The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: http://www.tandfonline.com/loi/ijmf20

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To cite this article: Serdar Alan, Omer Erdeve, Ufuk Cakir, Hasan Akduman, Aysegul Zenciroglu, Mustafa Akcakus, Turan Tunc, Zeynel Gokmen, Can Ates, Begum Atasay, Saadet Arsan & on behalf of TurkNICU-RSV Trial Group (2015): Outcome of the Respiratory Syncytial Virus related acute lower respiratory tract infection among hospitalized newborns: a prospective multicenter study, The Journal of Maternal-Fetal & Neonatal Medicine

To link to this article: http://dx.doi.org/10.3109/14767058.2015.1079614

Published online: 12 Sep 2015.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE

http://informahealthcare.com/jmf
ISSN: 1476-7058 (print), 1476-4954 (electronic)

J Matern Fetal Neonatal Med, Early Online: 1–8
 DOI: 10.3109/14767058.2015.1079614

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ORIGINAL ARTICLE

Outcome of the Respiratory Syncytial Virus related acute lower respiratory tract infection among hospitalized newborns: a prospective multicenter study

Serdar Alan[1], Omer Erdeve[2], Ufuk Cakir[2], Hasan Akduman[2], Aysegul Zenciroglu[3], Mustafa Akcakus[4], Turan Tunc[5], Zeynel Gokmen[6], Can Ates[7], Begum Atasay[2], and Saadet Arsan[2]; on behalf of TurkNICU-RSV Trial Group*

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Abstract

Aim: To determine the incidence and outcomes of respiratory syncytial virus (RSV)-related acute lower respiratory tract infection (ALRI) including morbidity, nosocomial infection and mortality among newborn infants who were admitted to the neonatal intensive care units (NICUs).

Methods: A multicenter, prospective study was conducted in newborns who were hospitalized with community acquired or nosocomial RSV infection in 44 NICUs throughout Turkey. Newborns with ALRI were screened for RSV infection by Respi-Strip®-test. Main outcome measures were the incidence of RSV-associated admissions in the NICUs and morbidity, mortality and epidemics results related to these admissions.

Findings: The incidence of RSV infection was 1.24% (*n*: 250) and RSV infection constituted 19.6% of all ALRI hospitalizations, 226 newborns (90.4%) had community-acquired whereas 24 (9.6%) patients had nosocomial RSV infection in the NICUs. Of the 250 newborns, 171 (68.4%) were full-term infants, 183 (73.2%) had a BW >2500 g. RSV-related mortality rate was 1.2%. Four NICUs reported seven outbreaks on different months, which could be eliminated by palivizumab prophylaxis in one NICU.

Conclusion: RSV-associated ALRI both in preterm and term infants accounts an important percent of hospitalizations in the season, and may threat other high-risk patients in the NICU.

Keywords

Neonatal intensive care unit, newborn, nosocomial, outbreak, respiratory syncytial virus

History

Received 11 June 2015
Revised 26 July 2015
Accepted 31 July 2015
Published online 8 September 2015

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Introduction

Respiratory syncytial virus (RSV)-related acute lower respiratory tract infection (ALRI) is the most common viral respiratory infection in infants [1]. About 1–3% of infants are hospitalized for RSV bronchiolitis during the first year of life in Europe and the United States [2,3]. Rates of hospitalization are higher among infants aged 0–5 months then aged 6 to 11 months (16.9/1000 versus 5.1/1000, respectively) [4]. A recent epidemiological study from Korea has determined that RSV infection is one of the main causes of re-hospitalization in patients born at <35 weeks of gestational age (GA) [5].

Seasonal RSV outbreaks occur each year throughout the world. RSV infections in Turkey usually occur as well-defined community outbreaks during winter and early spring [6]. Risk factors for severe RSV bronchiolitis include prematurity with or without chronic lung disease (CLD), congenital heart disease (CHD), Down syndrome, neuromuscular disorders and immunodeficiencies [2,3,7,8]. Other risk factors for hospitalization include male sex, siblings living in the household, daycare attendance and exposure to tobacco smoke [9,10]. It is well known that newborns, especially preterms, are very vulnerable to RSV-related ALRI hospitalization. However, there are only scant prospective data for RSV-related morbidity and mortality in newborns who were admitted to a neonatal intensive care unit (NICU).

The primary objectives of this study were to determine the incidence and outcomes of RSV-related ALRI including morbidity, mortality and nosocomial spread among newborn infants who were admitted to the NICUs during the RSV season in Turkey. A secondary aim was to compare the clinical and demographic characteristics and outcomes of infants with community-acquired and nosocomial RSV infections in the NICUs.

Materials and methods

Patients and setting

A multicenter, prospective observational study was conducted in newborns who were hospitalized with community-acquired or nosocomial RSV infection in 44 NICUs throughout Turkey between October 2013 and March 2014. The trial was approved by the Ankara University Ethics Committee and registered as TurkNICU-RSV Trial at ClinicalTrials.gov under identifier number NCT01915394.

Inclusion criteria were an attending physician's diagnosis of RSV-related ALRI confirmed by the Respi-Strip® test (Coris BioConcept, Gembloux, Belgium) and requiring hospitalization in a NICU or detection of RSV infection in already hospitalized patients. Any congenital anomaly [such as CHD, congenital diaphragmatic hernia, Down syndrome, etc. or neuromuscular disorders] was defined as an exclusion criteria. Hospitalization criteria for the ALRI newborns were (a) respiratory distress (respiratory rate of >60 breaths/min, cough, wheeze, onset of dyspnea, retractions of the respiratory muscles, indicating lower respiratory tract involvement, and apnea) and hypoxemia (sustained saturation of peripheral oxygen: <90%), (b) circulatory collapse signs (tachycardia, hypotension, etc.) (c) poor feeding with respiratory signs. Infants who had acute upper respiratory infections with a positive Respi-Strip test but did not necessitate hospitalization were excluded.

Preterm infants of corrected postmenstrual age upto ≤44 gestation weeks and term infants who are within 28 postnatal days are admitted to NICUs in Turkey. Additionally, the number of pediatric intensive care units and their capacities are very low in comparison to the NICUs since it is a new discipline just for 3 years. Therefore, infants who have been discharged from the hospital and return for admission for a respiratory infection are generally accepted to the NICUs. It is a rule to have an isolation room for each 10 bed capacity for new designed NICUs, but not for older ones.

Descriptions and study groups

''Community-acquired RSV infection'' was defined as RSV infection with acute respiratory symptoms not acquired in a hospital. ''Nosocomial RSV infection'' was defined as symptoms or signs of RSV infection developing 48-h or more after admission for other diagnoses. Although there is no consensus in the literature for definitions of nosocomial RSV outbreak [11–18], ''nosocomial RSV outbreak in the NICU'' was defined as ≥3 infants with nosocomial RSV infection in a NICU at the same time according to Turkish Neonatal Society Guideline (www.neonatology.org.tr).

RSV test

The Respi-Strip® test involves a nitrocellulose membrane sensitized with a monoclonal antibody directed against RSV, while a mobile anti-RSV monoclonal antibody is conjugated to colloidal gold particles. If the sample contains RSV, the conjugate–RSV complex will remain bound to the anti-RSV antibody adsorbed onto the nitrocellulose, revealed as a red line that develops on the strip [13]. Nasopharyngeal swab specimens were obtained by participants in all NICUs and the strip test was performed according to manufacturer's instructions.

Data collection

A questionnaire about characteristics and RSV policies of the NICUs was collected from all NICUs prior to the study to define their capacity, visitation policy and RSV prophylaxis.

If the Respi-Strip test was positive, investigators filled out a case-specific data collection sheet which included signs and symptoms, treatments and outcome of the patient. In case of any nosocomial RSV outbreak, participating investigators informed the principle investigators monthly about outcomes. NICUs were responsible for reporting the number of all hospitalized patients and the number of all ALRI patients in the NICU each month to principle investigators. All data were gathered monthly and rates of ALRI-related hospitalizations and RSV infections in the NICUs, demographic characteristic, sign and symptoms, treatments given and outcomes (morbidity and mortality) were all recorded.

Statistical analysis

Continuous variables were compared using *t*-tests and/or Mann–Whitney U-tests, as applicable, whereas categorical

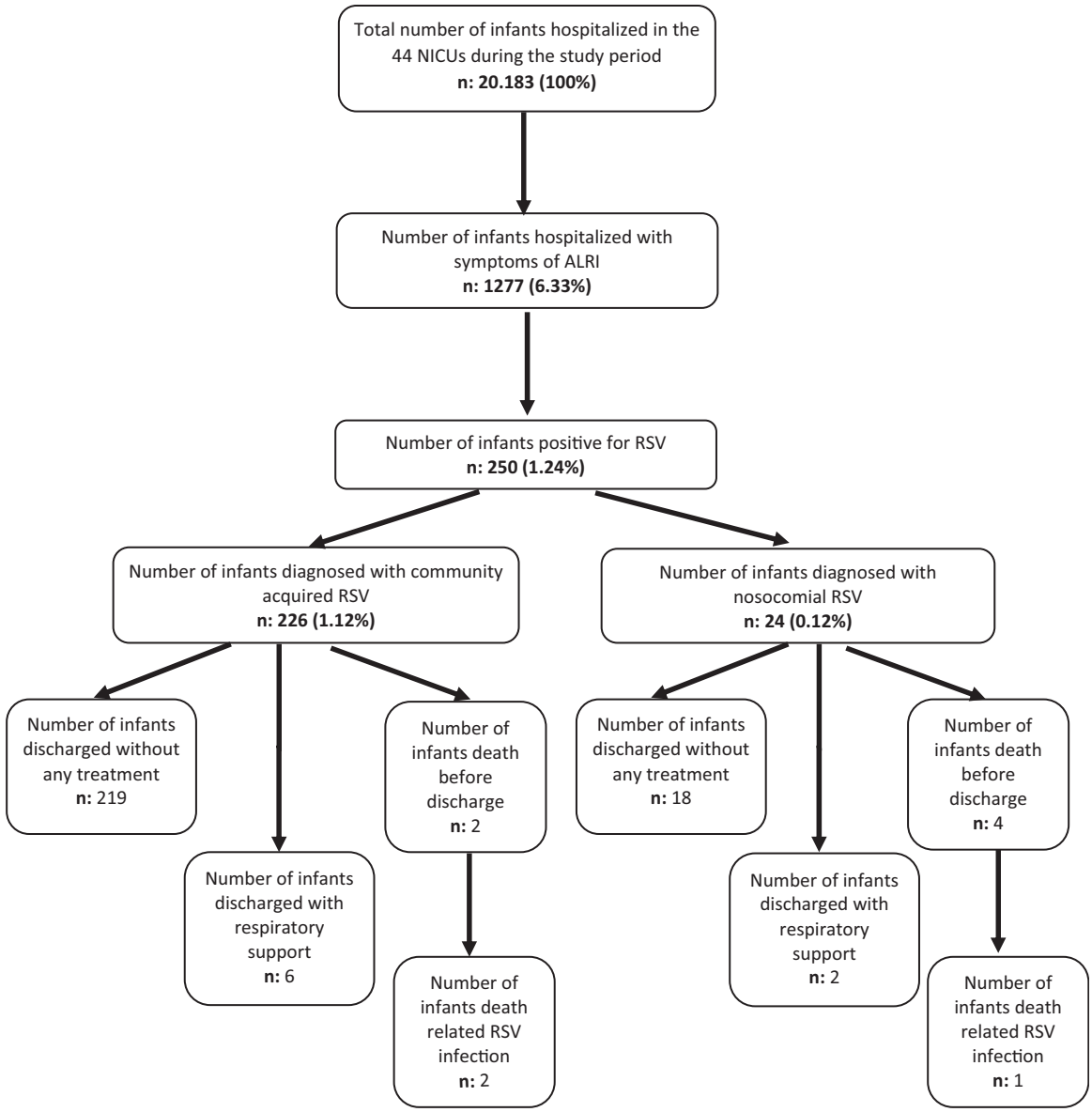

Figure 1. Distribution of hospitalized patients according to RSV infection. ALRI, acute lower respiratory infection; NICU, neonatal intensive care unit.

variables were compared using the chi-square or Fisher's exact tests. Continuous variables are reported as mean ± standard deviation and/or median (minimum–maximum), and categorical variables as percentage and distribution of frequency. Statistical analyses were performed using the IBM Statistical Package for Social Sciences (SPSS) version 15 (SPSS, Chicago, IL), with statistical significance defined as a two-sided p values <0.05.

Results

Characteristics of the NICUs

Forty-four NICUs across seven geographic regions throughout Turkey participated in the trial. These NICUs include a total of 1604 incubators/open beds, with a median of 30 beds (range, 15–150 beds). Eighty-eight of the 1604 beds (5.5%) in the NICUs were defined as single isolation rooms.

Twenty-five NICUs defined themselves as family-centered and allowed all day parental visits. The others had restricted visiting policies. Preterm infants with ≤28 weeks GA or CLD at discharge received palivizumab prophylaxis during the RSV season according to Turkish Neonatal Society Guideline.

Distribution of patients according to NICUs and study months

Among 20 183 newborns hospitalized in participating NICUs during the study period, 1277 with symptoms of ALRI (6.3%) underwent Respi-Strip® testing and 250 (19.6%) of them were positive for RSV (Figure 1). Thirty-three NICUs (75%) admitted at least one RSV-positive infant during the study period. The median number of admitted RSV-positive newborns was 3 (0–45) during the season.

Infants with RSV infection were hospitalized most frequently in February ($n = 82$, 32.8%), followed by March ($n = 77$, 30.8%) and January ($n = 74$, 29.6%) (Figure 2). Infants born in January had a higher rate for RSV-related hospitalization ($n = 92$, 36.8%), followed by those born in February ($n = 75$, 30%) and December ($n = 39$, 15.6%).

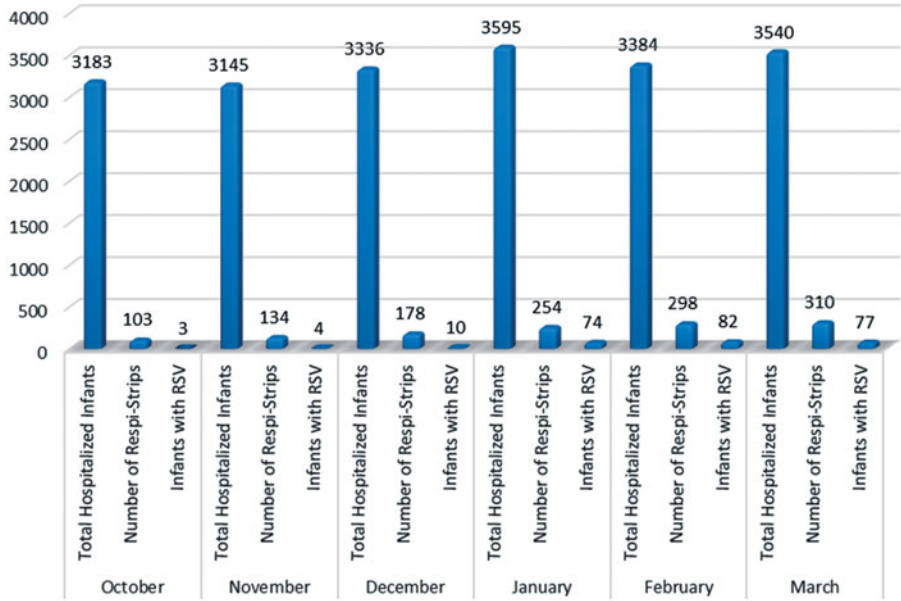

Figure 2. Distribution of total hospitalized infants, infants with RSV and number of RSV strip tests between October and March.

Table 1. Demographic characteristics, clinical course and outcomes of newborn infants with RSV infection.

	RSV-positive newborns (*n*: 250)
Demographic data	
Male, % (*n*)	58.8 (147)
Postnatal age at diagnosis (day), median (range)	23 (4–153)
Gestational age (weeks), mean ± SD	36.8 ± 3.4
Gestational age groups (weeks), *n* (%)	
≤28.6	7 (2.8)
29–32.6	27 (10.8)
33–36.6	45 (18)
>37	171 (68.4)
Birth weight (g), mean ± SD	2856 ± 810
Birth weight groups (g), *n* (%)	
≤1000	10 (4)
1001–1500	11 (4.4)
1501–2000	20 (8)
2001–2500	26 (10.4)
>2500	183 (73.2)
Signs and symptoms on the admission, *n* (%)	
Apnea	24 (9.6)
Cough	210 (84)
Rhinorrhea	153 (61.2)
Fever	13 (5.2)
Cyanosis/increase in oxygen requirement	68 (27.2)
Underlying condition, *n* (%)	
Prematurity (≤36.6 weeks)	79 (31.6)
Underlying disorders except prematurity (at least one)	29 (11.6)
Congenital heart disease	9 (3.6)
Broncho-pulmonary dysplasia	11 (4.4)
Congenital respiratory tract anomaly (diaphragmatic hernia)	3 (1.2)
Need for respiratory support treatment before RSV infection	6 (2.4)
Length of hospital stay (days), median (range)	8 (2–180)
Total mortality rate, *n* (%)	6 (2.4)
Mortality related to RSV infection, *n* (%)	3 (1.2)

Demographic and clinical features of the study patient

The median age for RSV infection was 23 d of life (4–153). The mean GA and birth weight (BW) were 36.8 ± 3.4 weeks and 2 8 56 ± 810 g, respectively. Among 250 infants, 171 (68.4%) were full-term, 183 (73.2%) had a BW >2500 g and male: female ratio was 1.43 (Table 1).

The most common sign and symptoms were cough (84%, *n:* 210) and rhinorrhea (61.2%, *n:* 153), followed by cyanosis (27.2%, *n:* 68), apnea (9.6%, *n:* 24) and fever (5.2%, *n:* 13). Rates of risk factors such as prematurity, CLD, CHD and congenital respiratory tract anomalies were 31.6%, 4.4%, 3.6% and 1.2%, respectively. However, more than half of the study patients (56.8%) had no underlying condition.

Two hundred thirty-seven (94.8%) of the study infants needed oxygen treatment, 22% (*n:* 55) had non-invasive ventilation (NIV) and 10.8% (*n:* 27) had mechanical ventilation as a respiratory support treatment in the NICU. Inhalation treatments such as salbutamol, physiological saline and ipratropium bromide were used in 71.2%, 62.8% and 14.4% of patients. Inhaled acetylcysteine, hypertonic saline, epinephrine and dornase-alpha were also administered to a small group of newborns (3.6%). Steroids as inhaled steroid (*n:* 17), systemic steroid (*n:* 31) or both (*n:* 1) were administered to 19.6% (*n:* 49) of the patients. Antibiotic therapy utilization rate for atelectasis and possible concomitant bacterial infection was 25.6% (*n:* 64) and in most (84.3%, *n:* 54) macrolide group was preferred.

Outcomes of the study patients

The median day of hospital stay was 8 d (2–180). Although 235 (94%) were discharged healthy, nine infants (3.6%) were on medical treatment or oxygen supply at discharge. Six of these infants were born ≤32 weeks of gestation. One infant did not have any underlying condition, and of the two remaining infants, one had CHD and one congenital diaphragmatic hernia.

The mortality rate was 2.4% (*n*: 6) in all study infants. Three of them died related to other underlying conditions such as necrotizing enterocolitis (*n:* 1) and CHD (*n:* 2). The RSV-related mortality rate was 1.2% (*n:* 3); two of them were born prematurely (28 and 32 weeks of gestation) and one was born at 39 weeks of gestation.

Table 2. Demographic characteristics, clinical course and underlying conditions of patients with community-acquired and nosocomial RSV infection.

	Community-acquired RSV *n*: 226	Nosocomial RSV *n*: 24	*p* value
Demographic data			
Male, % (*n*)	57.1 (129)	66.7 (16)	0.366
Postnatal age at diagnosis (day), median (range)	24 (6–153)	18 (4–133)	0.264
Gestational age (weeks), mean ± SD	37.1 ± 2.9	33.6 ± 5.3	0.001
Gestational age groups (weeks), *n* (%)			
≤28.6	2 (0.9)	5 (20.8)	<0.0001
29–32.6	22 (9.7)	5 (20.8)	
33–36.6	42 (18.6)	3 (12.5)	
>37	160 (70.8)	11 (45.8)	
Birth weight (g), mean ± SD	2931 ± 742	2155 ± 1072	0.001
Birth weight groups (g), *n (%)*			
≤1000	4 (1.8)	6 (60)	<0.0001
1001–1500	8 (3.5)	3 (27.3)	
1501–2000	19 (8.4)	1 (5)	
2001–2500	23 (10.2)	3 (12.5)	
>2500	172 (76.1)	11 (45.8)	
Length of hospital stay (days), median (range)	8 (2–45)	22.5 (5–180)	<0.0001
Signs and symptoms on the admission, *n* (%)			
Apnea	20 (8.8)	4 (16.7)	0.264
Cough	201 (88.9)	9 (37.5)	<0.0001
Rhinorrhea	150 (66.4)	3 (12.5)	<0.0001
Fever	12 (5.3)	1 (4.2)	1
Cyanosis/increase in oxygen requirement	50 (22.1)	18 (75)	<0.0001
Underlying condition, *n* (%)			
Prematurity (≤36.6 weeks)	66 (29.2)	13 (54.2)	0.012
Underlying disorders except prematurity (at least one)	10 (4.4)	19 (79.2)	<0.0001
Congenital heart disease	3 (1.3)	6 (25)	<0.0001
Broncho-pulmonary dysplasia	7 (3.1)	4 (16.7)	0.014
Congenital respiratory tract anomaly (diaphragmatic hernia)	0	3 (12.5)	0.001
Need for respiratory support treatment before RSV infection	0	6 (25)	<0.0001
Palivizumab prophylaxis before infection, *n* (%)	2 (0.9)	0	1

Comparison of the patients with community-acquired and nosocomial RSV infections

Of the 250 infants hospitalized for RSV infection, 226 (90.4%) had community-acquired and 24 (9.6%) had nosocomial RSV infection. A comparison of their demographic data shows that mean GA (37.1 ± 2.9 versus 33.6 ± 5.3 weeks, $p = 0.001$) and BW (2 9 31 ± 742 versus 2 1 55 ± 1072 g, $p = 0.001$) were significantly lower in the nosocomial RSV group (Table 2). Two of the 226 (0.9%) infants with community-acquired were on palvizumab prophylaxis, whereas 10 of the 24 (41.7%) with nosocomial RSV infection were candidates for prophylaxis at discharge ($p < 0.0001$).

Table 2 shows the clinical characteristics of RSV infection and underlying conditions in two groups. Most newborns with nosocomial RSV (79.2%) had at least one underlying condition, whereas most with community-acquired infection (95.6%) were otherwise healthy. Although the rate of medical treatments including inhaled normal saline, salbutamol, ipratropium bromide and steroids were similar in both groups, the rate of mechanical ventilation support was significantly higher in patients with nosocomial infection (33.3% versus 8.4%, $p = 0.001$).

Epidemics in the NICUs

Four NICUs reported seven outbreaks throughout the study period. Two NICUs reported consecutive outbreaks from January to March. One of these four NICUs, which had three consecutive outbreaks, reported administering palivizumab prophylaxis to uninfected infants with risk factors of prematurity, diaphragmatic hernia and cyanotic CHD.

Discussion

All of the newborns with ALRI were screened for RSV infection by Respi-Strip® test, and the incidence of RSV infection was found to be 1.24% in participating NICUs. Furthermore, RSV infection constituted 19.6% of hospitalized ALRI newborns during the RSV season and majority of the NICUs (75%) admitted at least one RSV-infected patient during the season.

Nearly all children are infected at least once by the time they are at 2 years of age, but peak incidence of RSV-related respiratory infection occurs between ages 2 and 3 months [19]. Nair et al. described that roughly 22% of all ALRI was defined as a RSV-related ALRI in children younger than 5 years worldwide [20]. A prospective study of 298 healthy term newborns found that 14% had RSV-related ALRI during their first year of life, the median age at the time of RSV ALRI was 6 months (range: 4–8 months) [21]. Cho et al. concluded that RSV was the most common viral agent (42.6%, 46/108 newborns) among previously healthy term newborns who needed hospitalization with ALRI according to their single center prospective data [22]. Our study population consisted of newborns with or without underlying risk factors including prematurity and CHD. We found that the rate of RSV-related ALRI was 19.6% among hospitalized newborns with ALRI. This ratio was highly variable between NICUs

involved in the study. The differences in findings can be explained by heterogeneity of the NICUs.

There is no consensus on severe RSV-related ALRI infection among infants in the literature. Although some trials accepted severity index (SI) score system (according to blood gas parameters, length of hospital stay and mechanical ventilation need) to provide objective assessment of disease severity [23,24], severe RSV-related ALRI was defined according to necessitating hospital admission in the large series trials [20,25]. When receiving non-invasive or mechanical ventilation support depending on clinician's choice was accepted as severe RSV, 32.8% of the newborns had severe RSV infection in the present trial.

The mainstay of treatment is supportive care including respiratory support, fluid and nutrition management in infancy and early childhood [19]. Gonçalves et al. showed that 83.8% of the newborns needed oxygen treatment, 37% of the infants had respiratory support and 15.4% had mechanical ventilation in their cohort [26]. Cho et al. showed that oxygen requirement was needed in 45.7% of previously healthy newborns with RSV and only two infants (2/46, 4.4%) had mechanical ventilation support [22]. In the present study, 22% of the newborns had NIV and 10.8% had mechanical ventilation. There is no solid scientific evidence supporting the use of any pharmacological agent (including bronchodilators, corticosteroids and anti-microbials) currently available. Neither systemic nor inhaled corticosteroids have consistent benefit in the treatment of acute RSV infection [19]. However, we demonstrated that these agents were used in many patients for clinical management, including steroid treatment in about one-fifth of the patients according to clinician choice. One fourth of patients received antibiotics for atelectasis or any possible concomitant bacterial pneumonia in our series. Levin et al. [27] suggested that composite evidence of bacterial pneumonia in otherwise low-risk infants with RSV presenting with respiratory failure was 20% or higher and the use of empirical antibiotics for 24 to 48 h pending culture results might be justified and could be used until concomitant bacterial pneumonia was excluded. Although this study was small sized and did not permit definitive conclusions, this subject still needs to be studied.

The 2005 worldwide estimates of mortality caused by RSV-associated ALRI in children under the age of 5 range between 66 000 and 199 000 deaths, with 99% of these deaths occurring in the developing world [20]. According to two national data sources from United States between 2000 and 2011, mortality during RSV-related hospitalization in infants and children aged <2 years is uncommon, occurring in 3 to 4/10 000 admissions in 2009 and 2011 [28]. However, data are lacking specifically for neonatal period in large series. RSV-related mortality rate was 1.2% (*n:* 3) with two preterm and one term infants in our cohort. All three patients had severe ALRI and were on mechanical ventilator support during RSV management. Thompson et al. found that the RSV association mortality rates was 3.1 per 100 000 person-years in infants younger than 1 year in 1990s [29]. Gonçalves et al. described only one death in their retrospective newborn cohort (3.8/1000), but reason of death did not specify whether the death was related to RSV or not [26]. Cho et al. found that no death occurred in their single center newborn cohort [22]. Similarly, a retrospective multicenter cohort study of 202 preterm children of 32 to 35 weeks GA who were hospitalized for RSV infection observed no deaths [30]. However, as a study on nosocomial infection-related mortality among children admitted to intensive care unit reported that when RSV infection was present in children with serious comorbidities, mortality may exceed 25% [31]. Recently, Lee et al. found that RSV-related death rate was 5.4% (*n:* 10 patients) among children who needed pediatric intensive care admission due to severe RSV infection [32].

We found that infants with RSV-related ALRI were more frequently hospitalized in February, followed by March and January. A multicenter large-scale study by the Turkish Neonatal Society found that most RSV infections occurred during the period between October and March with peaks observed in January and March during two consecutive RSV seasons (2008–2010) [6]. Our finding of an association between birth month and risk of hospitalization for RSV is consistent with previous studies [33,34]. In the United States, 1-month-old infants born in January were at about 10-fold higher risk of RSV-related hospitalization than 1-month-old infants born in October [35]. In comparison, we found that infants born in January and February with a postnatal age ≤30 d were at highest risk for RSV-related hospitalization.

Over the past 40 years, RSV has also been found to be a pathogen in the NICU [11–18,35]. Nosocomial outbreaks of RSV in NICUs may be particularly severe, with unexpected clinical manifestations and high mortality rates [11–13]. Whereas seasonal RSV outbreaks predictably occur in the community, the incidence in the NICU may be quite variable. Published studies of RSV in the NICU report only isolated outbreaks [11–18]. Recently, three nosocomial RSV outbreaks in the NICUs were reported from Turkey [13–15]. Similar to the outbreaks in our trial, the previous outbreaks occurred between January and March. Previous studies of nosocomial RSV outbreaks showed that most infected infants were preterm especially with GA ≤32 weeks [11,33–39]. Our study showed similar results, with prematurity and underlying disorders being risk factors for nosocomial RSV infection.

Palivizumab is the only licensed product available for prevention of RSV-related ALRI in infants, with a history of preterm birth and children with CLD or with hemodynamically significant CHD [38]. Palivizumab prophylaxis has been reported to reduce hospitalization rates in infants born at GA ≤28 with or without CLD in Turkey [39]. Oncel et al. found that 2.4% of the preterm newborns under the influence of palivizumab prophylaxis had RSV-related hospitalization in Turkey [40]. Furthermore, studies regarding nosocomial RSV outbreaks have suggested that, in addition to meticulous control procedures, the use of palivizumab might have a role in controlling RSV outbreaks or may result in milder RSV infection in the NICU [11–18]. However, the American Academy of Pediatrics does not recommend palivizumab for health care-associated RSV infection in the NICU, because it has not been rigorously shown to control outbreaks [41]. Although seven outbreaks from four different NICUs were recorded in our study, only one NICU reported use of palivizumab prophylaxis to the infants at risk to control the nosocomial spread in the NICU.

The present study had several limitations. First, although Respi-Strip® tests are feasible, inexpensive, easy-to-perform, yield rapid results and have a 100% positive predictive value [13], these tests have a sensitivity of 90.3% and a specificity of 88.2% for diagnosing RSV infection [42]. Thus, these tests may have missed about 10% of infants infected with RSV. Second, our study was conducted only during the peak RSV season in our country [6]. A whole year lasting study may yield stronger data especially for nosocomial infection in the NICU.

Declaration of interest

The authors declare that they have no conflict of interest. This trial was supported by the Children Diseases Foundation, which is an independent organization funded by physicians from Ankara University School of Medicine, Department of Pediatrics.

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