



# Risk of Respiratory Syncytial Virus Infection in Cyanotic Congenital Heart Disease in a Subtropical Area

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**Objective** To compare the risk of respiratory syncytial virus (RSV)-associated hospitalization and analyze the epidemiology of RSV infection in patients with cyanotic and acyanotic congenital heart disease (CHD), we analyzed the nationwide health insurance database from 2005-2010.

**Study design** This study included 1050 patients with cyanotic CHD and 7077 patients with acyanotic CHD. Patients with acyanotic CHD were further classified into hemodynamically significant (hs)-acyanotic and non-hs-acyanotic groups according to whether they underwent surgery or took at least 2 anticongestive medications.

**Results** RSV-associated hospitalization was higher in the cyanotic group than in hs-acyanotic and non-hs-acyanotic groups both before 1 year of age (4.8% vs 2.1% vs 1.5%,  $P < .001$ ) and between 1 and 2 years of age (0.9% vs 0.56% vs 0.14%,  $P = .003$ ). The hospitalization duration, intensive care, ventilator support prevalence, hospitalization cost, and mortality rate were significantly higher in the cyanotic group than in the other 2 groups. Logistic regression revealed that cyanotic CHD was the most significant risk factor for the ventilator support and RSV-associated mortality. In both patients with cyanotic and acyanotic CHD, RSV-associated hospitalization rate was higher in patients aged younger than 1 year and in spring and autumn in Taiwan, a subtropical country.

**Conclusions** The results show that patients with cyanotic CHD have a higher risk of severe RSV infection than do those with acyanotic CHD. RSV prophylaxis is more important and may reduce costs more for patients with cyanotic CHD. (*J Pediatr* 2016;171:25-30).

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Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections (LRTIs) in young children, and approximately 1%-4% of infants require hospitalization for RSV LRTI before 1 year of age.<sup>1,2</sup> The hospitalization rate is higher in those with underlying diseases such as prematurity and congenital heart disease (CHD).<sup>3-7</sup> In several studies, patients with CHD had a higher risk of requiring intensive care, oxygen use, and ventilator support when infected with RSV.<sup>3,8-10</sup> The risk of mortality was also higher in these patients.<sup>9,11</sup> However, other studies reported contradictory data.<sup>12</sup> These conflicting data can be attributed to 2 reasons. First, different countries with various climates, latitudes, public health, and even viral specific factors of RSV exhibit distinct epidemiology and severity.<sup>13,14</sup> Second, a SD of hemodynamically significant (hs) CHD has not been established. Several studies have discussed the cost-effectiveness of palivizumab prophylaxis for hs CHD.<sup>7,15,16</sup> However, no consensus has been reached regarding the criteria for defining hs CHD.

Regarding RSV prophylaxis for patients with hs CHD, the recent American Academy of Pediatrics (AAP) guideline recommends palivizumab prophylaxis in all patients with hs-acyanotic CHD during the RSV seasons. According to this guideline, palivizumab prophylaxis is indicated for patients with cyanotic CHD only after being determined appropriate by a cardiologist.<sup>17,18</sup> However, the applicability of this guideline to subtropical countries, such as Taiwan, is unknown. Furthermore, whether the RSV infection in hs-acyanotic CHD is more severe than that in cyanotic CHD is still questionable.

The nationwide National Health Insurance (NHI) program was implemented in Taiwan in 1995 and covered more than 97% of the population by 2006. Palivizumab prophylaxis for RSV infection in patients with CHD has been covered by the NHI program since December 2011. Therefore, we could analyze the epidemiology of RSV infection in patients with CHD in the pre-palivizumab era. Here, using this nationwide database, we compared the

AAP	American Academy of Pediatrics
CHD	Congenital heart disease
hs	Hemodynamically significant
ICD-9-CM	<i>International Classification of Diseases, Ninth Revision, Clinical Modification</i>
LRTI	Lower respiratory tract infection
NHI	National Health Insurance
RSV	Respiratory syncytial virus

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prevalence and severity of RSV infection in cyanotic and acyanotic CHD. We also defined the epidemiology of RSV infection in subtropical area like Taiwan.

## Methods

From the health care records in the NHI Research Database for the period 2003–2010, we selected patients who were born between 2005 and 2008 and who met the criteria for CHD, on the basis of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes, for RSV hospitalization study. This ensured that all of our patients had complete follow-up for 2 years. We categorized patients with CHD into 2 groups: a cyanotic group and an acyanotic group. The distribution of the subtypes of CHD and its ICD-9-CM code are listed in **Table I** (available at [www.jpeds.com](http://www.jpeds.com)). To avoid overestimation because of insignificant or spontaneously resolved defects, patients were enrolled only when they had a CHD-specific admission or more than 3 outpatient clinic visits.<sup>6</sup> In addition, we did not include patients with atrial septal defects or peripheral pulmonary stenosis in our study group because these lesions do not cause hs changes and are common findings in neonates and young infants.<sup>17</sup> We further subdivided the acyanotic group into hs-acyanotic and non-hs-acyanotic groups. Patients who underwent surgery or took at least 2 anticongestive medications for heart failure control were categorized into the hs-acyanotic CHD group. In our study, the definition of prematurity was birth at a gestational age  $\leq 32$  weeks or with a body weight  $\leq 1500$  g, and chromosomal anomaly was defined using the ICD-9-CM diagnostic code 758.

We collected hospital health care records from 2005–2010 and analyzed the RSV-associated hospitalization rate in children aged younger than 2 years. The criteria for identifying RSV infection were RSV-associated bronchiolitis and viral pneumonia (**Table II**; available at [www.jpeds.com](http://www.jpeds.com)). Because CHD is categorized as a catastrophic illness in the NHI program, the program covers all medical expenses during admission, except for the difference in the ward fee. Therefore, we used the health insurance application fee as the hospitalization cost. To avoid underdetection and undercoding of RSV infection, we also analyzed viral LRTI (possibly caused by RSV infection)-associated hospitalization rate. The criteria for identifying viral LRTI in our study were acute bronchiolitis and viral pneumonia with unspecified pathogen (**Table II**) in addition to RSV infection as defined previously.

We then analyzed the prevalence of RSV-associated hospitalization between 2005 and 2010. To calculate the annual CHD population-based incidence of RSV-associated hospitalization, annual episodes were divided by the age-specific, midyear population of children between 2005 and 2010 from the same database.

## Statistical Analyses

The SPSS program, v 15.0 (SPSS Inc, Chicago, Illinois) was used to perform statistical analysis. We used 1-way ANOVA to compare numerical data with a normal distribution and the nonparametric Kruskal-Wallis H test to compare data with a skewed distribution. The data are presented as the mean  $\pm$  SD. The categorical data were analyzed using the  $\chi^2$  and Fisher exact tests. We used logistic regression for multiple risk analysis. Statistical significance was defined as a *P* value of  $<.05$ .

## Results

We identified 8127 patients with CHD who were born between 2005 and 2008 in the database. Among them, 1050 were categorized as the cyanotic group, 2854 were categorized as the hs-acyanotic group, and 4223 were categorized as the non-hs-acyanotic group. The basic demographic data are shown in **Table III**. Sex differences were observed in the 3 groups, with a higher female ratio in the acyanotic group. Approximately 44.8% and 54.0% of patients in the cyanotic and hs-acyanotic groups, respectively, took at least 2 anticongestive medications, and 95.0% in the cyanotic group and 76.0% in the hs-acyanotic group underwent surgery before 2 years of age.

## RSV-Associated Hospitalization

The RSV-associated hospitalization data are shown in **Table IV**. The RSV-associated hospitalization prevalence was the highest in the cyanotic group, both before 1 year of age and between 1 and 2 years of age. In addition, according to our criteria, the RSV-associated hospitalization prevalence was higher in the hs-acyanotic group than in the non-hs-acyanotic group.

Because of possible underdetection or undercoding of RSV infection resulting in viral LRTI, we analyzed the LRTI-associated hospitalization prevalence in the 3 groups (**Table IV**). The LRTI-associated hospitalization prevalence was significantly higher in the cyanotic group than in the hs-acyanotic group and in the hs-acyanotic group than in the non-hs-acyanotic group, both before 1 year of age and

**Table III.** Basic demographic data among cyanotic, hs, and non-hs-acyanotic CHD

	Total (8127)	Cyanotic (1050)	Hs-acyanotic (2854)	Non-hs-acyanotic (4223)	<i>P</i> value
Male (%)	46.7%	53.2%	45.7%	45.8%	.005
$\geq 2$ anticongestive medications (%)	24.9%	44.8%	54.0%	0	$<.001$
Cardiac operation before 2 y of age (%)	39.1%	95.0%	76.0%	0	$<.001$
Chromosome anomaly (%)	3.3%	4.8%	6.1%	1.1%	$<.001$
Prematurity (%)	1.3%	1.4%	1.7%	0.9%	.01

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