

## Risk factors of bronchiolitis

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### Abstract

**Background** Bronchiolitis peak incidence is in children aged 2 - 6 months. History of atopy in parents, non-exclusive breastfeeding, exposure to cigarette smoke, and infants living in crowded areas may be risk factors for bronchiolitis. Gestational age at birth is also influences the mortality of lower respiratory tract infection.

**Objective** To evaluate the following conditions as possible risk factors for bronchiolitis: history of atopy, non-exclusive breastfeeding, preterm infants, exposure to cigarette smoke, and  $\geq 6$  persons residing in the home.

**Methods** A sex-matched case-control study was conducted by collecting data from medical records at Sanglah Hospital, Denpasar. The case group subjects met the diagnostic criteria for bronchiolitis and were aged 1-24 months. The control group included patients with diagnoses unrelated to the respiratory system. Data was analyzed using bivariate (Mc.Nemar) and multivariate methods (logistic regression) with 95% confidence intervals and statistical significance value of  $P < 0.05$ .

**Results** There were 96 subjects in our study, consisted of 48 subjects in the case group and 48 in the control group. The case and control groups were similar in baseline characteristics. The presence of history of atopy (OR 34.7; 95%CI 3 to 367,  $P = 0.003$ ), non-exclusive breastfeeding (OR 4.3; 95%CI 1.4 to 13,  $P = 0.010$ ), exposure to cigarette smoke (OR 3; 95%CI 1 to 9.2,  $P = 0.047$ ), and  $\geq 6$  persons living in the home (OR 7.9; 95%CI 2.6 to 24,  $P < 0.0001$ ) were found to be significant risk factors for bronchiolitis, while the preterm infants seem not significant as a risk factor of bronchiolitis (OR 3; 95%CI 0.31 to 78.99,  $P = 0.625$ ).

**Conclusion** History of atopy, non-exclusive breastfeeding, exposure to cigarette smoke, and  $\geq 6$  persons living in the home are found to be risk factors, while preterm infants seem not a risk factor for bronchiolitis. [Paediatr Indones. 2013;53:21-5.]

**Keywords:** bronchiolitis, risk factors, children

Bronchiolitis is a disease of the lower respiratory tract characterized by bronchiole obstruction. Bronchiolitis is a major public health problem in the world,<sup>1</sup> and often occurs in children under 2 years of age, with the highest incidence in the children aged 2-6 months.<sup>2</sup>

Some factors that have been associated with an increased risk of bronchiolitis in children include history of atopy, duration of breastfeeding, gestational age, exposure to cigarette smoke, and  $\geq 6$  persons living in the home. The influence of parental history of asthma on the occurrence of bronchiolitis is still controversial. Breast milk contains several elements that may prevent disease by respiratory syncytial virus (RSV) and other microbes in the first 4 months of life.<sup>3</sup> Gestational age at birth also affects mortality in children with lower respiratory tract infections. Preterm infants have a higher risk for developing bronchiolitis compared to full term infants.<sup>2</sup> Exposure to cigarette smoke in infants has been reported to be a strong risk factor for acute bronchiolitis.<sup>4</sup> Children who live with relatives in a home with more than 6 children are more likely to have lower respiratory

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tract infections, including bronchiolitis, compared to families with fewer than 6 siblings.<sup>5</sup> In our study, we aimed to evaluate the following conditions as risk factors of bronchiolitis: history of atopy, non-exclusive breastfeeding, preterm infants, exposure to cigarette smoke, and  $\geq 6$  people living in the home.

## Methods

A case-control study was conducted in all children aged 1-24 months who were admitted to the Department of Child Health, Udayana University Medical School/Sanglah Hospital, Denpasar from March to May 2011. Data was collected from medical records.

Subjects in the case group were children diagnosed with bronchiolitis according to standard diagnostic parameters of Sanglah Hospital, Denpasar. Subjects in the control group were children without primary and secondary diagnoses related to the respiratory system, such as acute diarrhea, Dengue fever, or febrile seizures. Patients with congenital heart disease or Down syndrome were excluded. We also excluded patients with incomplete data. The first step was to identify the bronchiolitis and non-bronchiolitis groups and match them by gender. Next, we retrospectively obtained the history of atopy, non-exclusive breastfeeding, gestational age, exposure to cigarette smoke, and population density of the home. This study was approved by the Ethics Committee of Udayana University Medical School/Sanglah Hospital, Denpasar.

The required sample size was calculated using matching case control, with an assumed odds ratio (OR) of each variable (history of atopy, non-exclusive breastfeeding, preterm infants, exposure to cigarette smoke, and  $\geq 6$  people living in the home). The sample size was calculated with the largest OR of non-exclusive breastfeeding, type I error of 5%, and power

of 80%. The number of subjects needed was 48 per group. Data was analyzed for each factor separately by bivariate analysis (Mc.Nemar). Multivariate analysis was performed using backward stepwise logistic regression. Results are presented in the form of OR with 95% confidence intervals, and a statistical significance value of  $P < 0.05$ .

## Results

One hundred patients fulfilled the inclusion criteria, but four were excluded due to congenital heart disease (3 patients) and clinical Down syndrome (1 patient). There were 48 subjects in each group, the case group (bronchiolitis) and the control group (non-bronchiolitis). None of our subjects had severe dehydration, obesity, or birth weight  $> 4000$  grams. Baseline characteristics of subjects are shown in **Table 1** and were similar between groups.

The possible risk factors of bronchiolitis using Mc.Nemar are shown in **Table 2**. Univariate analysis revealed that all variables tested were risk factors for bronchiolitis, except gestational age (preterm infant). Furthermore, based on multivariate analysis, the presence of history of atopy, non-exclusive breastfeeding, exposure to cigarette smoke, and  $\geq 6$  persons living in the home were risk factors for bronchiolitis (OR 34.74; 95%CI 3.28 to 366.93,  $P=0.0030$ , (OR 4.3; 95%CI

**Table 1.** Baseline characteristics of subjects

Characteristics	Case group (n=48)		Control group (n=48)	
Median age (IQ), months	6	(3-12)	10	(6-13)
Nutritional status, n (%)				
Undernourished	15	(31)	21	(44)
Well-nourished	33	(69)	27	(56)
Birth weight, n (%)				
< 2500 g	6	(13)	2	(4)
2500-4000 g	42	(87)	46	(96)

IQ: interquartile range (25<sup>th</sup> -75<sup>th</sup> percentile)

**Table 2.** Univariate analysis of risk factors for bronchiolitis

Variables	Case	Control	OR	95% CI	P value
History of atopy, n (%)	17 (35)	1 (2)	17.00	3.08 to 359.90	0.001
Non-exclusive breastfeeding, n (%)	32 (67)	16 (33)	4.20	1.66 to 12.50	0.002
Preterm infants, n (%)	3 (6)	1 (2)	3.00	0.31 to 78.99	0.625
Exposure to cigarette smoke, n (%)	32 (67)	17 (35)	2.67	1.26 to 6.04	0.014
$\geq 6$ people living in the home, n (%)	34 (71)	11 (23)	12.5	3.46 to 78.30	0.001

**Table 3.** Multivariate analysis of risk factors for bronchiolitis

Variables	OR	95% CI	P value
History of atopy	34.74	3.28 to 366.93	0.003
Non-exclusive breastfeeding	4.30	1.42 to 13.01	0.010
Exposure to cigarette smoke	3.05	1.01 to 9.20	0.047
≥ 6 people living in the home	7.92	2.61 to 24.03	<0.0001

1.42 to 13.01, P=0.010), (OR 3.05; 95%CI 1.01 to 9.20, P= 0.047), and (OR 7.92; 95%CI 2.61 to 24.03, P<0.0001), respectively (Table 3).

## Discussion

Acute viral bronchiolitis is one of the most common causes of hospitalization during infancy. Respiratory syncytial virus causes bronchiolitis and by the age of two years most children have been infected, with the highest incidence in those aged 2-6 months. More boys than girls are reportedly admitted with acute bronchiolitis, at a male to female ratio of 2.24 to 1.<sup>1,2</sup> However, a cross-sectional study in Jakarta showed a greater proportion of males than females, with a ratio of 1.44:1 (PR 3.42; 95%CI 1.10 to 10.64, P=0.034).<sup>6</sup> In our study, more males than females had bronchiolitis, with ratio of 2.6:1. The higher male incidence may be due to a relatively narrower respiratory tract caliber in males than females.<sup>6</sup>

Breast milk has antibodies against RSV, including immunoglobulin (Ig) G and IgA, as well as interferon-gamma (IFN- $\gamma$ ), all of which may serve to neutralize RSV activity.<sup>7</sup> In addition, the immunoregulators and immunomodulators contained in breast milk may enhance maturation of the infant immune system.<sup>8</sup> Studies in children who were not breastfed have been shown to be at a higher risk of RSV infection (OR 1.7; 95%CI 1.2 to 2.5),<sup>9</sup> and suffer from bronchiolitis (OR 4.0; 95%CI 1.6 to 8.7, P=0.01).<sup>10</sup> In our study, non-exclusive breastfeeding was a risk factor of bronchiolitis (OR 4.30; 95%CI 1.42 to 13.01).

Prenatal exposure to cigarette smoke may affect morphogenesis or postnatal development of the lungs and immune system of the child. The mechanism by which passive smoking increases respiratory symptoms and decreases lung function in children is not known. Parental smoking has been shown to enhance allergic sensitization in infants and school children with a close

family history of atopic disease.<sup>11</sup> An American study found that cigarette smoke extract (CSE) inhibited RSV-induced IFN- $\alpha$  in plasmacytoid dendritic cells (pDCs), as well as the release of interleukins (IL-1 $\beta$  and IL-10) and interferon-gamma-induced protein 10 (CXCL10). However, the production of additional cytokines and chemokines such as IL-6, TNF- $\alpha$ , CCL2, CCL3, CCL5 and CXCL8 was not altered. Quantitative RT-PCR analysis indicated that CSE decreased the expression of toll-like receptor (TLR)-7 and interferon regulatory factor (IRF)-7 in RSV-infected pDCs. Furthermore, determination of IRF-7 phosphorylation by flow cytometry showed that CSE prevented IRF-7 activation. These data provide evidence that cigarette smoke suppresses key pDC functions upon viral infection by a mechanism that involves downregulation of TLR-7 expression and decreased activation of IRF-7.<sup>12</sup> History of exposure to cigarette smoke (> 1 smoker) in children increased the risk of RSV infection (RR 1.35; 95% CI 1.20 to 1.52).<sup>13</sup> Children with smoking mothers have been found to be at risk of bronchiolitis (RR 1.1; 95% CI 1.08 to 1.31).<sup>14</sup> Another study reported the prevalence of acute respiratory tract infections to have increased from 81.6% to 95.2% in infants with exposure to cigarette smoke.<sup>6</sup> Exposure to cigarette smoke was reported to be a risk factor for bronchiolitis [(OR 6.63; P <0.001)<sup>15</sup> and (OR 4.7; 95% CI 1.01 to 21.3)].<sup>16</sup> In our study, exposure to cigarette smoke was also a risk factor for bronchiolitis (OR 3.05; 95%CI 1.01 to 9.20, P=0.047).

Household sanitation is also closely related to morbidity from infectious diseases, especially respiratory infections. The housing environment plays a large role in the emergence and spread of these infections and population density in the home has an influence on respiratory events in children under five years of age. In a home with a very high population density and inadequate ventilation, there is increased moisture in the home. Children

who live with  $\geq 2$  family members had an increased risk of hospitalization for RSV infection (OR 1.72;  $P = 0.024$ ).<sup>15</sup> The risk severity of RSV infection in children increased when living with a large number of family members (OR 1.73; 95%CI 1.10 to 2.46).<sup>5</sup> A case-control study showed that the population density in the home was a risk factor for bronchiolitis (OR 3.06; 95% CI 1.92 to 4.89).<sup>17</sup> Similarly, we found that children with  $\geq 6$  people in the home was a risk factor of bronchiolitis (OR 7.92; 95%CI 2.61 to 24.03,  $P < 0.0001$ ).

In the early months of life, preterm infants have increased risk of hospitalization with RSV infection. The immaturity of the humoral and cell-mediated immune systems and inhibited lung development before the age of 36 weeks, reduces the capacity of the remaining lung function.<sup>18</sup> However, we did not see a significant difference in the proportion of infants' gestational ages in the case and control groups since the overall proportion of premature infants was only 4.1%. Hence, we were unable to better assess the incidence of bronchiolitis in preterm infants.

Atopy is a predisposing factor of bronchiolitis. Children with a history of atopy produce less IFN- $\gamma$ . Respiratory syncytial virus infection would suppress the function of IFN- $\gamma$  causing the level and function of IFN- $\gamma$  to decrease. In addition, children with a history of atopy in parents lead to the development of Th2 immunity and impaired development of Th1 immunity. Strong Th2 cell response in children with atopy in the elderly, causing Th2 cells secrete IL-4 and IL-13 that stimulate B lymphocytes to differentiate into plasma cells which then produce IgE producing growing severity of infection.<sup>5,19</sup> Children whose mothers suffered from asthma had 1.52 times increased risk of acute bronchiolitis (95%CI 1.26 to 1.87).<sup>14</sup> A history of atopy was a significant factor associated with the occurrence of bronchiolitis (OR 20.41; 95%CI 1.09 to 333.33).<sup>6</sup> Similarly, we found that a history of atopy was a risk factor for bronchiolitis (OR 34.74; 95%CI 3.28 to 366.93,  $P = 0.003$ ).

There were several limitations in this study. Retrieving data retrospectively from medical records and validation of the information was sometimes difficult to do. In addition, we did not measure the duration of cigarette exposure, the total number of cigarettes smoked per day, nor the spatial areas of subjects' homes.

In conclusion, we find that history of atopy, non-exclusive breastfeeding, exposure to cigarette smoke, and a population density of  $\geq 6$  persons in the home are significant risk factors for bronchiolitis. However, preterm birth is not a risk factor for bronchiolitis.

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