Environmental Tobacco Smoke Exposure and Respiratory Syncytial Virus Infection in Young Children Hospitalized with Acute Lower Respiratory Tract Infection

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Objective: *The present study was performed to determine the relationship between environmental tobacco smoke (ETS) exposure and acute lower respiratory tract infection (LRI) caused by respiratory syncytial virus (RSV) in children.*
Material and Method: *The authors did the study in 71 children (median age 12 months; 60% male) who were admitted to King Chulalongkorn Memorial Hospital with acute LRI between June and September 2004. 27% had RSV infection.*
Results: *RSV-LRI required longer duration of oxygen therapy than non RSV-LRI (4.5 $\pm$ 1.7 vs 2.8 $\pm$ 1.3 days; $p < 0.001$). Desaturation in room air was more common in the former group compared to the latter group (37 vs 11%; $p = 0.01$). There was no difference in urinary cotinine level between the two groups (median 0.5 vs 0.6 mcg/mg Cr; ns). Among RSV-LRI, those with desaturation had higher urinary cotinine level than those without desaturation (median 0.8 vs 0.0 mcg/mg Cr; $p = 0.04$).*
Conclusion: *ETS exposure was not associated with RSV-LRI but increased the risk of desaturation in these patients.*

Keywords: *RSV, Passive smoking, Children, Cotinine, Acute lower respiratory tract infection*

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Respiratory syncytial virus (RSV) is a common cause of acute lower respiratory tract infection (LRI) in young children. The infection can be severe and is associated with high morbidity, especially among those who are in the high-risk group[1]. RSV infection can lead to significant long-term sequel such as recurrent wheezing or asthma[2,3]. Identification and avoidance of factors predisposed to RSV infection are important in preventing the disease and its sequel.

It has been known that ETS exposure increases the risk of respiratory illness in children[4-7]. Several studies also reported the association between ETS exposure and RSV infection in young children[8-13]. Whether or not ETS exposure is associated with RSV-LRI and its severity is still, however, controversial. The objective of the present study was to investigate the relationship between ETS exposure and the occurrence as well as the severity of RSV-LRI in young children.

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Material and Method

Young children aged 0-5 years who were admitted to King Chulalongkorn Memorial Hospital with acute LRI during a seasonal period of RSV infection (June - September 2004) were recruited into the present study. Written informed consents were obtained from the parents or caregivers prior to the present study. Patients with cyanotic heart diseases and those who

were currently treated with cimetidine or ranitidine were excluded. The study protocol was approved by the Ethics Committee for Human Research Study of the hospital.

Collected data included history of illness, personal history (history of preterm, underlying diseases, duration of breastfeeding), family history (in-house smoking, number of the people sharing the bedroom with the patient) and duration of oxygen therapy in this hospitalization. Initial pulse oximetry was recorded while the patient was quietly breathing in room air. Desaturation was defined if the patient demonstrated arterial oxygen saturation recorded by pulse oximetry (SpO_2) < 92%. Nasopharyngeal secretion was collected by suctioning on the first day of admission and was immediately processed to the laboratory where RSV antigen assay was performed by using indirect immunofluorescent antibody technique. Random single clean catch urine sample was also obtained on the same day and was processed within 24 hours to the Department of Biochemistry where urinary cotinine and creatinine levels were measured. If the specimen (either nasopharyngeal secretion or urine) delivery process could not be done on that day, it would have been kept at 4 C and sent to the laboratory on the following day. All urine specimens had been frozen at -20 C until the biochemistry measurement was performed. The urinary cotinine and creatinine levels were evaluated by the same medical technologist who was blinded to the patients' data throughout the study period. The cotinine and creatinine measurements were done by using spectrophotometry technique previously described by Cope G, et al[14].

During hospitalization, all patients were treated and followed up by general pediatricians who were not involved in the present study. Oxygen therapy was provided until the patients demonstrated normal respiration and adequate oxygenation ($SpO_2 \geq 92\%$) in room air.

Data acquisition and analysis

The continuous variables including age, duration of breastfeeding, initial SpO_2 in room air, duration of oxygen therapy and urinary cotinine/mg creatinine level were expressed as mean $\pm$ SD for Gaussian distribution data and as median for non - Gaussian distribution. Comparison of two groups of continuous variables was done by using unpaired Student's t-test or Mann-Whitney U-test where applicable. Chi-square or Fisher's Exact test (where applicable) was used to calculate the relationship between the two groups of categorical data. Multinominal logistic regression analysis was used to define independent risk factors associated with desaturation in RSV + ve group. The *p* value of less than 0.05 was considered for a statistical significance. GraphPad Instat Program (GraphPad Software Inc.; San Diego, CA) and SPSS version 13.0 for Windows (SPSS Inc.; Chicago, IL) were used for statistical analysis.

Results

Seventy-two patients were hospitalized with acute LRI during the present study period. One patient had congenital cyanotic heart disease and was excluded from the present study. There was no patient that had been on cimetidine or ranitidine. Seventy-one patients were eligible for the study. RSV antigen was detected in 19 of these (27%). Of the 71 patients, 24 (34%) had underlying diseases (Table 1).

Demographic and other study data were compared between RSV-LRI and non RSV-LRI (Table 2). The patients with RSV-LRI had a shorter duration of breastfeeding when compared to those with non RSV - LRI (1.8 ± 1.5 *vs* 3.5 ± 2.5 months; $p = 0.007$). The urinary cotinine/mg creatinine level, number of patients exposed to in - house smoking, number of patients who had > 3 people sharing the same bedroom, history of preterm and relating underlying diseases were not different between the two groups (Table 2). In regard to the clinical course, initial desaturation in room air was found more commonly in RSV-LRI when compared to non RSV-LRI. (37% *vs* 11%; $p = 0.01$) (Table 2). The RSV-LRI required longer duration of oxygen therapy than the non RSV-LRI (4.5 ± 1.7 *vs* 2.8 ± 1.3 days; $p < 0.001$) (Table 2).

Among RSV - LRI patients, 7/19 (37%) had initial desaturation in room air. Patients with desaturation had a shorter duration of breastfeeding and higher

Table 1. Underlying diseases of the study patients (n = 71)

	RSV +ve*	RSV –ve
Reactive airway diseases	2	5
Neuromuscular diseases	1	5
Immune defects	1	2
Congenital heart diseases	1	3
Down syndrome	2	1
Bronchopulmonary dysplasia	1	2

* There were 2 patients that had 2 underlying diseases (bronchopulmonary dysplasia with reactive airway disease and Down syndrome with congenital heart disease, respectively)

Table 2. Demographic and other collected data of the study patients

	Total (n = 71)	RSV +ve (n = 19)	RSV –ve (n = 52)
Median age (range)	12 months (0.5-60 months)	9 months (0.5-48 months)	12 months (1-60 months)
Male	43 (60%)	12 (63%)	31 (60%)
History of preterm	13 (18%)	2 (11%)	11 (21%)
History of related underlying diseases	24 (34%)	6 (32%)	18 (35%)
Duration of breastfeeding (range)	3.0 ± 2.4 months (0-12 months)	1.8 ± 1.5 months* (0-6 months)	3.5 ± 2.5 months* (0-12 months)
Number of patients who had > 3 people sharing the bedroom with	46 (65%)	11 (58%)	35 (67%)
Number of patients with history of in-house smoking	20 (28%)	6 (32%)	14 (27%)
Median urinary cotinine level (range)	0.5 mcg/mg Cr (0-9.6 mcg/mg Cr)	0.5 mcg/mg Cr (0-5.8 mcg/mg Cr)	0.6 mcg/mg Cr (0-9.6 mcg/mg Cr)
Initial SpO_2 in room air (range)	94 ± 3% (85-98%)	93 ± 13% (85-98%)	94 ± 7% (86-98%)
Number of patients with initial desaturation (SpO_2 < 92%) in room air	12 (17%)	7 (37%)*,[2]	5 (11%)*,[2]
Duration of oxygen therapy (range)	3.4 ± 1.6 days (0-8 days)	4.5 ± 1.7 days*,[1] (2-8 days)	2.8 ± 1.3 days*,[1] (0-8 days)

* $p < 0.05$

[1] = Unpaired t-test, [2] = $p < 0.05$ (Chi-square test)

urinary cotinine level when compared to those without desaturation (0.9 ± 0.7 *vs* 2.3 ± 1.6 months; $p = 0.03$ and 0.8 *vs* 0.0 mcg/mg creatinine; $p = 0.04$, respectively) (Table 3). Urinary cotinine was detected in 100% and 33% of RSV-LRI who had desaturation and no desaturation, respectively (Table 3). Positive urinary cotinine increased the risk of desaturation in RSV-LRI patients (Odds ratio = 28.3; 95%CI = 1.3-618.4; $p = 0.01$). When using multinomial logistic regression analysis, the authors found that a positive urinary cotinine was the only independent risk factor of desaturation in RSV-LRI patients (Likelihood ratio = 7.1; $p = 0.008$). These associations were not found in RSV –ve patients (the results are not shown).

Discussion

The present study could not demonstrate the relationship between ETS exposure (assessed by urinary cotinine assay) and the occurrence of RSV infection in young children hospitalized with acute LRI. Many previous studies reported that ETS exposure was a risk factor of RSV-LRI[8-11]. However, some studies, including a study in Thailand, could not demonstrate this[12,13,15]. The characteristics of the control groups used for comparing with the RSV +ve group varied among the studies and could be the cause of this divergence. Some of the studies defined normal children who did not have LRI as a control group[8,9,11]. while some did not clearly define whether the control groups were those who did not have LRI or those who had LRI caused by other etiologies[10,12,13]. In the present study, the authors compared the frequency of ETS exposure between the children who had RSV-LRI and those who had LRI caused by other etiologies. The

Table 3. Comparisons between desaturation (SpO_2 < 92%) and non desaturation (SpO_2 ≥ 92%) groups in RSV +ve patients

	SpO_2 < 92% (n = 7)	SpO_2 ≥ 92% (n = 12)	p-value
Median age (range)	6 months (0.5-36 months)	10 months (4-48 months)	ns*
Male	3 (43%)	9 (75%)	ns
History of preterm	1 (14%)	1 (8%)	ns
History of related underlying diseases	3 (43%)	3 (25%)	ns
Duration of breastfeeding (range)	0.9 ± 0.7 months (0 – 2 months)	2.3 ± 1.6 months (0-6 months)	0.03
Number of patients who had > 3 people sharing the bedroom with	4 (57%)	7 (58%)	ns
Number of patients with history of in-house smoking	2 (29%)	4 (33%)	ns
Median urinary cotinine level (range)	0.8 mcg/mg Cr (0.5-3.8 mcg/mg Cr)	0.0 mcg/mg Cr (0.0-5.8 mcg/mg Cr)	0.04
Number of patients who had urinary cotinine detected	7 (100%)	4 (33%)	0.01**

* ns = no statistical significance (Fisher's Exact test)
**Odds ratio = 28.3 (95%CI = 1.3-618.4)

authors found that ETS exposure was not more associated with RSV infection than other causes of LRI. Suwanjutha S, et al performed a similar study in a larger population in Thailand but used parental reports for assessing ETS exposure in children[15]. They did the comparison between RSV-LRI and non RSV-LRI children and could not demonstrate the association between ETS exposure and RSV-LRI either[15].

Prevalence and risk factors of RSV infections vary among the countries[1,15-20]. Many studies in Western countries reported several environmental factors that were associated with RSV-LRI[1,8-13,20]. However, very few studies in tropical countries reported these issues[15,16]. In addition to the different control groups used in the studies, different climates, genetic background, and socioeconomic conditions in different regions of the world as well as different techniques used for RSV antigen detection in the studies can be the causes of the divergent findings among these studies.

Even though the authors could not demonstrate that ETS exposure was more associated with RSV-LRI than other causes of LRI, the authors did find that ETS exposure was an independent risk factor of desaturation in children with RSV-LRI. This association was not found in children with LRI caused by other etiologies. Previous studies reported that a history of ETS exposure could affect the severity of RSV-LRI[13,21]. Kotts and Auais also reported the deleterious effects of nicotine on the lungs in human and animal studies in the 2005 American Thoracic Society Conference[22,23]. They suggested that nicotine could induce several inflammatory cytokines productions and lead to inflammations in the respiratory system. In an animal study, nicotine exposure enhanced the inflammatory response in RSV-infected mice by increasing the expression of nerve growth factor in respiratory epitheliums[23]. In the present study, the increased risk of desaturation among RSV-LRI patients who were exposed to ETS could be related to the synergistic

effects of nicotine exposure and RSV infections in the lungs.

Breastfeeding is another factor that may be associated with RSV infection. Holberg CJ et al found that no or less than 1 month breastfeeding increased the risk of RSV-LRI in infants aged 1 to 3 months[12]. In the present study, the authors found that patients with RSV-LRI had a shorter duration of breastfeeding when compared to those with acute LRI caused by other agents.

Seasonality of RSV infection varies among the countries. In temperate climates, the infections are more prevalent in winter months whereas in the tropical climates, the infections are more prevalent in the rainy season[1]. In the present study, prevalence of RSV infections in young children hospitalized with acute LRI during the rainy season (June - September) was 27%, the same as were reported in the all-year studies in Thailand and Indonesia[15-19], but lower than those reported in Northern America and Europe[1].

Acute complications of RSV-LRI include hypoxemia and acute respiratory failure[1]. In the present study, initial desaturation in room air was more commonly found in RSV-LRI than non RSV-LRI. The patients with RSV-LRI required longer duration of oxygen therapy than those with non RSV-LRI. It has been known that RSV can cause respiratory epithelial cells damages and induce several inflammatory immune responses in the lungs[24]. Whether or not RSV causes more severe cytopathic and immunologic responses than other respiratory pathogens, however, still needs to be investigated.

In conclusion, the present study could not demonstrate that ETS exposure was more associated with RSV-LRI than other causes of LRI in young children. However, the authors found that ETS exposure increased the severity of RSV-LRI. Protecting young children from ETS exposure should be another approach to prevent the morbidity and mortality caused by severe RSV infection in young children hospitalized with acute LRI.

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Abreviations

ETS = Environmental tobacco smoke, LRI = Lower respiratory tract infection, RSV = Respiratory syncytial virus, SpO_2 = Arterial oxygen saturation recorded by pulse oximetry

References

1. Law BJ, Carbonell-Estrany X, Simoes EA. An update on respiratory syncytial virus epidemiology: a developed country perspective. Respir Med 2002; 96(Suppl B): S1-7.
2. Wennergren G, Kristjansson S. Relationship between respiratory syncytial virus bronchiolitis and future obstructive airway diseases. Eur Respir J 2001; 18: 1044-58.
3. Kneyber MCJ, Steyerberg EW, de Groot R, Moll HA. Long-term effects of respiratory syncytial virus (RSV) bronchiolitis in infants and young children: a quantitative review. Acta Paediatr 2000; 89: 654-60.
4. Rylander E, Pershagen G, Eriksson M, Bermann G. Parental smoking, urinary cotinine, and wheezing bronchitis in children. Epidemiology 1995; 6: 289-93.
5. Bakoula CG, Kafritsa YJ, Kavadias GD, Lazopoulou DD, Theodoridou MC, Maravelias KP, et al. Objective passive-smoking indicators and respiratory morbidity in young children. Lancet 1995; 346: 280-1.
6. Ehrlich RI, Du TD, Jordaan E, Zwarenstein M, Potter P, Volmink JA, et al. Risk factors for childhood asthma and wheezing. Importance of maternal and household smoking. Am J Respir Crit Care Med 1996; 154: 681-8.
7. Ilicali OC, Keles N, De er K, Sa un OF, Guldiken Y. Evaluation of the effect of passive smoking on otitis media in children by an objective method: urinary cotinine analysis. Laryngoscope 2001; 111: 163-7.
8. Carbonell-Estrany X, Quero J. Hospitalization rates for respiratory syncytial virus infection in premature infants born during two consecutive seasons. Pediatr Infect Dis J 2001; 20: 874-9.
9. Gurkan F, Kiral A, Dagli E, Karakoc F. The effect of passive smoking on the development of respiratory syncytial virus bronchiolitis. Eur J Epidemiol 2000; 16: 465-8.
10. Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. Pediatrics 1988; 82: 199-203.

11. Hayes EB, Hurwitz ES, Schonberger LB, Anderson LJ. Respiratory syncytial virus outbreak on American Samoa. Evaluation of risk factors. Am J Dis Child 1989; 143: 316-21.
12. Holberg CJ, Wright AL, Martinez FD, Ray CG, Taussig LM, Lebowitz MD. Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life. Am J Epidemiol 1991; 133: 1135-51.
13. Lanari M, Giovannini M, Giuffre L, Marini A, Rondini G, Rossi GA, et al. Prevalence of respiratory syncytial virus infection in Italian infants hospitalized for acute lower respiratory tract infections, and association between respiratory syncytial virus infection risk factors and disease severity. Pediatr Pulmonol 2002; 33: 458-65.
14. Cope G, Nayyar P, Holder R, Gibbons J, Bunce R. A simple near-patient test for nicotine and its metabolites in urine to assess smoking habit. Clin Chim Acta 1996; 256: 135-49.
15. Suwanjutha S, Sunakorn P, Chantarojanasiri T, Siritantikorn S, Nawanoparatkul S, Rattanadilok Na BT, et al. Respiratory syncytial virus-associated lower respiratory tract infection in under-5-year-old children in a rural community of central Thailand, a population-based study. J Med Assoc Thai 2002; 85(Suppl 4): S1111-9.
16. Djelantik IG, Gessner BD, Soewignjo S, Steinhoff M, Sutanto A, Widjaya A, et al. Incidence and clinical features of hospitalization because of respiratory syncytial virus lower respiratory illness among children less than two years of age in a rural Asian setting. Pediatr Infect Dis J 2003; 22: 150-7.
17. Sunakorn P, Chunchit L, Niltawat S, Wangweerawong M, Jacobs RF. Epidemiology of acute respiratory infections in young children from Thailand. Pediatr Infect Dis J 1990; 9: 873-7.
18. Suwanjutha S, Chantarojanasiri T, Watthana-kasetr S, Sirinavin S, Ruangkanchanasetr S, Hotrakitya S, et al. A study of nonbacterial agents of acute lower respiratory tract infection in Thai children. Rev Infect Dis 1990; 12(Suppl 8): S923-8.
19. Limudomporn S, Prapphal N, Suttiboon V, Punnaragse V. Respiratory syncytial virus pneumonia in pediatric patients: seasonal occurrence and clinical aspects. Chula Med J 1988; 32: 531-6.
20. Liese JG, Grill E, Fischer B, Roeckl-Wiedmann I, Carr D, Belohradsky BH. Incidence and risk factors of respiratory syncytial virus-related hospitalizations in premature infants in Germany. Eur J Pediatr 2003; 162: 230-6.
21. Bradley JP, Bacharier LB, Bonfiglio J, Schechtman KB, Strunk R, Storch G, et al. Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy. Pediatrics 2005; 115: e7-14.
22. Kott KS, Sakimura J, Jhawar S, McDonald RJ, Gershwin LJ, Bric JM, et al. Second hand smoke effects on cysteinyl leukotrienes in well infants. Am J Respir Crit Care Med 2005; 2: A598.
23. Auais A, Mohtasham L, Renzetti G, Piedimonte G. Combined effect of respiratory syncytial virus (RSV) and nicotine on nerve growth factor (NGF) expression in the developing respiratory tract of rats. Am J Respir Crit Care Med 2005; 2: A601.
24. Ogra PL. Respiratory syncytial virus: the virus, the disease and the immune response. Paediatr Respir Rev 2004; 5(Suppl A): S119-26.

ผลของการได้รับควันบุหรี่จากสิ่งแวดล้อมต่อการติดเชื้อเรสไปราตอรีซินไซเชียลไวรัสในผู้ป่วยเด็กเล็กที่เข้ารับการรักษาในโรงพยาบาลด้วยโรคติดเชื้อเฉียบพลันระบบทางเดินหายใจส่วนล่าง

สุชาดา ศรีทิพยวรรณ, นวลจันทร์ ปราบพาล, เพียรศักดิ์ แซ่หว่อง, ปิยะรัตน์ โตสุโขวงศ์, รุจิภัตต์ สำราญสำรวจกิจ, จิตลัดดา ดีโรจนวงศ์

วัตถุประสงค์: *ศึกษาเพื่อหาความสัมพันธ์ระหว่างการได้รับควันบุหรี่จากสิ่งแวดล้อมกับการติดเชื้อเรสไปราตอรีซินไซเชียลไวรัส*

วัสดุและวิธีการ: *ศึกษาในผู้ป่วยเด็กอายุ 0-5 ปีที่เข้ารับการรักษาในโรงพยาบาลด้วย เรื่องโรคติดเชื้อเฉียบพลันระบบทางเดินหายใจส่วนล่าง โดยศึกษาในผู้ป่วย 71 ราย (ค่ามัธยฐานของอายุ 12 เดือน; เป็นเพศชายร้อยละ 60) ซึ่งเข้ารับการรักษาในโรงพยาบาลด้วยโรคติดเชื้อดังกล่าวระหว่างเดือนมิถุนายน-กันยายน พ.ศ. 2547 พบว่า ร้อยละ 27 ของผู้ป่วยติดเชื้อเรสไปราตอรีซินไซเชียลไวรัส ผู้ป่วยที่ติดเชื้อไวรัสดังกล่าวได้รับการรักษาด้วยออกซิเจนนานกว่าและตรวจพบภาวะพร่องของออกซิเจนในเลือดแดงบ่อยกว่าผู้ป่วยที่ไม่ได้ติดเชื้อไวรัสดังกล่าว (4.5 $\pm$ 1.7 vs 2.8 $\pm$ 1.3 วัน; $p < 0.001$ และร้อยละ 37 vs 11; $p = 0.01$ ตามลำดับ)*

ผลการศึกษา: *ไม่พบความแตกต่างระหว่าง 2 กลุ่มในเรื่องของระดับโคตินีนในปัสสาวะ (ค่ามัธยฐานของระดับโคตินีนในปัสสาวะ 0.5 vs 0.6 ไมโครกรัม/มิลลิกรัมครีอะตินีน; ns). ในผู้ป่วยที่ติดเชื้อเรสไปราตอรีซินไซเชียลไวรัส พบว่าผู้ป่วยที่มีภาวะพร่องของออกซิเจนในเลือดแดงมีระดับโคตินีนในปัสสาวะสูงกว่าผู้ป่วยที่ไม่มีภาวะพร่องของออกซิเจนในเลือดแดง (ค่ามัธยฐานของระดับโคตินีนในปัสสาวะ 0.8 vs 0.0 ไมโครกรัม/มิลลิกรัมครีอะตินีน; $p = 0.04$)*

สรุป: *การได้รับควันบุหรี่จากสิ่งแวดล้อมไม่มีความสัมพันธ์กับโรคติดเชื้อเฉียบพลันระบบทางเดินหายใจส่วนล่างที่เกิดจากเชื้อเรสไปราตอรีซินไซเชียลไวรัส แต่เกี่ยวข้องกับการเกิดภาวะพร่องออกซิเจนในเลือดแดงในผู้ป่วยกลุ่มดังกล่าว*