BRIEF REPORT

# Association of Cough Status With Bacterial Infections in Febrile Infants

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ABSTRACT

**OBJECTIVES:** To examine the association between cough status and bacterial infections (BIs) to more accurately stratify risk and predict BIs in febrile infants.

**METHODS:** A retrospective cohort study was performed by identifying all infants ≤60 days old with temperature ≥38°C at an urban pediatric emergency department from 2014 to 2016. The Rochester Risk model was used to stratify risk. Cough status (with or without) was the main covariate of interest. The primary outcome was a BI, including urinary tract infection, bacteremia, or meningitis. Analyses consisted of descriptive statistics, simple and multiple regression to compare the odds of BI on the basis of cough status, as well as $\chi^2$ statistics to compare the BI rates among high-risk infants with and without cough.

**RESULTS:** Of 508 febrile infants ≤60 days old, 46 (9.1%) had a BI, 13 of which were either bacteremia or meningitis. There were no BIs among low-risk infants with a cough. The odds of BI increased progressively, peaking at 14.6 (95% confidence interval: 4.3–49.7) for high-risk infants without a cough. The adjusted odds of BI among infants with cough was 0.47 (95% confidence interval: 0.22–0.99).

**CONCLUSIONS:** In our findings, an inverse relationship is demonstrated between presence of cough and odds of BI, suggesting that cough status may be a useful marker of viral infections in febrile infants. Considering that detecting cough status is noninvasive, inexpensive, and immediately available, it represents an attractive value-based risk factor to enhance current BI prediction models.

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**POTENTIAL CONFLICT OF INTEREST:** Dr Yaeger previously published an article that included a subset of patients from this study (Yaeger JP, Moore KA, Melly SJ, Lovasi GS. Associations of Neighborhood-Level Social Determinants of Health with Bacterial Infections in Young, Febrile Infants. *J Pediatr*. 2018;203:336–344). However, the work for this current study uses a larger sample population, involves a different research question, evaluates a different outcome, and uses different methods and statistical analyses. The data from this research were also presented as an abstract at the Pediatric Hospital Medicine Conference in July 2018. This article is being submitted only to *Hospital Pediatrics* and will not be submitted elsewhere while under consideration.

Dr Klouda conceptualized and designed the study, collected data, drafted the initial manuscript, and revised the manuscript; Dr Wang conducted the initial and final analyses and reviewed and revised the manuscript; Dr Yaeger conceptualized and designed the study, designed the data collection instruments, collected data, and reviewed and revised the manuscript; and all authors approve the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Management of the febrile infant is a cornerstone of pediatrics because ~250 000 infants <60 days of age are brought to medical attention for fever each year.[1–3] Because of immature immune systems,[4] febrile infants are at risk for a bacterial infection (BI), including urinary tract infection, bacteremia, and meningitis. Diagnosis of a BI is challenging because fever is often the single, sentinel sign of infection, and infected infants can often appear well. However, if left untreated, BIs can have devastating consequences.[5]

In previous studies, researchers have consistently demonstrated a lower risk of BIs among febrile infants with a viral respiratory tract infection.[6–16] This finding has proved valuable in refining the risk of BIs[8,17]; however, viral detection tests are expensive and are not consistently performed on-site in rural and community settings, meaning that results may not be available for several days. In addition, positive viral test results from the nasopharynx do not always correlate with clinical disease.[18,19] In findings from earlier studies in the 1980s, it is suggested that febrile infants with signs and symptoms of respiratory infection may have fewer BIs.[20,21] These studies, however, were limited by small sample sizes, the use of varying definitions of respiratory symptoms, and few infants with bronchiolitis. More recently, this topic has been more systematically examined, as several studies have demonstrated that febrile infants with clinically diagnosed respiratory viral infections, such as bronchiolitis, have lower rates of BIs.[22–24] Clinical history markers, including cough, wheezing, and rhinorrhea, are noninvasive, inexpensive, instantly available, and may improve the accuracy in detecting infants at high risk of BI. The objective of this study was to evaluate whether cough status may be associated with BIs. We hypothesized that the presence of cough would indicate presence of a viral infection and lower odds of BI.

## METHODS

This pilot study was part of a larger retrospective cohort study from a single, urban, inner-city pediatric emergency department (ED) with ~70 000 annual encounters. The aim of the larger study was to develop a novel BI predictive model using clinical history risk factors. Our institutional review board approved this study. First, we identified all infants 0 to 90 days old who were brought to the ED between January 1, 2014, and December 31, 2016. Next, using a standard abstraction tool, 3 members of the research team manually reviewed the electronic medical record (EMR) of each infant for presence of fever. Inclusion criteria for this study were as follows: (1) age 0 to 60 days old; (2) fever, defined as a temperature ≥38°C, within 6 hours of arriving to the ED or reported by the caregiver from a measurement before arrival; and (3) documentation of cough status (with or without). We used the Rochester Risk (RR) model to differentiate high-risk from low-risk infants (Supplemental Table 4).[25] Documentation and laboratory studies were performed at the discretion of the treating clinician. One author (J.P.Y.) reviewed the abstracted EMR data to assign risk status. On the basis of our clinical experience, it is common practice for low-risk clinical history markers to be omitted from the clinician's documentation. Therefore, we considered missing data as negative for purposes of risk stratification.

We collected demographic characteristics, including age, sex, race and ethnicity, and insurance type for each infant. Gestational age was recorded as term (≥37 weeks) or preterm (<37 weeks). To identify chronic medical conditions, 1 author (J.P.Y.) manually reviewed all records and created a dichotomous variable (yes or no) on the basis of the likelihood that the condition may contribute to the development of a BI.[26] Examples of chronic medical conditions included vesicoureteral reflux, panhypopituitarism, and idiopathic neutropenia.[26] We considered a social concern as being present if it was documented as a factor in the clinical decision-making. Per standard practice, ED clinicians consistently used a standard template that included a "Review of Systems" noting the presence or absence of cough. Cough status was recorded if explicitly documented as present or absent in the EMR.

The main outcome was BI, defined as either urinary tract infection, bacteremia, or meningitis. Urine cultures were considered positive results if there were signs of inflammation in the urinary tract, including ≥5 white blood cells per high-power field (unspun) or the presence of leukocyte esterase (at least trace), and growth of at least 10 000 colony-forming units per milliliter of a single organism from a catheterized specimen that was treated clinically as a pathogen.[27] Bacteremia and meningitis were defined as growth of a single organism from blood or cerebrospinal fluid cultures that was treated clinically as a pathogen.

We performed descriptive statistics on patient characteristics, including means, medians, and interquartile ranges for continuous variables and frequencies and percentages for categorical variables. Using simple logistic regression, we estimated the odds of BI among groups with different RR (low or high) and cough status (with or without). We also performed multiple logistic regressions to further evaluate the association of cough with BIs after adjusting for potential confounders. A priori variables consisted of age, sex, race and ethnicity, insurance type, RR status, cough status, duration of symptoms, and respiratory season. We used stepwise model selection to identify variables for inclusion. We also used $\chi^2$ statistics for proportions to compare rates of urinary tract infections, bacteremia, and meningitis between high-risk infants with and without cough. Statistical analyses were performed with SAS (version 9.4; SAS Institute, Inc, Cary, NC).

## RESULTS

A total of 508 infants were ≤60 days old with fever and cough data available. Four infants were excluded because of absence of documented cough status, none of whom had a BI. The median age was 40 days, a majority were male, half were Hispanic, and >90% had public insurance (Table 1). Almost half of infants were high risk (47%), and 223 (44%) had a cough. Forty-six infants (9%) had a BI, 13 of which were due to bacteremia or meningitis (Table 2). For risk stratification purposes, 8% of data were missing, over half of which was due to

**TABLE 1** Subject Characteristics ($N = 508$)

| Characteristic | *n* (%) |
|---|---|
| Median age in d (IQR) | 40 (26) |
| Male | 291 (57) |
| White or other | 52 (10) |
| African American | 195 (38) |
| Hispanic | 256 (50) |
| Unknown race or ethnicity | 5 (1) |
| Term | 474 (93) |
| Chronic medical condition | 14 (3) |
| Public insurance | 465 (92) |
| Rochester high risk | 237 (47) |
| Cough present | 223 (44) |
| BI | 46 (9) |

IQR, interquartile range.

unclear documentation of the infant's course in the newborn nursery.

Cough was absent in 34 infants with a BI (74%). The frequency of BIs in high-risk infants was 18% compared with 1% in low-risk infants. For the simple regression analysis, because no low-risk infants with cough had a BI, we used the low-risk without cough group as the reference. The odds of BI increased in a stepwise fashion, peaking with high-risk infants without cough, whose odds of BI was 14.6 (95% confidence interval [CI]: 4.3–49.7) (Table 3). For the multiple regression analysis, presence of cough was associated with lower odds of BI (adjusted odds ratio: 0.47; 95% CI: 0.22–0.99), and high-risk RR status was associated with higher odds of BI (adjusted odds ratio: 25.5; 95% CI: 7.4–88.3). High-risk infants without cough were significantly more likely to be diagnosed with a urinary tract infection compared with high-risk infants with cough (22.9% vs 9.3%; $P = .007$). Infants with missing observations for purposes of RR stratification were older than infants with complete data (median = 44 days versus 37 days; $P < .00001$) and had lower rates of BI (7.7% vs 10.7%), although this difference was not statistically significant. We were unable to detect a significant difference in rates of bacteremia or meningitis for high-risk infants on the basis of cough status. Of 3 low-risk infants with a BI, none had a cough.

**TABLE 2** Etiology and Type of BI, Categorized by Age

| | 0–30 d | 31–60 d | Total |
|---|---|---|---|
| No. febrile infants | 148 | 360 | 508 |
| No. infants with any BI, *n* (%) | 21 (14.2) | 25 (6.9) | 46 (9.1) |
| No. infants with bacteremia or meningitis, *n* (%) | 4 (2.7) | 9 (2.5) | 13 (2.6) |
| No. infants with UTI, *n* (%) | 17 (11.5) | 16 (4.4) | 33 (6.5) |
| Organism recovered from urine (*n*) | *Escherichia coli* (12)<br>*Klebsiella pneumoniae (3)*<br>*Enterococcus faecalis (1)*<br>Group B *Streptococcus* (1) | *E coli* (13)<br>*E faecalis* (1)<br>*Citrobacter koseri* (2) | — |
| No. infants with UTI and bacteremia, *n* (%) | 0 | 2 (0.6) | 2 (0.4) |
| Organism recovered from urine and blood (*n*) | — | *E coli (2)* | — |
| No. infants with bacteremia only, *n* (%) | 3 (2) | 5 (1.4) | 8 (1.6) |
| Organism recovered from blood (*n*) | Group B *Streptococcus* (3) | Group B *Streptococcus* (2)<br>*Salmonella* species (1)<br>*K pneumoniae (1)*<br>*Staphylococcus aureus (1)* | — |
| No. infants with meningitis only, *n* (%) | 1 (0.7) | 0 | 1 (0.2) |
| Organism recovered from cerebrospinal fluid (*n*) | *E coli* (1) | — | — |
| No. infants with bacteremia and meningitis, *n* (%) | 0 | 2 (0.6) | 2 (0.4) |
| Organism recovered from blood and cerebrospinal fluid (*n*) | — | Group B *Streptococcus* (2) | — |

UTI, urinary tract infection; —, not applicable.

## DISCUSSION

To our knowledge, this is the first study to examine the relationship between cough status and BIs in febrile infants. Our results indicate that absence of cough is associated with BIs in febrile infants ≤60 days old. This is the same inverse relationship observed in other studies that identified a higher frequency of BIs in febrile infants without a respiratory viral infection.[8–10,12–15,22,24] Cough status may be a useful marker of viral infections in febrile infants as suggested by our results. This is compelling because cough status is inexpensive, noninvasive, and often already collected during the clinical encounter, making it an attractive tool to improve value. Specialized equipment or staff are not needed, and the result is immediately available. Furthermore, the use of cough as a risk factor for BIs is attractive because it often indicates the presence of a current respiratory viral infection. In this study, it is indicated that an additional, easily obtained element of the clinical history may provide further guidance in the calculation of BI risk for febrile infants. As with any clinical decision, the application of these results would be contingent on the balance of risk tolerance and aversion in a particular clinician-caregiver dyad. Previously, Byington et al[8,28] identified a group of moderate-risk infants, categorized as high risk with virus, who could be safely discharged earlier and with fewer doses of empirical antibiotics than high-risk infants without virus. In our study, there was no such moderate-risk group because the frequency of BI was >10% for high-risk infants regardless of cough status. However, no low-risk infants with cough had a BI, suggesting that cough status may be used to identify febrile infants at extremely low risk of BI. Future researchers should investigate this finding to determine if low-risk febrile infants with cough may represent an additional BI risk subgroup and may benefit from a different management strategy than low-risk infants without cough or high-risk infants.

This study has several limitations. First, as a retrospective study, the treating clinician used their discretion in obtaining a medical

**TABLE 3** Odds Ratio Estimates by Risk and Cough Status

| RR | Cough Status | BI Rate; % (95% CI) | OR (95% CI) |
|---|---|---|---|
| Low | With | 0 out of 126 (0–2.4) | — |
| Low | Without | 3 out of 145; 2.1% (0.4–6.2) | 1 (reference) |
| High | With | 12 out of 97; 12.5% (7.1–20.5) | 8.7 (2.3–32.5) |
| High | Without | 31 out of 140; 22.1% (16–29.8) | 14.6 (4.3–49.7) |

OR, odds ratio; —, not applicable.

history and performing laboratory tests, resulting in missing data, which we considered as negative for purposes of risk stratification. In a sensitivity analysis, it was demonstrated that infants with missing data were older and had a lower rate of BI, suggesting this was a reasonable approach. Second, this study represents the experience at 1 institution. Further investigation is needed at other sites to attempt to replicate these findings. Third, although there is no reason to suspect that cough status was recorded erroneously in the EMR, it is possible. We think that high rates of completion of a standard template to collect the medical history and cough status mitigates this concern, but further investigation of the reliability of reported cough status may be warranted. Fourth, because of a limited sample size, this study was not powered to detect small but potentially clinically meaningful differences in BIs across the 4 risk groups.

## CONCLUSIONS

In findings from this pilot study, it is demonstrated that cough status is inversely associated with BIs and may represent an inexpensive, noninvasive, value-based clinical history marker of viral infections for febrile infants. Future researchers should use larger data sets to detect the infrequent BI rate in low-risk infants with cough. In addition, researchers should examine how cough status compares with viral testing results as well as how this information, and other clinical history markers, may be integrated with current low-risk models to improve the prediction of BIs in febrile infants.


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