td>23/226 (10.2%)</td>
<td>159/881 (18.1%)</td>
<td>–7.9% (–12.6% to –3.2%)</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>94/250 (37.6%)</td>
<td>62/941 (6.6%)</td>
<td>31% (24.8%–37.2%)</td>
</tr>
</tbody>
</table>

Tmax indicates maximum temperature; YOS, Yale Observation Score; IQR, interquartile range; ANC, absolute neutrophil count; ABC, absolute band count.

### TABLE 2. Pathogens

<table>
<thead>
<tr>
<th>Bacteremia</th>
<th>UTI</th>
<th>Meningitis</th>
<th>Enteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>E coli (8)</td>
<td>E coli (89)</td>
<td>K pneumoniae (9)</td>
<td>Salmonella (1)</td>
</tr>
<tr>
<td>GBBS (7)</td>
<td>K pneumoniae (9)</td>
<td>Citrobacter (1)</td>
<td></td>
</tr>
<tr>
<td>K pneumoniae (2)</td>
<td>Enterococcus (2)</td>
<td>S pneumoniae (1)</td>
<td></td>
</tr>
<tr>
<td>S pneumoniae (2)</td>
<td>E coli (4)</td>
<td>Enterobacter (1)</td>
<td></td>
</tr>
<tr>
<td>Salmonella (2)</td>
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<td>Enterobacter (1)</td>
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<td></td>
</tr>
<tr>
<td>Enterococcus (1)</td>
<td>Proteus (1)</td>
<td>S aureus (1)</td>
<td>Bacteroides (1)</td>
</tr>
<tr>
<td>S aureus (1)</td>
<td>Pseudomonas (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteroides (1)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

### TABLE 3. SBI by RSV Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>RSV Positive (N = 269)</th>
<th>RSV Negative (N = 979)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SBI</td>
<td>17/244 (6.8%)</td>
<td>116/925 (12.2%)</td>
<td>0.6 (0.3%–0.9%)</td>
</tr>
<tr>
<td>UTI</td>
<td>14/261 (5.4%)</td>
<td>98/966 (10.1%)</td>
<td>0.5 (0.3%–0.9%)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>3/267 (1.1%)</td>
<td>22/968 (2.3%)</td>
<td>0.5 (0.1%–1.6%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0/251 (0%)</td>
<td>8/938 (0.9%)</td>
<td>0.06 (0.04%–0.17%)</td>
</tr>
</tbody>
</table>

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Comparison of Enrolled and Missed Patients

The mean age of missed patients was 38 days (SD: ±15 days); and the mean maximum temperature was 38.6°C (SD: ±0.5°C). Overall, there was no significant difference in rate of SBI between enrolled and missed patients (11.9% vs 10.3%; RR: 1.2; P = .42). There was, however, a slightly higher rate of UTI in the enrolled patients than in missed patients (9.7% vs 6.6%; RR: 1.5; P = .04). In addition, there was a higher rate of RSV positivity in the missed patients (27% vs 22%; RR: 0.8; P = .06), which likely reflects selective RSV testing in missed patients. There were no differences between enrolled and missed patients with regard to bacteremia and meningitis.

DISCUSSION

In this prospective, multicenter study, we found that young febrile infants with RSV infections are less likely to have SBIs than those who test negative for RSV. The febrile infants with RSV infections, however, had clinically important rates of UTIs and, to a lesser extent bacteremia. Thus, it seems that one cannot necessarily obviate urine and blood testing in these febrile infants on the basis of RSV status alone.

Many investigators have demonstrated that young febrile infants are at risk for SBI. Numerous studies have sought to develop and/or evaluate protocols and decision rules to identify infants who are at risk for SBI. None of these protocols or decision rules, however, has examined the presence of a viral infection, specifically RSV or bronchiolitis, as a risk factor for SBI.

Some investigators have demonstrated that the presence of a clinically recognizable viral syndrome reduces the likelihood of a bacterial infection. In these studies, however, SBIs still occurred, although infrequently. Other investigators have shown that the presence of a viral infection may in fact predispose patients to subsequent bacterial infection. Few studies, however, have looked at the prevalence of SBI in febrile infants with RSV or bronchiolitis at the time of presentation. In 1 such study, the investigators prospectively examined febrile children who were younger than 2 years and had bronchiolitis and reported a 1.9% rate of UTI and no cases of bacteremia or meningitis among 156 febrile infants with bronchiolitis. Of the 36 febrile infants ≤60 days of age with bronchiolitis in that study, none had SBIs, although there was not sufficient power in this smaller subset to draw definitive conclusions.

Several retrospective studies have sought to determine the prevalence of SBI in young infants with bronchiolitis. One study evaluated the records of 282 hospitalized infants ≤60 days of age with bronchiolitis and found an SBI rate of 1.8%, whereas a similar study of 211 infants who were ≤90 days of age and presented to the ED with bronchiolitis reported no cases of SBI. These 2 studies included infants irrespective of presence of fever and did not specifically evaluate RSV testing. In a retrospective study of 2396 hospitalized infants with RSV, bronchiolitis, or pneumonia, the investigators reported 39 (1.6%) cases of SBI, although the specific organisms were suggestive of contaminants and not known pathogens.

A recent retrospective cohort study of 174 febrile infants who were younger than 8 weeks and had RSV infections identified 2 (1.1%) with SBI (both of whom had UTIs), which was significantly lower than the SBI rate of 12.6% in age-matched RSV-negative infants (RR: 0.09; 95% CI: 0.02–0.38). All of these studies were potentially limited by several factors because of the retrospective nature of the investigations: 1) the lack of a standardized evaluation of all infants, 2) the possibility that febrile infants with bronchiolitis were classified as having only an SBI once laboratory results became known, and 3) the possible inclusion of infants who were previously treated with antibiotics.

In the current study, 11.4% of febrile infants overall had SBIs, which is consistent with the SBI rate of 5.4% to 12.6% in febrile infants reported in the literature. Most SBIs in our study patients were UTIs, and the overall rate of UTI was 9.1% of interest. 5.4% of RSV-positive infants had UTIs compared with 10.1% in RSV-negative infants. Although these rates are similar to other studies that examined UTI in young febrile infants, the rate of UTI in the patients with RSV infection in our study was higher than that reported in previous studies of these infants. This may be explained by the retrospective nature of most of the previous studies and the lack of urine culture results on all enrolled patients in those studies.

In the current study, we applied conservative criteria to define UTI, requiring a positive UA in the definition if the colony count was 1 × 10^4 to 5 × 10^4 cfu/mL. We developed the criteria for the definition of UTI to reduce the likelihood of misclassifying infants with asymptomatic bacteriuria. Previous investigations have found a 0.5% prevalence rate of asymptomatic bacteriuria in young febrile infants. It has also been reported that routine UA may not be a sensitive marker for UTI in these young febrile infants; thus, the lack of pyuria in some patients does not exclude the possibility of a true UTI. The enhanced UA, which uses a hemocytometer, cell count, and Gram stain, is likely a more sensitive screening test for a true UTI.

The rate of RSV positivity was 21.5% in all infants and 60% in infants with bronchiolitis. This is similar to the overall rates of RSV infection in infants with bronchiolitis reported in previous studies. Of interest, only 38% of infants with documented RSV infection had clinical bronchiolitis. Other investigators have demonstrated that young infants with RSV infections frequently lack clinical signs and symptoms of bronchiolitis. To enhance the generalizability of our findings, we also examined patients with and without bronchiolitis, regardless of the RSV status, because RSV testing may not be available in all EDs.

There were important differences between our study and previous studies on this topic. First, because our study was prospective, all evaluations and data collection were standardized. Of enrolled pa-
patients, 93% had lumbar punctures performed and 91% had all 3 urine, blood, and CSF examined. Because our study was large, it was powered to detect important differences in SBI between groups. Because we conducted our study in multiple EDs, the results are likely widely generalizable to infants who are evaluated in a wide spectrum of EDs.

This study had some limitations worth noting. The initial sample size calculation was based on an overall SBI rate. Therefore, there was insufficient power to analyze differences in specific infection rates, such as bacteremia and meningitis, between RSV-positive and RSV-negative infants and in different age groups. The specific type of RSV testing was also not standardized across institutions. Although the rapid RSV immunoassay is highly sensitive and specific, the reference standard culture was not performed at all institutions. It is also possible that RSV positivity may have reflected colonization in some infants rather than acute infection, as RSV shedding may occur up to 21 days after infection. This is unlikely in our study, however, given the young age of the study population, with limited lifetime exposure to RSV and that all patients in the study had fever, suggesting acute infection. A final limitation is that the comparison of enrolled patients and missed patients revealed a slightly higher rate of UTI in the enrolled patients, which may suggest a small selection enrollment bias. Nevertheless, the rate of UTI in missed eligible patients was substantial, and the overall rate of SBI was not different between enrolled and missed patients.

We conclude that febrile infants who are ≤60 days of age and have RSV infections are at a lower risk for SBI than patients without RSV infection. The overall rate of SBI in RSV-infected infants, however, remains appreciable, mostly because of UTIs. In the youngest infants, those 28 days and younger, the risk of SBI is substantial and is not altered by the presence of RSV infection. Therefore, RSV infection does not obviate the need for a complete evaluation for SBI in these youngest infants. In older infants, those 29 to 60 days of age, RSV-infected patients continue to have a clinically important rate of UTIs. Therefore, urine testing cannot be omitted by the presence of RSV infection in these febrile infants. Additional study of an even larger cohort is needed to assess the risk of bacteremia and meningitis with greater confidence in young febrile infants with RSV infection.

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The results of this study were presented in part at the Ambulatory Pediatric Association National Meeting; Baltimore, Maryland; May 2002; and at the Society of Academic Emergency Medicine; St. Louis, Missouri; May 2002.

Other members of the Multicenter RSV-SBI Study Group included Melanie Stein-Etess, DO; Roy Vega, MD; Michael Bachman, MD; and Cara Mayerson, DO, from the Departments of Pediatrics and Emergency Medicine, Long Island Jewish-Schneider Children’s Hospital, New Hyde Park, New York; and Cynthia Jacobstein, MD, from the Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, and Division of Emergency Medicine, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania.

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**DISCOURAGING NOTE**

“Despite everything we’ve done—increased prenatal care, improved nutrition, various drugs to stop preterm labor—we’ve made no progress at all in stemming the growing tide of premature births. . . . Almost all the studies that have tried to reduce prematurity have failed. It’s very discouraging.”


Submitted by Student
Risk of Serious Bacterial Infection in Young Febrile Infants With Respiratory Syncytial Virus Infections

Deborah A. Levine, Shari L. Platt, Peter S. Dayan, Charles G. Macias, Joseph J. Zorc, William Krief, Jeffrey Schor, David Bank, Nancy Fefferman, Kathy N. Shaw, Nathan Kuppermann and for the Multicenter RSV-SBI Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics

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