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Pediatrics 2003;112;282

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American Academy of Pediatrics

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

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ABSTRACT. *Objective.* Neonates with fever generally undergo a full, invasive septic evaluation to exclude serious bacterial infection (SBI). The risk of SBI in febrile older infants and children with documented respiratory syncytial virus (RSV) infection has been found to be negligible. The purpose of this study was to investigate the prevalence of SBI in febrile infants who were younger than 8 weeks and had documented RSV infection and to compare the risk of SBI with control subjects who were febrile and RSV-negative.

Methods. This was a retrospective cohort study of infants who were age 8 weeks or less and presented with documented fever to the emergency department at an urban children's hospital in October through April during a 4-year period. RSV-positive cases were gender- and age-matched to febrile RSV-negative control subjects. Clinical characteristics and the rate of SBI were compared between the 2 groups.

Results. A total of 174 previously healthy infants with fever and a positive RSV antigen test were identified and matched with 174 previously healthy infants with fever and a negative RSV test. Infants with RSV infection were more likely to present with upper respiratory infection symptoms, increased work of breathing, and apnea. Overall, 2 patients in the RSV group had SBI (both with urinary tract infections), compared with 22 in the control group (relative risk: 0.009), 17 of which were urinary tract infections.

Conclusions. The risk of SBI in febrile infants with RSV infection seems to be very low, particularly in comparison with a control group of RSV-negative infants. These data suggest that full septic evaluations are not necessary in nontoxic-appearing infants with a positive RSV test. It seems to be prudent to examine the urine in these infants, as there is a clinically relevant rate of urinary tract infection. *Pediatrics* 2003;112:282-284; fever, infants, respiratory syncytial virus, septic evaluations.

ABBREVIATIONS. SBI, serious bacterial infection; RSV, respiratory syncytial virus; ED, emergency department; UTI, urinary tract infection; CSF, cerebrospinal fluid; WBC, white blood cell.

Fever is a common presenting complaint in the pediatric emergency department. The neonate who presents with fever is a particular challenge, as the clinical evaluation is often difficult and there is a relatively high rate of serious bacterial

infection (SBI) in this population. The established evaluation of the neonate with fever generally involves a conservative and invasive workup designed to exclude any SBI. The typical workup includes a complete blood count, blood culture, urinalysis, urine culture, and analysis of spinal fluid with culture.¹ In recent years, there have been efforts to define selected populations who may be at low risk for SBI^{2,3} and might be eligible for a modified evaluation. In particular, it has been believed that neonates with objective evidence of a viral infection may not need the complete septic workup.⁴⁻⁶

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract disease in neonates and young children and is responsible for 50% to 90% of hospitalizations for bronchiolitis.⁷ Patients with RSV infection may present with a variety of symptoms, including upper respiratory congestion, respiratory distress, apnea, and fever. Previous studies have demonstrated that the risk of SBI in infants and children with clinical bronchiolitis is minimal.^{4-6,8} Many of the subjects in previous studies, however, were not febrile and most were older than 8 weeks. Despite these studies, clinicians are left with uncertainty regarding the evaluation necessary to exclude SBI in the population of infants who have RSV and are younger than 8 weeks and febrile. The purpose of this study was to investigate the prevalence of SBI in febrile infants who were younger than 8 weeks and had documented RSV infection and to compare the risk of SBI with gender- and age-matched control subjects who were febrile and RSV-negative.

METHODS

This is a retrospective cohort study of infants who were treated at Vanderbilt University Medical Center and presented to the emergency department (ED) between October and April during 1997-2001. Patient charts were identified via a search of *International Classification of Diseases, Ninth Revision* codes and a review of the ED admitting logbook. All infants were 8 weeks of age or 56 days of life or younger, with estimated gestational age ≥ 34 weeks. All patients had documented fever ($\geq 100.4^{\circ}\text{F}$) and had RSV enzyme-linked immunosorbent assay antigen testing via nasopharyngeal wash (directogen kit by Becton Dickinson, Franklin Lakes, NJ; sensitivity: 97%/specificity: 97%). RSV testing was universally done on admitted febrile infants for isolation purposes during that time period. The usual evaluation of febrile infants at our institution includes a complete blood count; urinalysis; and culture of blood, urine, and spinal fluid. Which studies are performed is at the discretion of the physician evaluating the patient. Only patients who were admitted to the hospital were included in this study. Infants with congenital heart disease, bronchopulmonary dysplasia, hydrocephalus or other neurologic disorders, metabolic disorders, hematologic abnormalities, or other significant medical history were excluded.

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Received for publication Oct 28, 2002; accepted Jan 31, 2003.

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Control subjects consisted of gender- and age-matched infants who were admitted with fever and a negative RSV test. Gender was matched because of the possibility of differing risk of urinary tract infection (UTI) between boys and girls. Controls were also matched to within 1 week of the age of the subjects as risk of SBI might differ by age of the patient. All control subjects presented during the same October-to-April periods. Potential control subjects with significant past medical problems were excluded.

Data were collected on age, gender, temperature on presentation, preceding signs and symptoms, and history of apnea. Laboratory data collected included RSV antigen results, complete blood count with differential, blood culture, catheterized urinalysis and urine culture, and cerebrospinal fluid (CSF) analysis and culture. Only sepsis/meningitis evaluations performed on initial presentation were included. SBI was defined as growth of any known bacterial pathogen on any of the cultures obtained. All bacterial growths that ultimately were determined to be contaminants by the clinical team were not considered to be SBI.

Data are presented as the mean \pm standard deviation. Analysis of continuous variables was performed with the *t* test, and categorical data were analyzed with the χ^2 or Fisher exact test as indicated. Relative risk ratios and 95% confidence intervals were calculated. Statistical analysis was performed using Statview (SAS Institute, Inc, Cary, NC) and InStat software (Graphpad, Inc, San Diego, CA). The Vanderbilt University Institutional Review Board approved the study protocol.

RESULTS

A total of 174 patients who were younger than 8 weeks, had a positive RSV test, and met the inclusion and exclusion criteria were identified. An additional 174 age- and gender-matched control subjects who met the same inclusion and exclusion criteria were also identified. All patients and control subjects were hospitalized for their illness. There were 89 (51%) boys in each group with a mean age of 4.6 ± 2.0 weeks. Mean temperature on presentation to the ED for cases was $101.5 \pm 0.9^\circ\text{F}$ and for control subjects $101.5 \pm 0.9^\circ\text{F}$ ($P = .85$).

Table 1 describes clinical presentation differences between the 2 groups. Subjects with RSV infection were more likely to have upper respiratory infection symptoms compared with the control subjects, and the presence of RSV infection was strongly associated with increased work of breathing. In addition, RSV patients were more likely to have had a documented apneic episode at presentation compared with control subjects.

The mean white blood cell (WBC) count did not differ significantly between the 2 groups. The mean WBC count was $11.8 \pm 3.9 \times 10^9/\text{L}$ in cases and $12.0 \pm 6.9 \times 10^9/\text{L}$ in control subjects ($P = .83$). The percentage of neutrophils in the WBC was also similar between the groups, with a mean of 35.9% in the cases and 36.6% in control subjects ($P = .70$).

The culture results are described in Table 2. Overall, there were 2 positive cultures in the RSV group as opposed to 22 positive cultures in the control group

TABLE 2. Culture Results in Patients With and Without RSV Infection

	RSV-Positive (No. Positive/ No. Tested)	Controls (No. Positive/ No. Tested)
Bacteremia	0/170	5/171
Urinary tract infection	2/147	17/166
Meningitis	0/111	1/153
Overall serious bacterial illness	2/174	22/174*

* One patient had a positive culture from both blood and spinal fluid.

(relative risk: 0.09; 95% confidence interval: 0.02–0.38; $P < .0001$). Both positive cultures in the RSV group were from urine specimens and grew *Escherichia coli*. There were no positive blood or CSF cultures in the RSV group. In the control group, positive cultures included 17 from urine, 5 from blood, and 1 from CSF (1 subject had both a positive blood and CSF culture).

DISCUSSION

Our results provide important information in demonstrating that the risk of SBI is low in the population of febrile infants with RSV infection. The risk of bacteremia or meningitis seems to be minimal, particularly when compared with a control population of febrile infants without RSV infection. These data, in conjunction with data from previous studies, confirm that the risk of SBI in patients with RSV infection is very low.

In 1988, Hall et al⁸ conducted a prospective cohort study to determine the risk of secondary SBI in hospitalized patients who were younger than 3 years and had documented RSV infection. They found that 1.2% of these patients had secondary SBI. Their study also included high-risk patients such as those with congenital heart disease, prematurity, and bronchopulmonary dysplasia. The low prevalence of secondary SBI is still notable despite their inclusion of high-risk subjects. This study did not, however, concentrate on our population of interest, the previously healthy febrile infant with RSV. Fewer than one half of their subjects were febrile, and most were not younger than 8 weeks. The study also concentrated primarily on secondary infections, rather than on those with concurrent bacterial illness at presentation.

Kupperman et al⁹ conducted a prospective study examining febrile children who were younger than 2 years with and without bronchiolitis. Forty-six percent of the subjects with bronchiolitis were RSV-positive. They found that none of the patients with

TABLE 1. Clinical Presentation of Febrile Infants With and Without RSV Infection

	RSV-Positive (n = 174)	Controls (n = 174)	Relative Risk (SD)	P Value
URI symptoms	154	92	1.7 (1.4–1.9)	<.0001
Respiratory distress	66	13	5.1 (2.9–8.9)	<.0001
Lethargy	72	66	1.1 (0.8–1.4)	.58
Fussiness	27	66	0.4 (0.3–0.6)	<.0001
History of apnea	21	3	7.0 (2.1–23.0)	.0002

SD indicates standard deviation; URI, upper respiratory infection.

bronchiolitis had bacteremia, compared with 2.7% of control subjects. In addition, 1.9% of those with bronchiolitis had urinary tract infections compared with 13.6% of control subjects. Their population differed from ours as only 15% were younger than 2 months, and many did not have RSV infection. Nevertheless, their findings were very similar to ours, despite the population differences.

Liebelt et al⁴ conducted a retrospective chart review of 211 infants who were younger than 3 months and had clinical bronchiolitis (82% were RSV-positive). They found no cases of bacteremia, UTI, or meningitis in this population. Although they concentrated on a neonatal population, it is important to note that only 42% of their patients were febrile. Antonow et al⁵ conducted a retrospective study of 282 infants who were younger than 60 days and had bronchiolitis. Eighty-three percent were RSV-positive, and documented fever was present in 65%. They found a 3% rate of SBI (2% UTI, 0.7% bacteremia, 0.7% meningitis). The 2 patients with either meningitis or bacteremia were clearly very ill on presentation. More recently, Purcell and Fergie⁶ reviewed the medical records of 2396 infants and children who were younger than 2 years and admitted with RSV bronchiolitis. In this study, 33% were younger than 90 days; fever was not clearly reported. Twelve (0.5%) had a positive blood culture, but all were believed to be contaminants. Twenty-seven (1.1%) had urine cultures positive for a typical uropathogen. They concluded that performing a full septic workup in infants and children with bronchiolitis and a positive RSV antigen test, with or without fever, is not routinely indicated.

In our study, we concentrated solely on febrile infants who were younger than 8 weeks, a population that is particularly difficult to evaluate clinically and has an increased risk of SBI. Other studies suggest that the rate of SBI in febrile infants with RSV is low, but these studies might underestimate the risk as they also include older populations or include both those with and without fever. Therefore, our data are a valuable addition to previous information regarding management of febrile infants with RSV.

This study has several limitations. Most important, this was a retrospective study. There was a possibility that we missed patients in our search. Therefore, we conducted a double search, using both a computerized medical record search and a hand search of the admitting log to minimize this effect. Secondary to its retrospective nature, we relied on the testing that had already been performed and its accuracy. Although not every patient underwent the full septic evaluation, almost all patients had blood culture testing. Full hospital charts were reviewed to ensure that

no serious complications or infections were missed. Although the RSV antigen is highly specific, there is a possibility that there were false-negative results contributing to a misclassification bias. If anything, any misclassification bias involving false-negative testing would have strengthened the results of the study.

In reviewing the literature, our data provide important information about a population of patients that had been understudied in previous investigations. Febrile patients who are younger than 8 weeks are the most difficult population to determine whether complete septic evaluations could be modified. We limited our investigation to this population and, on the basis of the data, conclude that the risk of SBI is very low. However, there is still a clinically relevant rate of UTI. Therefore, we continue to recommend obtaining urine cultures in febrile infants with RSV. It is important to note that our data reveal minimal power in the height of the temperature and WBC count in discriminating between SBI and viral illness. Our results, looked at in conjunction with other studies, also suggest that blood cultures and spinal fluid analysis can be withheld in infants who do not seem to be septic. It is important to stress that the practitioner must use clinical judgment in evaluating each patient, especially those who seem toxic. Overall, complete septic evaluations do not seem to be necessary in previously healthy, febrile infants with documented RSV infection, as the risk of SBI is low.

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