National Survey on the Impact of Viral Testing for the ED and Inpatient Management of Febrile Young Infants

Brett Burstein, MD CM, PhD,* Alexander Sasha Dubrovsky, MD CM, MSc,* Andrew Walsh Greene, MD CM, MSc,* Caroline Quach, MD, MScb,c

OBJECTIVE: Well-appearing febrile infants with viral illnesses cannot be distinguished from those with occult life-threatening infections. Infants with respiratory viruses are less likely to have serious bacterial infections; however, current risk-stratification criteria predate widespread viral testing and there are limited data to safely inform physician management with this now common diagnostic tool. This study sought to explore the possible impact of respiratory virus testing on clinical decision-making for the management of febrile young infants <6 weeks old.

METHODS: A scenario-based survey was sent to emergency department (ED) and inpatient physicians at all 16 Canadian tertiary pediatric centers. Participants were asked questions regarding management decisions with and without results of respiratory virus testing.

RESULTS: Response rate was 78% (n = 330; 190 ED, 140 inpatient). Detection of a respiratory virus reduced admission rates among 3-week-old (83% vs 95%, P < .001) and 5-week-old infants (36% vs 52%, P < .001). Similarly, empirical antibiotic treatment was decreased by detection of a respiratory virus for 3-week-old (65% vs 92%, P < .001) and 5-week-old infants (25% vs 39%, P < .001). Management of 5-week-old infants differed between ED and inpatient physicians, both in the presence and absence of a respiratory virus. There was no consensus among inpatient physicians regarding admission duration for well infants with a detectable respiratory virus and otherwise negative workup.

CONCLUSIONS: Respiratory virus testing appears to influence clinical decision-making for febrile infants <6 weeks, reducing both rates of admission and antimicrobial treatment. Important work is needed to better understand how to safely incorporate viral testing for the management of this vulnerable patient population.
Nearly 20% of all emergency department (ED) visits for infants in the first 3 months of life are for the evaluation of fever.\textsuperscript{1,2} Although most of these infants have viral illnesses, approximately 10% will present with serious bacterial infections (SBIs), notably urinary tract infections, bacteremia, and meningitis.\textsuperscript{3-5} Identifying infants with viral illnesses from those occult SBIs is often not possible on the basis of history and physical examination alone. There are currently no nationally endorsed guidelines for the management of this patient population. There are, however, expert-based recommended approaches originally published more than 20 years ago.\textsuperscript{3,4} In general, these recommendations have suggested performing a full sepsis evaluation, including lumbar puncture, on all febrile neonates (>38.0°C) with hospital admission for empirical parenteral antibiotics, whereas nontoxic-appearing febrile infants aged 29 to 90 days can be managed by using low-risk criteria.\textsuperscript{5-7} However, available risk-stratification criteria predate the widespread use of respiratory virus testing and thereby do not incorporate the potential role of detecting a viral etiology on risk of SBIs. Although recent studies have suggested that infants with confirmed respiratory viruses are less likely to have SBIs,\textsuperscript{8-10} there are limited data to safely inform physician management with this now commonly used diagnostic tool.

To our knowledge, no study has assessed the impact of respiratory virus testing on clinical decision-making in the management of febrile young infants. As a first step in exploring the possible impact of viral testing, we conducted a scenario-based survey among both groups of physician stakeholders in the febrile infant’s care trajectory: pediatric ED and inpatient physicians. We hypothesized that respiratory virus testing would influence management decisions regarding empirical antibiotic treatment and patient disposition. Specifically, this study sought to (1) describe the management of febrile infants at 2 presenting age points, 3 weeks and 5 weeks; (2) compare the management of pediatric ED and inpatient physicians; and (3) determine how management of these patients is influenced by respiratory virus testing.

\textbf{METHODS}

\textbf{Participants}

The study population included ED and inpatient physicians at all 16 Canadian pediatric tertiary care centers. Pediatric ED physicians were contacted by using the 2014 iteration of the Pediatric Emergency Research of Canada (PERC) database as described previously.\textsuperscript{11} PERC is a research consortium aimed at facilitating multicenter studies and maintains an E-mail list of active physicians with a primary clinical appointment within a Canadian pediatric ED. In parallel, inpatient physicians were contacted by using E-mail information provided by Pediatric Division chiefs, and included all physicians attending on the general pediatric wards at 14 of 16 centers; 2 centers provided information of inpatient physicians agreeing in advance to be contacted for survey purposes. Physicians were grouped for analysis as either ED or inpatient physician according to clinical setting in which they practice more frequently, regardless of primary clinical appointment.

\textbf{Survey Administration}

An electronic scenario-based survey was developed and piloted for technical usability, clarity, and timing (LimeSurvey Software, Hamburg, Germany). The pilot group was composed of 10 individuals not included in the study. The survey was available in both Canadian national languages (French and English) and is provided in Appendix 1 (Online Supplemental Information). The survey described 2 hypothetical cases of febrile infants without an infectious focus, aged 3 and 5 weeks old. The 2 clinical scenarios presented were identical, differing only by the age of the infant in the case stem. Participants were asked multiple-choice and open-ended questions regarding management decisions with and without results of respiratory virus testing. Demographic data were also collected regarding the participant’s training, primary clinical setting, and access to respiratory virus testing. The survey was administered from August to November 2014. Automatically generated survey reminders were sent biweekly for the first 8 weeks, followed by 2 final reminders in the last week of data collection. Surveys were submitted online anonymously and investigators remained blinded to individual responses.

\textbf{Statistical Analysis}

Data are presented as proportions for categorical data. The chi\textsuperscript{2} and McNemar tests were used to compare unpaired and paired proportions, respectively (GraphPad Prism software, v6.03 La Jolla, CA). A 2-tailed \( P < .05 \) was considered statistically significant, except for analyses of diagnostic investigations selected by physicians (Fig 1) that were corrected for multiple comparisons by applying a Bonferroni-type correction and using a 2-tailed \( P < .005 \). All survey fields were mandatory and therefore submitted surveys contained no missing data. No data on nonrespondents were obtained.

\textbf{Ethics Approval}

The study was approved by the Research Ethics Board of the McGill University Health Center and by the PERC Scientific Committee.

\textbf{RESULTS}

\textbf{Survey Response and Participant Demographics}

Eighteen inpatient physicians from 2 centers did not agree to be contacted for survey purposes. Surveys were e-mailed to a total of 430 physicians, among whom 6 respondents no longer work in a pediatric ED or inpatient setting and were therefore excluded. A total of 424 physicians were eligible to participate, of which 190 (57.8%) ED and 140 (42.4%) inpatient physicians completed the survey (77.8%). In terms of physician training, 85.5% of all participants were Canadian and board certified in pediatrics (Fellow of the Royal College of Canada, FRCP). Details of the primary clinical setting and training of respondents are shown in Table 1.

\textbf{Investigations Selected in 3- and 5-Week-Old Infants}

Physicians were asked to select investigations to be performed for a well-appearing febrile 3-week-old and 5-week-old infant at the time of presentation. Investigations most commonly selected for
Infants of both ages were urine culture, urine analysis, complete blood count, and blood culture (Fig 1). Overall, lumbar puncture was performed less frequently in 5-week-old compared with 3-week-old infants (48.5% vs 95.3%, \( P < .001 \)). Similarly, respiratory virus testing was performed less frequently in 5-week-old infants (34.2% vs 45.5%, \( P < .001 \)).

**Effect of Respiratory Virus Testing**

We examined the effect of a detectable respiratory virus on the decision to initiate empirical antibiotic treatment and patient disposition (Fig 2). Among all respondents, when given the results of viral testing, detection of a respiratory virus reduced admission rates among both 3-week-old (82.7% vs 94.5%, \( P < .001 \)) and 5-week-old infants (35.8% vs 52.1%, \( P < .001 \)). Similarly, initiation of empirical antibiotic treatment was decreased by detection of a respiratory virus among both 3-week-old (64.5% vs 91.5%, \( P < .001 \)) and 5-week-old infants (24.5% vs 39.1%, \( P < .001 \)).

Among physicians reporting that the detection of a respiratory virus would affect patient management, shorter antibiotic course (41.0%), shorter length of stay (56.0%), patient cohorting for infection control (10.0%), fewer investigations (8.0%), and parental reassurance (5.0%) were cited as factors that would be influenced. Additionally, these physicians reported that knowing the specific respiratory virus isolated (eg, rhinovirus versus adenovirus versus influenza) would

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**FIGURE 1** Investigations selected in 3-week-old (A) and 5-week-old infants (B). Data expressed as proportions selected by ED (n = 190, black bars) and inpatient physicians (n = 140, gray bars); CSF HSV, cerebrospinal fluid for herpes simplex virus; CBC, complete blood count; AST-ALT, aspartate transaminase and alanine transaminase. \( **P < .001 \) 5-week-old versus 3-week-old; \( ^{†††}P < .001 \) ED versus inpatient physicians.

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**TABLE 1** Clinical Setting and Training of Respondent Physicians

<table>
<thead>
<tr>
<th>Clinical setting of Practice</th>
<th>All Physicians, ( n (%) )</th>
<th>Emergency Department, ( n (%) )</th>
<th>Inpatient Ward, ( n (%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician training</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCFP (Certification in the College of Family Physicians)</td>
<td>3 (0.9)</td>
<td>3 (1.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>CCFP AND Emergency Medicine Fellowship</td>
<td>13 (3.9)</td>
<td>13 (8.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>FRCP Emergency Medicine (Fellow of the Royal College of Physicians of Canada)</td>
<td>17 (5.2)</td>
<td>17 (8.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>FRCP Pediatrics</td>
<td>282 (85.5)</td>
<td>145 (76.3)</td>
<td>137 (87.9)</td>
</tr>
<tr>
<td>FRCP Pediatrics</td>
<td>162 (49.1)</td>
<td>39 (20.5)</td>
<td>123 (87.9)</td>
</tr>
<tr>
<td>FRCP Pediatrics AND Pediatric Emergency Medicine fellowship</td>
<td>102 (30.9)</td>
<td>102 (53.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>FRCP Pediatrics AND non-Pediatric Emergency Medicine subspecialty fellowship</td>
<td>18 (5.5)</td>
<td>4 (2.1)</td>
<td>14 (10.0)</td>
</tr>
<tr>
<td>Non-Canadian Board Certified in Pediatrics</td>
<td>15 (4.5)</td>
<td>12 (6.3)</td>
<td>3 (2.1)</td>
</tr>
</tbody>
</table>
influence decisions of empirical antibiotic use (14.3%), admission (17.0%), and hospitalization duration (20.9%).

**Hospitalization Duration**

We analyzed trends in hospitalization duration as reported by inpatient physicians (Fig 3), as discharge planning for admitted patients is typically determined in this clinical setting rather than the ED. There was no consensus among inpatient physicians on the appropriate duration of hospitalization for clinically well-appearing infants with a detectable respiratory virus and otherwise negative workup. There was a clear effect of infant age, with more physicians reporting discharge times at ≤24 hours for 5-week-old infants (80.7% vs 45.0%, *P* < .001). Conversely, admission duration for 3-week-old infants was highly variable, with nearly equivalent proportions...
of inpatient physicians selecting lengths of stay ranging from <24 hours to 48 hours.

**Availability of Respiratory Virus Testing and Test Result Turnaround Time**

We examined the relationship between test access and result availability on the decision to perform respiratory virus testing. Nearly all respondent physicians (98.8%) confirmed having access to respiratory virus testing at their center, whereas most (69.7%) reported that the test results are generally only available after ≥12 hours. We analyzed the decision to perform respiratory virus testing by ED physicians in relation to test result turnaround time. Among ED physicians, those reporting a more rapid turnaround time for results were more likely to perform respiratory virus testing (Fig 4).

Significantly more viral testing was performed among ED physicians with test results available in <6 hours compared with those reporting test results available only after 24 hours, for both 3-week-old (59.0% vs 32.0%, \( P = .02 \)) and 5-week-old infants (41.0% vs 14.0%, \( P < .01 \)).

**Institutional Patterns of Respiratory Virus Testing**

We found significant variations in rates of respiratory virus testing between centers (Fig 5). Viral testing between centers ranged from 16.7% to 68.0% for 3-week-old infants, and from 0.0% to 63.0% for 5-week-old infants. Equally striking was the difference in viral testing within several individual centers, between infants of either 3 weeks or 5 weeks of age.

**Differences Between ED and Inpatient Physicians**

We compared the management decisions of ED and inpatient physicians. In terms of investigations, inpatient physicians were more likely than ED physicians to select C-reactive protein (CRP) for both 3-week-old (57.9% vs 37.4%, \( P < .001 \)) and 5-week-old infants.
infants (52.9% vs 34.2%, P < .001; Fig 1). Admission rates and empirical antibiotic use were similar among ED and inpatient physicians for 3-week-old infants, whereas management of 5-week-old infants differed significantly. Inpatient physicians were more likely than ED physicians to admit 5-week-old infants, both without results of respiratory virus testing (67.9% vs 40.5%, \( P < .001 \)) and in the presence of a detectable respiratory virus (42.1% vs 31.1%, \( P = .03 \)). Similarly, inpatient physicians were more likely to initiate empirical antibiotic therapy for 5-week-old infants (51.4% vs 30.0%, \( P < .001 \)), an effect that was not statistically significant when a respiratory virus was isolated (28.6% vs 21.6%, \( P = .17 \)).

**DISCUSSION**

Results from this case-based survey of most Canadian pediatric ED and inpatient physicians showed that the management of febrile infants aged <6 weeks differs in relation to infant age, as well as between ED and inpatient physicians. Overall, there exists significant practice variation in terms of investigations, empirical antibiotic treatment, and patient disposition. Importantly, among both ED and inpatient physicians, detection of a respiratory virus influenced physician decisions, reducing the rates of admission and antibiotic use for both 3- and 5-week-old infants. There was a wide variation on the perceived appropriate duration of hospitalization for well-appearing febrile infants with an identified respiratory virus, particularly in the first month of life. Our study also suggests that there may be significant differences in the utilization of respiratory virus testing, which varies by center and the turnaround time for test results.

Previous studies have shown that febrile infants aged <3 months with laboratory-confirmed viral infections are at lower risk of SBI.1–10 However, no studies have yet assessed the impact of respiratory virus testing on clinical care for this patient population. A recent retrospective study sought to assess the impact of targeted rapid influenza testing and its effect on ED patient management.12 This large national study included 4.9 million ED visits, including 53% pediatric patients <18 years. The authors concluded that rapid influenza testing influenced physician behavior, reducing diagnostic testing and antibiotic use. A triage-initiated rapid influenza testing protocol for febrile children aged 3 to 36 months significantly decreased additional diagnostic testing, time in the ED, and costs in those testing positive.15 Similarly, in a prospective randomized controlled trial of 391 patients aged 2 months to 21 years presenting to an urban pediatric ED, physician knowledge of a rapid influenza-positive test produced significant reductions in tests performed, antibiotic use, ED length of stay, and associated costs.14 These studies all assessed the impact of viral testing in older populations than our study. Moreover, these studies demonstrate the influence of rapid point-of-care viral tests on management, and it is not surprising that among ED physicians in our study, those reporting shorter test result turnaround times were more likely to perform viral testing.

Several studies on the management of febrile infants in the first 90 days of life have shown wide practice variation and limited compliance with published guidelines.15–23 Our finding of differences in management between pediatric ED and inpatient physicians is consistent with previous reports showing practice variation between pediatricians and general ED physicians,15–20 as well as among pediatricians.21–23 Most of these studies were undertaken before or shortly after the 1993 publication of clinical guidelines and long before the widespread use of respiratory virus testing. More recent studies have continued to demonstrate heterogeneous practice patterns.2,8,24–25 A recent retrospective analysis of infants 28 to 90 days of age presenting to a pediatric ED described significant practice variation in relation to infant age.25 Age-stratified rates of admission (23%), antibiotic use (51%), lumbar puncture (49%), and viral testing (49%) for infants aged 28 to 59 days were similar to those reported in our survey. In a multicenter prospective cohort study of 257 infants ≤90 days old treated in 6 Canadian pediatric EDs, significant variation was noted in rates of lumbar puncture, antibiotic use, and respiratory virus testing.24 Another large retrospective cohort study of febrile infants from 35.070 visits presenting to 37 pediatric EDs between 2011 and 2013 demonstrated both substantial patient- and hospital-level variation.2 The latter study did not assess rates of respiratory virus testing, and none of these 3 recent studies examined the impact of viral testing on treatment and disposition decisions.

Our study also revealed no consensus among inpatient physicians on the duration of hospitalization of febrile infants with confirmed respiratory viruses, particularly in the first month of life. Similarly, a recent national survey of all 25 inpatient pediatric departments in Israel revealed significant variation in admission and discharge criteria of febrile infants ≤60 days old, with only 36% of centers reporting the existence of written institutional protocols.26 Byington et al2 demonstrated that the implementation of a system-wide, evidence-based care process model across 21 hospitals in Utah reduced variations in care with improved infant outcomes and lower costs. This care process model integrates ED and inpatient management, and incorporates the use of yearlong viral testing for risk-stratification and management decisions. The model defines discharge eligibility for clinically well febrile infants with a confirmed viral illness as 24 hours, consistent with recent data supporting the safety of this approach.27,28 The model recommends that infants with only rhinovirus detected be managed as viral-negative, noting that the detection of rhinovirus alone is not significant in predicting a low risk for SBI. Recent clinical data suggest that rhinovirus infection among young infants may not predict the same course of illness as other viral pathogens.29 Our study found that among physicians electing to perform respiratory virus testing, >20% would alter decisions of hospitalization duration depending on which specific respiratory virus was isolated, and the notion that not all viruses confer the same risk-lowering benefit warrants further investigation.

Our study unexpectedly revealed a difference between pediatric ED and
inpatient physicians who use CRP testing for both 3- and 5-week-old infants. It is not readily evident why such a difference would exist. CRP is not included among known risk-stratification criteria for febrile infants. Of note, white blood cell count, which is incorporated into current risk-stratification criteria, has been shown to not reliably predict bacteremia nor bacterial meningitis. Several investigators, admission, and antibiotic use patterns reported in our survey for common clinical behavior. However, the practice scenarios may not predict it is possible that participant responses to hypothetical scenarios may not predict clinical behavior. In addition, the practice patterns reported in our survey for common investigations, admission, and antibiotic use are consistent with recently published studies of clinical practice. Notably, a prospective observational study conducted at 6 of the 16 tertiary pediatric centers participating in our survey, reported nearly identical rates of diagnostic testing, respiratory virus test utilization, antibiotic treatment, and admission for febrile infants <90 days old. Several recent studies also support that clinicians alter management decisions based on the results of viral testing, as suggested by our survey. The differences reported here between ED and inpatient management decisions could be greater than what we report. It is possible that there were hospital-specific factors (eg, variation in test turnaround time or febrile infant protocols) influencing diagnostic testing and management decisions of individual respondents, although despite this possibility, utilization of viral testing and admission duration were highly variable both between centers and among infants of both ages.

CONCLUSIONS

To our knowledge, this is the first study to assess the potential impact of respiratory virus testing on the clinical management of febrile young infants. Findings from this large, nationwide study highlight ongoing clinical equipoise that remains among both pediatric ED and inpatient physicians; a unified ED and inpatient guidelines could be of benefit. Viral testing is already a widely used diagnostic test, although important work is needed to better understand how to best implement testing and safely incorporate results into our management of febrile young infants. It remains to be determined if infants testing positive with different respiratory viruses can be managed in the same manner. Furthermore, there is a critical need to determine the true absolute risk of concomitant viral and SBIs. The safety of a management strategy that uses viral testing for risk stratification of febrile young infants is an important area of future study.

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