



## Original Article

# Respiratory viruses in neonates hospitalized with acute lower respiratory tract infections

Hye Jung Cho, So-Yeon Shim, Dong Woo Son, Yong Han Sun, Hann Tchah and In-Sang Jeon

*Department of Pediatrics, Gachon University Gil Hospital, Incheon, Korea*

**Abstract** *Background:* The burden of respiratory syncytial virus (RSV) in neonates has not been clearly studied. The aims of this study were to determine the overall distribution of respiratory viruses in neonates hospitalized with acute lower respiratory tract infections (ALRI) and to describe the clinical characteristics of RSV infections in these neonates. *Methods:* From January 2009 through May 2010, neonates aged <1 month who were hospitalized with ALRI and did not have underlying disease were included in the study. Viruses were identified on multiplex reverse transcription polymerase chain reaction using nasal swab samples. Clinical variables were evaluated between the RSV and non-RSV infection groups. *Results:* Of the 108 infants included in the study, 46 (42.6%) had RSV; human rhinovirus (18.5%), human parainfluenza virus 3 (7.5%), and human metapneumovirus (3.7%) were the next most common infections. Codetections accounted for 8.3% of the cases. Crowding increased the risk of RSV infection compared to the non-RSV group (OR, 16.5;  $P = 0.001$ ). The RSV group had a greater incidence of dyspnea ( $P = 0.027$ ), pneumonia ( $P < 0.001$ ), requirement for oxygen ( $P < 0.001$ ), and prolonged hospitalization ( $P = 0.011$ ) than the non-RSV group. *Conclusions:* RSV was the most common viral etiology in neonates without underlying diseases who were hospitalized with ALRI. The disease severity of RSV infection was worse than that of other detected viral infections. Strict prevention strategies should be considered in overcrowded situations.

**Key words** newborn infants, respiratory syncytial virus infections, respiratory tract infections.

In recent years we have developed an understanding of respiratory infections through the detection of viruses using reverse transcription–polymerase chain reaction (RT-PCR). In addition to respiratory syncytial virus (RSV), human rhinovirus (hRV), human parainfluenza virus (hPIV), and human metapneumovirus (hMPV) have been found to be major causes of acute lower respiratory tract infections (ALRI) in infants and young children.<sup>1–3</sup> ALRI are leading causes of hospitalization and mortality among children worldwide, particularly young children.<sup>4,5</sup> Only a few studies, however, have reported on respiratory viruses in neonates with ALRI. Understanding the overall spectrum of respiratory viruses causing ALRI in hospitalized neonates is essential to establish preventive and therapeutic strategies in this population.

RSV is the most common etiological agent of ALRI in infants and young children.<sup>6,7</sup> To date, many reports have described the burden of RSV infections and its risk factors. Prematurity, low birthweight, and chronic lung disease (CLD) have been suggested as risk factors for RSV infections. Additionally, epidemiologic factors, such as crowding, having older siblings, day-care

center attendance and exposure to smoke are important risk factors.<sup>8–11</sup> Very few studies have focused on neonatal RSV-associated ALRI among healthy neonates aged <1 month.<sup>5,12</sup>

The primary objective of this study was to determine the distribution of respiratory viruses in otherwise healthy neonates hospitalized with ALRI. A secondary aim was to identify the clinical characteristics of RSV infections in this population.

## Methods

### *Patient and clinical variables*

This study was a prospective investigation of neonates with ALRI. From January 2009 to May 2010, neonates (<1 month of age) admitted to the neonatal intensive care unit (NICU) at Gachon University Gil Hospital due to ALRI were enrolled. ALRI were defined as equivalent to clinical pneumonia or acute bronchiolitis, which is characterized by acute-onset cough or difficulty breathing with increased respiratory rate (respiration rate  $\geq 60$  breaths/min). All neonates were isolated in a separate room in the NICU. After obtaining informed consent, nasal swab samples were obtained from neonates with ALRI within 1 h of hospitalization. Neonates with bacterial isolation from blood samples, or underlying medical conditions, such as premature birth (<35 weeks of gestational age), congenital heart disease, and CLD were excluded from this study. During the study period, one nurse, who was unaware of the present study,

Correspondence: So-Yeon Shim, MD, PhD, Department of Pediatrics, Gachon University Gil Hospital, 1198, Guwol-dong, Namdong-gu, Incheon 405-760, Korea. Email: simso525@daum.net

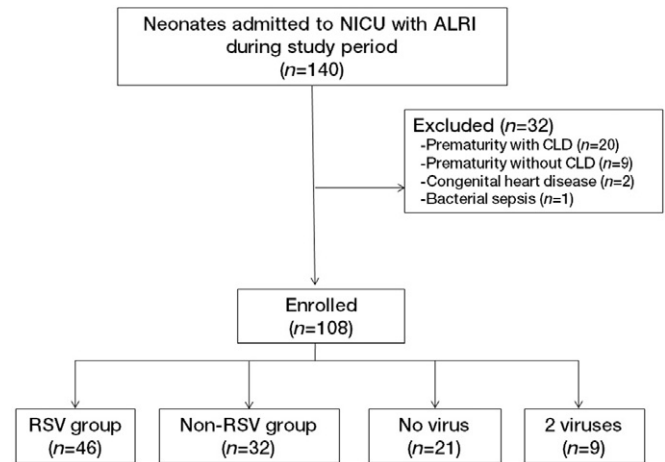
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recorded the following variables: history of premature birth, the presence of underlying medical conditions, breastfeeding, number of siblings, siblings attending day-care centers, number of residents at home, exposure to smoke, and residence in a neonatal day-care center in the previous 48 h. In South Korea, neonatal day-care centers are common places that provide caregivers for mothers and neonates after discharge from delivery hospitals. In these facilities, assistants take care of many neonates in a room, similar to a nursery. Respiratory infections were considered to be acquired at a neonatal day-care center if the neonates became symptomatic within 48 h of discharge from such a center. The clinical features and clinical courses during the hospitalization were summarized by one of the attending physicians who were blinded to this study. Clinical variables, such as rhinorrhea and/or cough, fever (defined as axillary temperature  $\geq 38^{\circ}\text{C}$ ), and requirement for oxygen therapy, were recorded. Apnea was defined as a lack of breathing activity for at least 20 s. Dyspnea referred to tachypnea (respiration rate  $\geq 60$  breaths/min) combined with the presence of pronounced chest wall retractions. Pneumonia was documented only if the clinical diagnosis was confirmed on chest radiography. On admission, a blood sample was taken to measure total white blood cell count and C-reactive protein, and for blood cultures. Neutropenia was defined as an absolute neutrophil count  $<1000/\text{mm}^3$ .

All included neonates were divided into the RSV group and non-RSV group based on the results of multiplex RT-PCR. Neonates with codetection or negative multiplex RT-PCR were excluded from the grouping. Demographics, clinical variables, and laboratory data were compared between groups. Ethics approval was obtained from the Ethics Committee of Gachon University Gil Hospital.

### Multiplex RT-PCR

For the multiplex RT-PCR, RNA was extracted from nasal swab samples using the Viral Gene-spin TM Viral DNA/RNA Extraction Kit (iNtRON, Seoul, South Korea), and cDNAs were synthesized. RT was performed using the Revert Aid TM First Strand cDNA Synthesis Kit (Fermentas, Burlington, ON, Canada). PCR amplification was performed using 10  $\mu\text{L}$  of Seeplex RV Master Mix 12 (Seegen, Seoul, South Korea), 4  $\mu\text{L}$  of 5X multiplex primer sets, 3  $\mu\text{L}$  of 8-methoxypsoralen solution, and 3  $\mu\text{L}$  of newly synthesized first-strand cDNA. Seeplex RV contained A and B sets of primers designed from highly conserved regions of genetic sequences for 12 respiratory viruses, including human coronavirus (hCoV)-229E/NL63, hCoV-OC43, hMPV, hRV, RSV A/B, influenza A/B, hPIV-1, 2, 3, and adenovirus. An initial pre-PCR step of  $94^{\circ}\text{C}$  for 15 min was performed followed by a total of 40 PCR cycles under the following conditions:  $95^{\circ}\text{C}$  for 30 s,  $60^{\circ}\text{C}$  for 1.5 min, and  $72^{\circ}\text{C}$  for 1.5 min. The final cycle was followed by an extension step at  $72^{\circ}\text{C}$  for 10 min to complete any partial polymerization. The amplified PCR products were separated on 2% agarose gel and stained with ethidium bromide. The type of respiratory virus was identified by comparison with the reference band size provided by the manufacturer.



**Fig. 1** Flowchart of neonates enrolled in the study. A total of 140 neonates were assessed for eligibility; 108 neonates were enrolled. ALRI, acute lower respiratory infection; CLD, chronic lung disease; NICU, neonatal intensive care unit; RSV, respiratory syncytial virus.

### Statistical analysis

Statistical analysis was performed using SPSS version 14.0 (SPSS, Chicago, IL, USA). Significance was examined using the chi-squared test for categorical variables, Fisher's exact test for binary variables, and the independent sample *t*-test for continuous variables. Normally distributed data are expressed as mean  $\pm$  SD. Non-parametric data are expressed as median (25–75th percentiles). Differences were considered significant for  $P < 0.05$ .

## Results

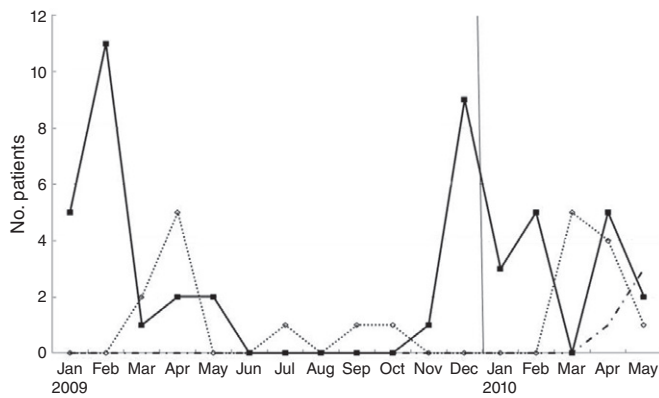
### Subjects

In the study period from January 2009 to May 2010, a total of 140 neonates with ALRI were admitted to the NICU (Fig. 1). Table 1 lists the distribution of 108 viral agents isolated from the enrolled infants. Among the viruses, RSV was the predomi-

**Table 1** Viral agents identified in enrolled neonates

Viral agents	Patients <i>n</i> (%)
Single infections	78 (72.2)
RSV A	29 (26.9)
RSV B	17 (15.7)
hRV	20 (18.5)
hPIV- 3	8 (7.5)
hMPV	4 (3.7)
Coinfections	9 (8.3)
RSV A + hRV	1 (0.9)
RSV B + hPIV-3	1 (0.9)
RSV B + hCoV-229E/NL63	1 (0.9)
hRV + hPIV-3	3 (2.8)
hRV + hCoV-OC43	1 (0.9)
hPIV-3 + hMPV	2 (1.9)
No virus detected	21 (19.4)
Total	108 (100.0)

hCoV, human coronavirus; hMPV, human metapneumovirus; hPIV, human parainfluenza viruses; hRV, human rhinovirus; RSV, respiratory syncytial virus.



**Fig. 2** Monthly distribution of respiratory infections according to virus. hMPV, human metapneumovirus; hRV, human rhinovirus; RSV, respiratory syncytial virus. —■—, RSV; -◇-, hRV; -○-, hMPV.

nant agent (42.6%), followed by hRV (18.5%), hPIV-3 (7.5%) and hMPV (3.7%). In nine neonates (8.3%), two viruses were simultaneously present, while no virus was identified in 21 neonates (19.4%). Most RSV cases appeared in November and persisted until May, and then gradually diminished. Most hRV cases occurred in the Spring (March–April). Four hMPV cases newly appeared during the late Spring of 2010 (April–May; Fig. 2).

Table 2 lists the neonates' demographic data. The median age at diagnosis in the RSV and non-RSV groups was 22 days and 24

days, respectively, and the proportion of males was 69.6% and 65.6%, respectively. No significant difference was observed between the groups according to the presence of environmental risk factors, such as number of siblings and siblings attending day-care center, number of residents at home, or exposure to smoke. A significantly higher proportion of infants in the RSV group had contracted infections from neonatal day-care centers (34.8% vs 3.1%,  $P = 0.001$ , odds ratio, 16.5; 95% confidence interval: 2.06–132.6).

### Clinical characteristics of RSV infections compared with other detected viral infections

Clinical data were compared between the RSV group ( $n = 46$ ) and non-RSV group ( $n = 32$ ; Table 3). Dyspnea was documented significantly more often in the RSV group (34.8% vs 12.5%,  $P = 0.027$ ). In contrast, fever  $\geq 38^{\circ}\text{C}$  was less frequent in the RSV group (15.2% vs 43.8%,  $P = 0.005$ ). Pneumonia and particularly consolidation in the right upper lobe were more often found in the RSV group (54.3% vs 15.6%,  $P < 0.001$ ; 45.7% vs 6.3%,  $P < 0.001$ , respectively). The RSV group more frequently required oxygen therapy (45.7% vs 6.3%,  $P < 0.001$ ) and had longer hospital stay ( $9.41 \pm 3.43$  days vs  $7.34 \pm 3.51$  days,  $P = 0.011$ ). All nine neonates with viral codetections were diagnosed with pneumonia, and three of them (33.3%) needed supplemental oxygen therapy.

No neonates died during the study period. Two neonates from each group required mechanical ventilation. Both neonates pre-

**Table 2** Demographic features

Variables	RSV group ( $n = 46$ ) $n$ (%)	Non-RSV group ( $n = 32$ ) $n$ (%)	$P$
Gestational age (weeks), mean $\pm$ SD	39.2 $\pm$ 3.9	39.0 $\pm$ 3.7	0.807
Birthweight (kg), mean $\pm$ SD	3.31 $\pm$ 0.81	3.41 $\pm$ 0.92	0.612
Age at diagnosis (days), median (25–75th percentile)	22 (17–27)	24 (11–28)	0.252
Male	32 (69.6)	21 (65.6)	0.714
Cesarean section	19 (41.3)	11 (34.4)	0.536
Breastfeeding	32 (69.6)	17 (53.1)	0.139
Infections at the neonatal day-care center	16 (34.8)	1 (3.1)	0.001
$\geq$ One sibling	34 (73.9)	25 (78.1)	0.670
Sibling attending day-care center	21 (45.7)	21 (65.6)	0.082
Residents at home, mean $\pm$ SD	3.94 $\pm$ 0.81	4.17 $\pm$ 0.62	0.303
Exposure to smoke	19 (41.3)	11 (34.4)	0.536

RSV, respiratory syncytial virus.

**Table 3** Clinical symptoms vs RSV infection

Variables	RSV group ( $n = 46$ ) $n$ (%)	Non-RSV group ( $n = 32$ ) $n$ (%)	$P$
Cough or rhinorrhea	43 (93.5)	30 (93.8)	1.000
Fever	7 (15.2)	14 (43.8)	0.005
Dyspnea	16 (34.8)	4 (12.5)	0.027
Apnea	3 (6.5)	0	0.265
Neutropenia	6 (13.0)	1 (3.1)	0.230
C-reactive protein (mg/dL), median (25–75th percentile)	0.09 (0.02–0.48)	0.07 (0.03–0.32)	0.845
Consolidation on right upper lobe	21 (45.7)	2 (6.3)	<0.001
Diagnosis as pneumonia	25 (54.3)	5 (15.6)	<0.001
Oxygen requirement	21 (45.7)	2 (6.3)	<0.001
Duration of hospitalization (days), mean $\pm$ SD	9.41 $\pm$ 3.43	7.34 $\pm$ 3.51	0.011

RSV, respiratory syncytial virus.

sented apnea on admission and definite respiratory symptoms, such as cough and rhinorrhea, were subsequently followed.

## Discussion

To the best of our knowledge, this is the first study to focus exclusively on previously healthy neonates with ALRI. To demonstrate the clinical impact of respiratory viral infection on neonates, we included only full-term neonates without underlying disease. In the present study, 80.5% of the neonates who were tested on multiplex RT-PCR had positive viral results. This detection rate is slightly higher than other similar reports for infants and small children.<sup>1,13</sup> One study based on hospitalized children with ALRI in Korea reported that RSV (33.2%) was the most common virus among 13 respiratory viruses and was followed by hRV (19.1%), influenza virus (16.9%), hMPV (15.4%), and hPIV (8.3%).<sup>14</sup> This distribution was similar to the present results, although the proportion of RSV was greater in the present study. We found that most respiratory viral infections in neonates are acquired from the community. In the present study, hRV was the second most commonly detected virus, accounting for 18.5% of detected viruses. Previous studies reported that hRV was the second most commonly detected virus,<sup>2,15</sup> and could result in serious lower respiratory tract disease in early life.<sup>3,16</sup> Recently, several studies reported that most young infants with hRV detection had symptomatic illness, whereas half of the children in which hRV was detected were asymptomatic.<sup>17,18</sup> In young infants, including neonates, the chances of colonization may be lower than in older children. Regarding these findings, hRV should be considered the main virus in the present study.

Interestingly, in this study, influenza was not detected, although the study period coincided with the pandemic of influenza A (H1N1) virus. According to the Ko *et al.* Korean, nationwide data for 2009, infants <6 months old accounted for only 4.7% of hospitalized children with H1N1 influenza infection.<sup>19</sup> It appears that younger infants have relatively lower risk for influenza because of lower exposure, but additional studies, including outpatient studies, are needed to support this conclusion.

Previous studies reported that viral codetections were found in 11–40% of subjects; in the present study only 8.3% presented codetection with two viruses. The relatively lower percentage of codetection in the present study may be due to lower colonization in neonates and lower chances of exposure to various viruses. An association between dual viral detection and more severe disease has not been properly established. Some authors consider that any dual viral infection increases severity of disease.<sup>20,21</sup> Other researchers, however, have found no difference when compared to single viral infections.<sup>13,22</sup> In the present study all neonates with codetection were diagnosed with lobar pneumonia. Based on these findings, we support an association of viral codetection with a more severe clinical course. Notably, RSV is the most common cause of ALRI-associated mortality, especially in preterm infants. In the present study there were no cases of mortality. A high level of maternal RSV IgG antibodies was considered one reason for this finding because it may offer protection from severe illness in term infants during the first few months of life.<sup>23</sup>

In South Korea, the RSV season ranges from October to March,<sup>24</sup> but it is reported that the season of RSV outbreaks varies considerably from year to year.<sup>9</sup> The present findings were similar to that expected in temperate climate zones; the incidence of RSV infections peaked from January to February 2009. This pattern, however, changed in 2010; there was no significant variation in the monthly distribution of RSV throughout the period from January to May.

According to previous reports, male gender, presence of older siblings, tobacco smoke exposure, and siblings attending day-care center were important risk factors for RSV infection.<sup>8,25–30</sup> In the present study there were no significant differences in these factors between the RSV and non-RSV groups. This implies that such risk factors could influence not only RSV infections but also other viral respiratory infections. In the present study a significantly higher proportion of the RSV group obtained infections from neonatal day-care centers. Neonates from neonatal day-care centers tended to be admitted as a group. Crowding situations in neonatal day-care centers may affect the transmission of RSV infections.

In agreement with previous studies, we found that RSV infections had a more severe clinical course than other viral respiratory infections.<sup>3,6</sup> Fattouh *et al.* reported that compared with non-RSV neonates, RSV neonates frequently had dyspnea and required supplemental oxygen with a higher rate of hospitalization.<sup>31</sup> In the present study, 54.3% of neonates in the RSV group were diagnosed with pneumonia, whereas only 15.6% were diagnosed with pneumonia in the non-RSV group. We performed chest radiography in all enrolled neonates and concluded that RSV infections were capable of causing pneumonia, especially in the right upper lobe.

To date, the majority of studies on RSV in neonates have been focused on neonates with underlying, high-risk medical conditions, such as premature infants, especially those with CLD or congenital heart disease. Immunoprophylaxis, which is effective at reducing RSV hospitalization, is recommended only for the highest risk infants because of cost-effectiveness.<sup>32</sup> Most infants who are hospitalized with RSV-related disease, however, have no underlying medical conditions.<sup>9</sup> Therefore, until a safe and effective vaccine is developed, prevention is essential to reduce RSV infections. In the present study, overcrowded environments, such as neonatal day-care centers, was a strong risk factor for RSV infection. Education regarding transmission-based precautions, such as hand hygiene and standard contact precautions, should be considered.

There were several limitations in this study. Because we focused only on neonates with infections severe enough to require hospitalization, we could not estimate the burden of viral respiratory infections not requiring hospitalization. Although our regional center is the largest one in the study area, it is unknown whether these data represent regionwide demographics. In the present study, only eight cases of codetection were confirmed. We could not determine the severity of codetection due to the small sample size. Further studies with larger sample sizes, including asymptomatic control groups and detailed subgroup analyses, are necessary.

## Conclusion

The overall distribution of respiratory viruses in neonates hospitalized with ALRI has been described in the present study. RSV was the most common viral ALRI etiology and hRV was the second most common. RSV had a more severe course than other detected viruses. Crowding situations increased the risk of RSV detection. Strict prevention strategies should be considered in overcrowded situations.

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