

# Opportunities for early therapy of respiratory syncytial virus (RSV) infection: what happens before hospitalization<sup>☆</sup>

John P. DeVincenzo<sup>a,b,c,\*</sup>, Jody B. Aitken<sup>a</sup>, Lisa G. Harrison<sup>a</sup>

<sup>a</sup> Department of Pediatrics, University of Tennessee and the Children's Foundation Research Center,

4th floor CFRC, LBCMC, 50 North Dunlap St., Memphis, TN 38103, USA

<sup>b</sup> LeBonheur Children's Medical Center Virology Laboratory, Memphis, TN, USA

<sup>c</sup> Methodist/LeBonheur Molecular Diagnostics Laboratory, Memphis, TN, USA

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## Abstract

RSV loads of infants are already declining near the time of hospitalization. For optimal effect, antiviral and other RSV therapeutics therefore may need to be applied before this occurs. 134 RSV-hospitalized infants were studied to determine the timing of events and their healthcare seeking behavior prior to hospitalization. Sixty-two percent of infants had contact with a health care professional  $\geq 1$  day prior to hospitalization and 46% had such a contact on  $\geq 2$  different days prior to hospitalization. The mean (S.D.) duration of RSV symptoms prior to hospitalization was  $3.9 \pm 2.3$  days and prior to first health care contact was  $2.6 \pm 1.8$  days. RSV-hospitalized infants routinely have contact with health care professionals at significantly early time points in their illness. These contacts are potential opportunities for initiation of early anti-RSV therapy.

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## 1. Background

Respiratory syncytial virus (RSV) infections result in the hospitalization of approximately 3% of previously healthy infants in their first year of life and up to 40% of infants of this same age range with underlying medical problems (Boyce et al., 2000). Based on discharge coding, this infection is the leading cause of hospitalization in this age group for any reason (Leader and Kohlase, 2002). The majority of these RSV hospitalizations occur in previously healthy infants. Antiviral strategies against RSV have met with limited clinical success. This may be due to a combination of several factors. First, immunopathology contributes significantly to overall disease. Second, compounds tested in RSV-infected infants have had limited in vitro and in vivo antiviral ef-

fect. Third, compounds tested to date have been applied to RSV-infected infants relatively late in their disease course. This latter factor needs to be carefully considered in the design of antiviral programs targeting RSV. We have previously determined that RSV loads in both upper and lower respiratory tracts are already declining at or near the time of hospitalization (Buckingham et al., 2002; Malley et al., 2000). This is true even in the most severely diseased infants requiring mechanical ventilation. To achieve the greatest reduction in area-under-the-curve RSV load, antivirals must be instituted early in the infection. Hospitalization for RSV in infants generally occurs on the fourth or fifth day of symptoms (Buckingham et al., 2002; Malley et al., 1998). RSV loads at specific time points before hospitalization will be lower than those at or shortly after hospitalization. The viral dynamics during the early RSV disease process needs further detailed study in order to define these time points. Clinical trials of neuraminidase inhibitors in influenza-infected children demonstrated a clinically beneficial effect when initiated within 48 h of symptom onset (Whitley et al., 2001). To initiate anti-RSV therapies in a similar time frame would therefore require initial dosing prior to hospitalization. In our current health care climate and practice, whether medical attention is routinely sought and whether infants can be

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\* Corresponding author. Tel.: +1-901-572-5377; fax: +1-901-572-4478.  
E-mail address: [jdevincenzo@utmem.edu](mailto:jdevincenzo@utmem.edu) (J.P. DeVincenzo).

identified prior to hospitalization is important in assessing the possibilities for successful development of RSV antivirals. The extent and timing of opportunities for early initiation of anti-RSV therapy have not been studied.

## 2. Methods

Infants were prospectively enrolled during the winters of 2000–2001 and 2001–2002. Infants were included if they were <2 years of age, hospitalized, RSV infection was documented during that hospitalization by routine laboratory procedures (DFA and or shell vial culture) ordered by their treating physician, and a parent or primary caregiver was available for an interview in person. The study was conducted at a single large pediatric hospital providing approximately 90% of a major United States metropolitan area's pediatric inpatient care. The hospital serves both an urban and a suburban population. A standardized questionnaire was administered by one of two study personnel within 1–2 days after their infant's RSV hospital admission. Answers from the questionnaire were used to generate the timing of disease symptoms. Regarding timing of symptoms, the questionnaire asked individually the date of onset of each of the following specific symptoms: (a) fever, (b) runny nose, (c) cough and (d) difficulty breathing. Of these four symptoms, the one with the earliest onset was taken to calculate the duration of symptoms prior to enrollment. The data contained in the medical record physician's history and physical was not used to establish timing of symptoms. Examination of the medical record provided the information regarding the hospital admission and inpatient stay. The study was approved by the University of Tennessee Institutional Review Board and informed consent was obtained. Statistical analyses included the use of Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Significance was set at <0.05 level.

## 3. Results

A total of 134 infants were enrolled and their parents/caregivers interviewed. The parents/legal guardians of all RSV-infected infants who were approached for the study gave informed consent for participation and were enrolled in the study. Characteristics of the subjects were typical of infants hospitalized for RSV infection (Table 1). Most subjects were not premature, were less than 6 months of age and were without the major established risk factors associated with greater RSV severity (congenital heart disease, and chronic lung disease). Likewise, the severity of disease was typical of previously healthy RSV-hospitalized infants (Wang et al., 1996) with a mean duration of hospitalization of approximately 5 days (Table 2). The percentage of infants admitted to the intensive care unit and requiring mechanical ventilation was higher than what is typical for this

Table 1

Baseline characteristics

	Mean (S.D.)	Median	Range
Age (days)	108 (102)	70	10–678
Gestational age (weeks)	37 (3.8)	38	24–40
Birth weight (kg)	2.7 (0.8)	2.9	0.6–4.7
Admit weight (kg)	5.2 (1.9)	4.8	2.1–10.7
Chronic lung disease (%)	6		
Sex (male) (%)	42		
Congenital heart disease (or other congenital anomaly) (%)	2.2		
History of reactive airway disease (%)	10.4		

population (Wang et al., 1995) since specific virology tests are more commonly ordered and performed on individuals with relatively greater disease severity.

The timing and duration of events preceding hospitalization are listed in Table 2. The duration of symptoms prior to hospitalization is similar to that seen in other studies (Buckingham et al., 2002; Malley et al., 1998) conducted at this institution and others with a mean of approximately 4 days. Runny nose was universally the first symptom of disease but it was initially recognized at the same time as cough or difficulty breathing in a minority of subjects. Most subjects (62%) had contact with a health care professional (HCP) at least 1 day prior to actual hospitalization while nearly half had such contact at least twice on different days prior to eventual hospitalization. While the mean (S.D.) and median duration of RSV symptoms prior to hospitalization

Table 2

Outcome and timing of RSV disease events and health care seeking behavior prior to hospitalization

	Mean (S.D.)	Median	25–75%
All subjects			
Symptom duration prior to admit (days)	3.9 (2.3)	3.5	2.0–5.0
Symptom duration prior to first contact with HCP <sup>a</sup> (days)	2.6 (1.8)	2.0	1.0–3.0
Contact with HCP <sup>a</sup> ≥1 day prior to admit (%)	62		
Contact with HCP <sup>a</sup> at least twice on different days ≥1 day prior to hospitalization (%)	46		
Duration of hospitalization (days)	5.2 (5.7)	3.0	2.0–6.5
Requiring ICU (%)	26		
Requiring mechanical ventilation (%)	21		
Subjects with HCP <sup>a</sup> contact ≥1 day prior to hospitalization			
Symptom duration prior to admit (days)	4.6 (2.4)	3.0	3.0–6.0
Symptom duration prior to first contact with HCP <sup>a</sup> (days)	2.5 (1.9)	2.0	1.0–3.0
Duration of hospitalization (days)	4.6 (3.8)	3.0	2.0–6.0
Requiring ICU (%)	24		
Requiring mechanical ventilation (%)	18		

<sup>a</sup> Health care professional.

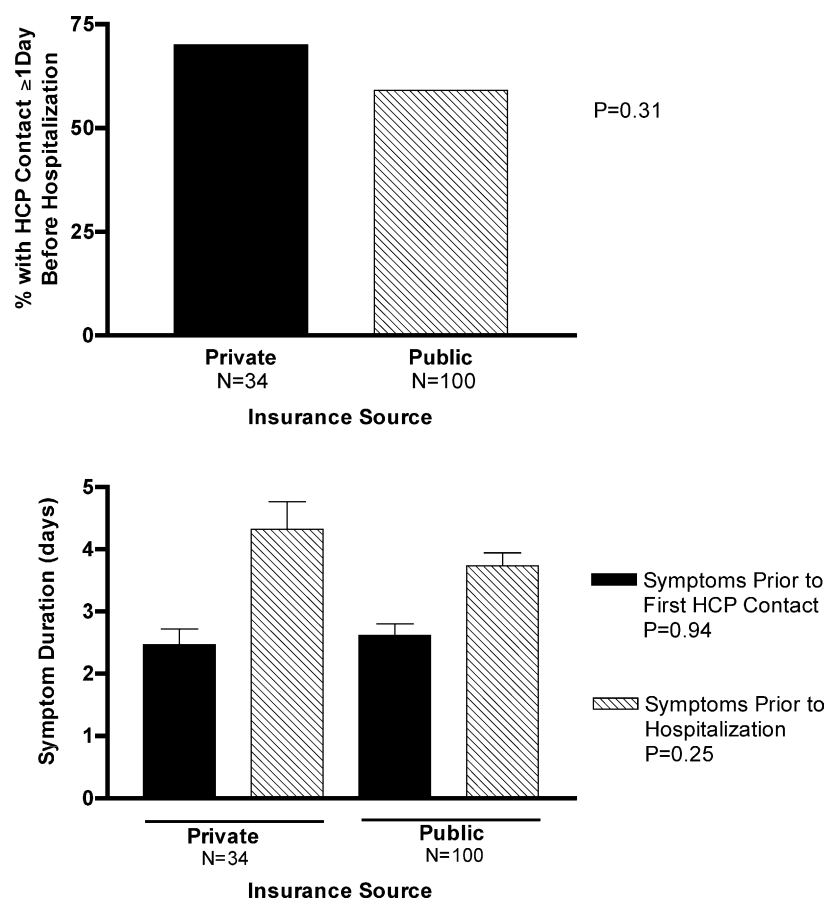


Fig. 1. Effects of insurance source on timing of early health care contact for infants subsequently hospitalized for respiratory syncytial virus infection.

were  $3.9 \pm 2.3$  and 3.5 days, the mean and median duration of symptoms prior to first health care contact were only  $2.6 \pm 1.8$  and 2.0 days.

There were no significant differences in the characteristics of hospitalization (duration of hospitalization, percent admitted to the ICU and percent requiring mechanical ventilation) between subjects with HCP contact for greater than 1 day prior to hospitalization as compared to the subjects as a whole. The mean duration of hospitalization for the subjects with a HCP contact  $\geq 1$  day prior to hospitalization was 4.6 (S.D. 3.8) days compared to 5.2 (S.D. 5.7) days for subjects as a whole ( $P = 0.40$ ).

Twenty-five percent of study subjects had private insurance with the remainder classified as having public health insurance. Public versus private insurance did not significantly influence the percentage with HCP contact prior to the day of hospitalization (59% versus 70%,  $P = 0.31$ ) (see Fig. 1). The percentage of subjects with private insurance who had early HCP contact was only slightly greater than those with public insurance ( $P = 0.31$ ). Insurance status did not influence the duration of symptoms prior to first health care contact (mean 2.47 days versus 2.58 days for private versus public insurance, respectively,  $P = 0.94$ ) (see Fig. 1). Likewise, insurance status did not influence the duration of symptoms prior to hospitalization ( $P = 0.25$ ).

#### 4. Discussion

The major findings in this study are that most infants with RSV disease severe enough to ultimately require hospitalization have contact with health care professionals at significantly earlier time points in their disease. These times are points during which experimental RSV therapies could potentially be initiated. Furthermore, the timing of this initial contact with the health care system is shortly after symptoms develop (median 2 days of symptoms). Although viral load has not been measured at these early symptom time points, it is likely that the RSV load on the second or third day of symptoms will be significantly lower than on the day of hospitalization. If an RSV antiviral could be applied at an early time when viral load is still low, the clinical effectiveness of that antiviral will be maximized. Since an RSV therapeutic that can be applied to outpatients is not available, HCPs currently have little reason to encourage parents/caregivers to bring their infants' early RSV symptoms to medical attention. However, this can be expected to change once an effective therapeutic is available. Rapid RSV diagnostics are available which can be performed at point of care sites. Thus, confirmation of RSV infection could be accomplished early in the course of the RSV infection as well, further facilitating early identification and treatment of RSV-infected infants.

Two general strategies for identification of outpatients targeted for RSV treatment could therefore be envisioned; a risk-based approach or a combined risk-based and infection-identification approach. The specifics of any of these two approaches could be altered depending upon an RSV antiviral's efficacy, side effect profile, and monetary cost, so as to minimize the cost benefit ratio. A risk-based strategy would take children with symptoms consistent with early RSV infection and define a subset of these patients for treatment based upon symptomatic standard risk factors which increase RSV disease severity. These factors might include age, gestational age, pre-existing lung disease, or heart disease, and status of the immune system. For the majority of infants, age is the most important risk factor predicting hospitalization. A previous study found that 23% of RSV-infected infants less than 3 months of age were hospitalized for their illness whereas only 15% of these RSV-infected infants less than 6 months of age were hospitalized (Fisher et al., 1997). Knowing what fraction of infants with upper respiratory symptoms are RSV-infected during an RSV epidemic would allow for further selected targeting of those actually infected. A combined risk-based and infection-identification approach might employ these above-mentioned strategies along with point of care rapid RSV testing which is now commercially available and approved for such use.

The study can be criticized for the fact that no independent verification of the parents/caregiver's responses was attempted. Thus, because these responses were by definition, subjective, the actual answer to the question posed by this study is that after 2 days of caregiver-recognized symptoms, contact is made with a health care professional. This question is arguably more important than the actual duration of symptoms prior to contact because actual timing of presentation will be ultimately determined by the parent/caregiver's recognition in virtually all instances. A further criticism can be made that the study population was of insufficient power to exclude small differences in health care contact between patients with public versus private insurance. Meaningful differences, however, can be ruled out by this study. Another limitation is that the study was conducted in a single institution. This limitation speaks to the generalizability of the study results since RSV care has been shown to vary from region to region (Wang et al., 1996) at least with respect to interventions employed during hospitalization, duration of hospitalization or of intensive care unit utilization. Another criticism is that since on certain days there were more infants admitted with RSV than could be interviewed, the study was a convenience sampling within all hospitalized RSV-infected infants less than 2 years of age. It is possible, though unlikely, that those families who were available for face to face interviews were more attentive than the population as a whole. More attentive parents/caregivers might have increased health care seeking behaviors.

It is possible that an antiviral medication which quickly and substantially lowers RSV concentrations may not im-

prove disease severity. If the cause of infant RSV disease involves primarily a pathogenic immune response which is set in motion within 2 days after symptom onset, antivirals could be postulated not to improve clinical outcome. Indeed a great deal of interest is being paid to immunomodulatory agents as RSV therapeutics. However, even if disease is primarily a result of a pathogenic immune response, earlier rather than later institution of an immunomodulatory intervention would be more likely to be beneficial. Several lines of evidence support the concept that effectively lowering RSV load would reduce disease severity. First, there appears to be a direct correlation between RSV disease severity (as defined by the need for mechanical ventilation) and RSV load (Buckingham et al., 2000). Although, the relationship between RSV load and disease severity needs further investigation (DeVincenzo and Buckingham, 2002; Wright et al., 2002), there also appears to be a correlation between higher RSV loads and longer durations of hospitalization (DeVincenzo et al., 2001, 2003). The second line of evidence supporting the putative efficacy of an antiviral in RSV-infected infants is the clinical experience with ribavirin. A statistically significant clinical improvement has been demonstrated with this therapy but its use only affords a modest antiviral effect and the magnitude of the resulting clinical improvement is small (DeVincenzo, 2000). Because of the requirements for administration and concerns over safety issues, no trial of ribavirin has initiated the therapy as an outpatient or at a time point early in the disease. Earlier use of an anti-RSV therapeutic with more potent antiviral effect may indeed demonstrate increased clinical efficacy as compared to ribavirin.

In conclusion, infants hospitalized for RSV routinely have contact with health care professionals at early time points in their illness. These contacts occur at times when the RSV load is likely to be low and are therefore potential opportunities for initiation of early anti-RSV therapy. This data should encourage the development of antivirals and other RSV therapeutics targeted at these early time points.

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