Infants 1–90 Days Old Hospitalized With Human Rhinovirus Infection

Jeffrey M. Bender,^{1,2*} Charla S. Taylor,¹ Joven Cumpio,³ Susan M. Novak,³
Rosemary C. She,³ Evan A. Steinberg,¹ and Elizabeth M. Marlowe³

¹Department of Pediatrics, Kaiser Permanente, Los Angeles Medical Center, Los Angeles, California

²Division of Pediatric Infectious Diseases, Department of Pediatrics, Children's Hospital Los Angeles, Los Angeles, California

³Southern California Permanente Medical Group Regional Reference Laboratories, Los Angeles, California

Background: Human rhinovirus (HRV) is a common cause of respiratory illness in children. The impact of HRV infection on 1- to 90-day-old infants is unclear. We hypothesized that HRV infection would be clinically similar to respiratory syncytial virus (RSV) infection in the hospitalized infants. **Methods:** We conducted a retrospective study of hospitalized infants, who were 1–90 days old, with HRV or RSV within the Southern California Kaiser Permanente network over a 1-year period (August 2010 to October 2011). **Results:** We identified 245 hospitalized infants who underwent respiratory virus testing. HRV was found in 52 infants (21%) compared to 79 infants (32%) with RSV ($P = 0.008$). Infants with HRV

infection experienced longer hospital stays compared to those with RSV (median length of stay 4 days vs. 3 days, $P = 0.009$) and had fewer short hospital stays ≤ 3 days ($P = 0.029$). There was a trend in infants with HRV infection to be younger ($P = 0.071$) and have more fevers ($P = 0.052$). **Conclusions:** Recent advances in diagnostics allow for identification of a broad range of viral pathogens in infants. Compared to RSV, HRV was associated with longer hospital stays. Additional studies and improved, more specific testing, methods are needed to further define the effects of HRV infection in infants 1–90 days old. J. Clin. Lab. Anal. 28:349–352, 2014. © 2014 Wiley Periodicals, Inc.

Key words: respiratory syncytial virus; febrile infant; serious bacterial infection; respiratory viruses

Abbreviations

HRV = human rhinovirus
RSV = respiratory syncytial virus
RVP = respiratory virus nucleic acid amplification panel
SBI = serious bacterial infection

INTRODUCTION

Human rhinovirus (HRV) is known as a common cause of illness in children (1) and is increasingly recognized as a large contributor to severe lower respiratory tract infections (2, 3). The management of the acutely ill infant 1–90 days old remains a challenge for clinicians as the presentations of viral and bacterial infections are nearly indistinguishable in this age group. The impact of HRV

infection on these young infants remains unclear as prior studies include children over 3 months of age. Furthermore, HRV is known to be commonly shed asymptomatically and is detectable by molecular testing weeks after an infection, especially in children. With expanded molecular respiratory virus testing becoming more commonplace in the hospital laboratory, a better understanding of HRV is needed to appropriately interpret positive results in this age group.

*Correspondence to: Jeffrey M. Bender, Division of Pediatric Infectious Diseases, Department of Pediatrics, Children's Hospital Los Angeles, 4650 Sunset Blvd, MS #51, Los Angeles, CA 90027. E-mail: jrbender@chla.usc.edu

Received 10 July 2013; Accepted 12 September 2013

DOI 10.1002/jcla.21692

Published online in Wiley Online Library (wileyonlinelibrary.com).

In contrast, the impact of respiratory syncytial virus (RSV) on infants has been well studied (4–6). A recent study showed that in children <2 years old, HRV infection was not associated with increased length of stay when compared to RSV (2). Another study of children <2 years old found no significant differences between HRV and RSV infections (7). We hypothesized that HRV infection would be clinically similar to RSV infection in hospitalized infants 1–90 days old. We sought to compare various clinical parameters of HRV and RSV infections in these young infants in order to better understand the role of HRV in this population.

MATERIALS AND METHODS

We conducted a retrospective study of hospitalized infants within the Southern California Kaiser Permanente (SCKP) network. Kaiser Permanente is a nonprofit, integrated, managed health care consortium. The SCKP region provides health care to over 3.3 million members. The institutional review board of SCKP reviewed and approved this study.

To be eligible for this study, infants were required to: (1) be 1–90 days old, (2) be hospitalized at one of the 14 SCKP hospitals, and (3) have a nasopharyngeal specimen that tested positive for HRV or RSV by respiratory virus nucleic acid amplification panel (RVP; Luminex Corp., Austin, TX). Co-infections were excluded. The RVP was performed according to the manufacturer's protocol. This test was only available for hospitalized patients and was performed at the discretion of the attending physician. The study assessed a 1-year period (August 1, 2010 to October 31, 2011).

Two of the authors (JMB and CST) reviewed the electronic medical records of the identified patients and abstracted data. Basic demographic data (age, sex, and presence of a high-risk medical condition) were obtained. Our primary measure of interest was length of stay. Secondary variables included: use of antibiotics (at any time during hospitalization), fever (at any time during hospitalization), serious bacterial infection (SBI) evaluation (culture obtained of at least two of the following: blood, urine, or cerebrospinal fluid), presence of an SBI (positive blood, urine, or cerebrospinal fluid culture), pneumonia (evidence of focal infiltrate as read by staff radiologists on chest radiograph), oxygen requirement (for respiratory distress and/or hypoxia), intensive care unit admission, mortality, and re-admission (within 1 month of initial hospitalization).

We compared the key clinical features between the two groups and analyzed the data using Fisher's exact test for categorical outcomes and Mann–Whitney/Wilcoxon two sample *t*-test for continuous variables. *P*-values and odds ratios were calculated as appropriate for each uni-

variate outcome variable. We incorporated variables with *P*-values of <0.10 from the univariate analysis into a logistic regression model. Odds ratios were again calculated. All statistical analyses were performed using Stata v10.0 software (StataCorp, College Station, TX).

RESULTS

We identified 245 hospitalized infants 1–90 days old who had RVP testing performed. We found 52 infants (21%) with HRV compared to 79 infants (32%) with RSV (*P* = 0.008). Influenza, adenovirus, human metapneumovirus, and parainfluenza were each identified in 1–3% of the infants tested. The six patients with HRV and another respiratory virus detected were excluded.

Table 1 demonstrates the clinical findings. Infants with HRV infection experienced longer hospital stays (median length of stay was 4 days compared to 3 days, *P* = 0.009) and on multivariate analysis had fewer hospital stays, ≤3 days (*P* = 0.029). There was no statistical difference in the presence of high-risk medical conditions. High-risk medical conditions seen with HRV infections in this study included five infants born prematurely (gestational age range: 29–34 weeks) compared to three infants with RSV born prematurely (gestational age range: 30–33 weeks; odds ratio 2.7 (0.49–18), *P* = 0.26).

Bacterial co-infections seen in the HRV group included *Klebsiella pneumoniae* bacteremia, *Streptococcus agalactiae* bacteremia, *Escherichia coli* urinary tract infection, and a *Streptococcus* species urinary tract infection. We identified one infant with RSV who also had *Enterococcus faecalis* bacteremia. Four of the infants with HRV on RVP testing also tested positive for enterovirus in CSF. There were no fatalities.

DISCUSSION

The evaluation of infants 1–90 days old for acute illness remains a challenge for clinicians. RSV and influenza virus have been well described as contributors to morbidity in young infants (4, 8). Recent advances in clinical diagnostics allow for identification of a broad range of viral pathogens. In our study, detection of HRV was associated with hospitalization of infants in lower numbers than RSV. As a group, infants 1–90 days old with HRV infection were hospitalized longer, but required less oxygen and had fewer episodes of clinical pneumonia. There was also a trend in infants with HRV infection to be younger and have more fevers. To our knowledge, no prior studies have looked at laboratory-proven HRV infections specifically in infants 1–90 days old.

RSV remains a significant source of infant morbidity and mortality (4) and is the most commonly detected virus in lower respiratory tract infections in children. HRV is

TABLE 1. Comparison of Infants 1–90 Days Old Infected With Rhinovirus or RSV Hospitalized at Southern California Kaiser Permanente hospitals Over a 1-Year Period (August 2010 to October 2011)

	Rhinovirus N = 52 (%)	RSV N = 79 (%)	Univariate odds ratio (95% confidence interval)	Unadjusted P-value	Multivariate odds ratio (95% confidence interval)	Adjusted P-value
Age <30 days	28 (53)	23 (29)	2.84 (1.29–6.29)	0.0045	2.21 (0.94–4.25)	0.071
Female sex	19 (37)	35 (44)	0.72 (0.33–1.57)	0.47		
High-risk medical condition	9 (17)	6 (7)	2.55 (0.74–9.26)	0.10		
Length of stay ≤3 days	20 (38)	43 (54)	0.52 (0.24–1.13)	0.074	0.33 (0.12–0.90)	0.029
Antibiotic use	35 (67)	46 (58)	1.47 (0.67–3.30)	0.36		
Fever	35 (67)	30 (38)	3.36 (1.52–7.54)	0.0013	2.79 (0.99–7.84)	0.052
SBI evaluation	33 (63)	26 (33)	3.54 (1.60–7.89)	0.0007	1.53 (0.55–4.27)	0.42
SBI	4 (8)	1 (1.3)	6.50 (0.61–324)	0.08	0.64 (0.08–5.03)	0.67
Pneumonia	7 (13)	34 (43)	0.21 (0.07–0.54)	0.0004	0.21 (0.07–0.59)	0.003
Oxygen requirement	16 (31)	44 (56)	0.35 (0.16–0.78)	0.007	0.36 (0.13–1.0)	0.050
ICU admission	8 (15)	7 (9)	1.87 (0.55–6.49)	0.27		
Re-admission	1 (2)	3 (4)	0.50 (0.009–6.41)	1		

now recognized as the second most common virus associated with severe disease (2, 7, 9). In one recent study of children less than 5 years old hospitalized for an acute respiratory illness, 17.4% tested positive for HRV (1), similar to our study. Though HRV was associated with hospitalization less frequently than RSV in our study, it was more common than influenza and other respiratory viruses and thus may warrant consideration in terms of prevention and treatment efforts.

Infants 1–90 days old with HRV infections experienced longer hospital stays compared to those infants with RSV infection. Further, there was a trend toward younger age and more fevers in infants with HRV. Infants presenting with fever without classical bronchiolitis symptoms may require more evaluation to rule out SBIs. However, even after accounting for age and presence of fever in the multivariate analysis, infants with HRV remained hospitalized longer than those with RSV. We hypothesize that the reason for prolonged hospital stay is multifactorial and may be related to the infant immune system. The role of respiratory viruses in the development of the young immune system remains unclear, but studies suggest that HRV may alter innate responses and lead to more severe disease (10, 11).

A number of researchers evaluated the risk of concomitant SBI in infants with RSV infection to be 1–3% (5, 6), similar to our findings in infants with RSV. The risk of SBI in our study was higher in infants with HRV infection, though this was not found to be significantly different from RSV on multivariate analysis. One study from Spain found HRV to be commonly associated with *Streptococcus pneumoniae* pneumonias in older children (12). In contrast, infants in our study were less likely to be diagnosed with pneumonia than those with RSV. Indeed, interpretation of positive HRV results in infants is confounded by

its high prevalence rate, broad spectrum of pathogenicity, and frequent presence during infection with other human pathogens.

This retrospective study has a number of limitations. SCKP does not currently have a standardized protocol in place for the evaluation of hospitalized infants. Although we did not perform prospective RVP testing on every infant presenting to SCKP hospitals, our study does reflect the real life experience of how viral testing may be used in the community. This study represents a single year. Testing for HRV was not done prior to 2010, but hospital admissions in this age group did not appear to be abnormal over the study period compared to prior years. Despite a relatively small sample size, SCKP covers a large and diverse population.

Our laboratory uses a United States Food and Drug Administration (FDA) approved platform for the detection of respiratory viruses that does not distinguish enterovirus from HRV. The four children with enterovirus in the cerebrospinal fluid were likely shedding enterovirus from nasal secretions as well and not HRV. On further analysis (results not shown), results of our study were not affected by these four possible enterovirus infections. Nonetheless, these cases demonstrate the confusion that such nonspecific assays may present and the importance of future FDA-approved commercial platforms to distinguish HRV from enterovirus.

Differentiating the nearly identical presentations of viral infections from more SBIs in acutely ill infants remains a challenge for those caring for children. The results of this study could help outline how expanding molecular respiratory viral testing may be utilized in such evaluations to provide more information for the clinician. Additional studies and improved, more specific testing, methods are

needed to further define the contribution of HRV infection in infants 1–90 days old.

ACKNOWLEDGMENTS

The authors thank the continued efforts of the staff in the clinical microbiology laboratory of the Southern California Permanente Medical Group Regional Reference Laboratories.

REFERENCES

1. Iwane MK, Prill MM, Lu X, et al. Human rhinovirus species associated with hospitalizations for acute respiratory illness in young US children. *J Infect Dis* 2011;204(11):1702–1710.
2. Mansbach JM, Piedra PA, Teach SJ, et al. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. *Arch Pediatr Adolesc Med*. 2012;166(8):700–706.
3. Louie JK, Roy-Burman A, Guardia-Labar L, et al. Rhinovirus associated with severe lower respiratory tract infections in children. *Pediatr Infect Dis J* 2009;28(4):337–339.
4. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med Pediatr Infect Dis J* 2009;360(6):588–598.
5. Levine DA, Platt SL, Dayan PS, et al. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. *Pediatrics* 2004;113(6):1728–1734.
6. Titus MO, Wright SW. Prevalence of serious bacterial infections in febrile infants with respiratory syncytial virus infection. *Pediatrics* 2003;112(2):282–284.
7. van Leeuwen JC, Goossens LK, Hendrix RM, van der Palen J, Lusthusz A, Thio BJ. Equal virulence of rhinovirus and respiratory syncytial virus in infants hospitalized for lower respiratory tract infection. *Pediatr Infect Dis J* 2012;31(1):84–86.
8. Bender JM, Ampofo K, Gesteland P, et al. Influenza virus infection in infants less than three months of age. *Pediatr Infect Dis J* 2010;29(1):6–9.
9. Calvo C, García-García ML, Blanco C, et al. Role of rhinovirus in hospitalized infants with respiratory tract infections in Spain. *Pediatr Infect Dis J* 2007;26(10):904–908.
10. García C, Soriano-Fallas A, Lozano J, et al. Decreased innate immune cytokine responses correlate with disease severity in children with respiratory syncytial virus and human rhinovirus bronchiolitis. *Pediatr Infect Dis J* 2012;31(1):86–89.
11. Takeyama A, Hashimoto K, Sato M, et al. Rhinovirus load and disease severity in children with lower respiratory tract infections. *J Med Virol* 2012;84(7):1135–1142.
12. Launes C, de-Sevilla MF, Selva L, Garcia-Garcia JJ, Pallares R, Muñoz-Almagro C. Viral coinfection in children less than five years old with invasive pneumococcal disease. *Pediatr Infect Dis J* 2012;31(6):650–653.