RISK FACTORS FOR HYPOXEMIA AND RESPIRATORY FAILURE IN RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS

PWK Chan, FYL Lok and SB Khatijah

Division of Respiratory Medicine, Department of Paediatrics, University of Malaya Medical Center, Kuala Lumpur, Malaysia

Abstract. Respiratory syncytial virus (RSV) bronchiolitis is a common infection in young children and may result in hospitalization. We examined the incidence of, and risk factors associated with, hypoxemia and respiratory failure in 216 children aged < 24 months admitted consecutively for proven RSV bronchiolitis. Hypoxemia was defined as SpO_2 < 90% in room air and severe RSV bronchiolitis requiring intubation and ventilation was categorized as respiratory failure. Corrected age at admission was used for premature children (gestation < 37 weeks).

Hypoxemia was suffered by 31 (14.3%) children. It was more likely to occur in children who were Malay (OR 2.56, 95%CI 1.05-6.23, p=0.03) or premature (OR 6.72, 95%CI 2.69-16.78, p<0.01). Hypoxemia was also more likely to develop in children with failure to thrive (OR 2.96, 95%CI 1.28-6.82, p<0.01). The seven (3.2%) children who were both premature (OR 11.94, 95%CI 2.50-56.99, p<0.01) and failure to thrive (OR 6.41, 95%CI 1.37-29.87, p=0.02) were more likely to develop respiratory failure. Prematurity was the only significant risk factor for hypoxemia and respiratory failure by logistic regression analysis (OR 1.17, 95%CI 1.06-1.55, p<0.01 and OR 1.14 95%CI 1.02-2.07, p=0.02 respectively). Prematurity was the single most important risk factor for both hypoxemia and respiratory failure in RSV bronchiolitis.

INTRODUCTION

Viral respiratory tract infections contribute significantly to childhood morbidity worldwide and, more importantly, mortality in predominantly poor developing nations. Viral bronchiolitis often affects the very young child and is most commonly caused by respiratory syncytial virus (RSV). RSV bronchiolitis is usually a mild self-limiting illness and almost all children will have experienced an episode of RSV infection by 24 months of age (Glezen *et al*, 1986). Severe RSV bronchiolitis resulting in hypoxemia and respiratory failure is well documented in several categories of children: those who were born prematurely and those with pre-existing medical conditions, *eg* chronic lung disease, congenital heart disease, and immunodeficiency (La Via *et al*, 1992; Wang *et al*, 1995). With advances in neonatal and medical care, children with pre-existing conditions and who are born prematurely are more likely to survive, providing a population susceptible to severe RSV bronchiolitis.

RSV bronchiolitis is an important cause of hospital admission in young Malaysian children with respiratory infections (Chan and Goh, 1999) and the development of respiratory distress appears to be associated with risk factors like prematurity, underlying illness and age less than 3 months (Chan *et al*, 1999). The clinical circumstances associated with hypoxemia and respiratory failure in RSV bronchiolitis are, however, less well defined in Malaysian children.

We examined the incidence of, and identified the risk factors associated with, the development of hypoxemia and respiratory failure in RSV bronchiolitis.

Correspondence: Dr Patrick WK Chan, Department of Pediatrics, University of Malaya Medical Center, 59100 Kuala Lumpur, Malaysia.
Tel: ++ (603) 7950-2065; Fax: ++ (603) 7955-6114
E-mail: patrickchan@um.edu.my

MATERIALS AND METHODS

The University of Malaya Medical Center is a university-affiliated hospital situated in Kuala Lumpur, the capital of Malaysia. It provides primary medical care for the predominantly urban population of the local area and offer tertiary medical services to the rest of the nation. We reviewed the medical records of 216 children admitted consecutively who fulfilled the following criteria: age less than 24 months; clinical diagnosis of viral bronchiolitis; RSV isolated in the naso-pharyngeal secretion by immunofluorescence, viral culture or both.

The clinical information was documented in a prospective manner using a standard clinical admission sheet and data was extracted retrospectively for this study. Children who were delivered at a gestational age of less than 37 weeks were considered as premature. In this category of children, the corrected age at admission was used for analysis. Children whose weight was less than the 3rd centile for age were considered as failing to thrive. Socio-economic status was determined according to the United Kingdom Registrar's Classification of Occupational class ranks based on the fathers' occupation and was divided into 5 categories: Class I, leading professional and business (*ie* doctor, manager); Class II, minor professional and business (*ie* teacher, pharmacists, store-keeper); Class III, skilled worker (*ie* clerk, factory foreman); Class IV, semiskilled worker (*ie* truck driver, factory worker, salesman); Class V, non-skilled worker (*ie* porter, laborer, waiter).

Hypoxemia: All children who were admitted with viral bronchiolitis would have a routine percutaneous oxygen saturation measurement (SpO_2) done at admission using a pulse oxymeter (Model N-185, Nelcor, USA). The SpO_2 measurement was only recorded if a good quality wave was achieved from the probe site. A SpO_2 measurement of less than 90% in room air was used as the definition of hypoxemia (Mai *et al*, 1995). A SpO_2 measurement of 90% was chosen as the cut-off based on the correlation curve study between arterial pO_2 and SpO_2 in children that showed a plateau of the steep curve beyond this point (Southall *et al*, 1987). In addition, a SpO_2 measurement of less than 90% was also consistent with documented hypoxemia using arterial pO_2. Sixteen children had congenital heart disease of which none was an anatomically cyanotic cardiac lesion. None of the children was known to have an underlying chronic haematological disorder *eg* sickle cell disease, methemaglobinemia.

Respiratory failure: Severe RSV bronchiolitis requiring intubation and positive pressure ventilation was considered as respiratory failure. Continuous positive airway pressure (CPAP) support for severe RSV bronchiolitis is not routinely used in our unit.

Statistical analysis

Data collected was analyzed using SPSS (version 7.5) for Windows 1998 (SPSS Inc, Chicago, Illinois, USA). Univariate analysis was initially performed to examine risk factors associated with hypoxemia and respiratory failure in our study population using chi-squared or Fisher's Exact test where appropriate. Multivariate logistic regression analysis with backward stepwise process was then done with variables identified by univariate analysis. All results were expressed as odd ratios (OR) and their appropriate 95% confidence intervals (CI). A p value of less than 0.05 was considered significant.

RESULTS

Hypoxemia was suffered by 31 (14.3%) children admitted with RSV bronchiolitis. Risk factors associated with the development of hypoxemia in RSV bronchiolitis included Malay ethnicity, prematurity, and failure to thrive. Children who were Chinese appeared to be less likely to develop hypoxemia in RSV bronchiolitis (Table 1). The age at admission, sex, socio-economic status and pre-existing cardiac disease were not associated with hypoxemia in RSV bronchiolitis.

Table 1
Univariate analysis of risk factors associated with hypoxemia in RSV bronchiolitis (N = 216).

Risk factor	No hypoxemia (n = 185)	Hypoxemia (n = 31)	OR	95% CI	p
Age					
< 1 month	1 (0.5%)	2 (6.5%)	12.69	1.11 - 14.52	0.05
< 2 months	20 (10.8%)	5 (16.1%)	1.59	0.55 - 4.60	0.28
< 3 months	33 (17.8%)	10 (32.3%)	2.21	1.02 - 5.09	0.06
Sex					
Boys	118 (63.8%)	17 (54.8%)	0.95	0.84 - 1.07	0.34
Girls	67 (36.2%)	14 (45.2%)	1.45	0.67 - 3.13	0.34
Ethnicity					
Malay	106 (57.3%)	24 (77.4%)	2.55	1.05 - 6.23	0.03[a]
Chinese	43 (23.2%)	2 (6.5%)	0.23	0.05 - 0.99	0.03[a]
Indian	36 (19.5%)	5 (16.1%)	0.80	0.29 - 2.22	0.67
Social class					
Class I	11 (5.7%)	2 (6.5%)	1.21	0.24 - 5.77	0.55
Class II	27 (14.5%)	5 (16.1%)	1.17	0.41 - 3.31	0.47
Class III	77 (41.8%)	7 (22.6%)	0.42	0.17 - 1.05	0.06
Class IV	64 (34.8%)	15 (48.4%)	1.87	0.85 - 4.11	0.11
Class V	6 (3.2%)	2 (6.4%)	1.06	0.12 - 0.37	0.96
Failure to thrive	29 (15.7%)	11 (35.5%)	2.96	1.28 - 6.82	<0.01[a]
Prematurity	14 (7.6%)	11 (35.5%)	6.72	2.69 - 16.78	<0.01[a]
Cardiac disease	14 (7.6%)	2 (6.5%)	0.84	0.18 - 3.90	0.83

[a]significant p value

Seven (3.2%) children developed respiratory failure due to RSV bronchiolitis. Prematurity and failure to thrive were the only 2 risk factors associated with respiratory failure in our study (Table 2).

Prematurity was the only independent risk factor for the development of hypoxemia (OR 1.17, 95%CI 1.06-1.55, p<0.01) and respiratory failure (OR 1.14, 95%CI 1.02-2.07, p = 0.02) in RSV bronchiolitis after multivariate logistic regression analysis.

DISCUSSION

Hypoxemia and respiratory failure are leading complications in RSV bronchiolitis that may result in long term respiratory morbidity and death in young children. Hypoxemia is more easily recognized with the increasing availability and utilization of percutaneous pulse oxymetry rather than depending on the clinical sign of cyanosis, a rather late and severe manifestation of hypoxemia. Assessment of cyanosis is made more difficult in the absence of good natural lighting, a pigmented child and if there is poor circulation; situations faced frequently in our clinical practice. More importantly, hypoxemia can be readily corrected with the administration of supplemental oxygen and if administered early, prevents the progression of worsening hypoxemia that may result in respiratory failure or death. The respiratory rate, usually considered the best indicator of the severity of respiratory tract infection, has not been found to be a reliable guide in the young child with RSV bronchiolitis (Simpson and Flenley, 1967; Mulholland *et al*, 1990). If possible, percutaneous pulse oxymetry should made available in the assessment of these children. Percutaneous pulse oxymetry is simple and easy to use and causes minimal distress to the unwell child, who would not tolerate the discomfort of an arterial punc-

Table 2
Univariate analysis of risk factors associated with respiratory failure in RSV bronchiolitis (N = 216).

Risk factor	No respiratory failure (n = 209)	Respiratory failure (n = 7)	OR	95% CI	p
Age					
< 1 month	2 (1.0%)	1 (14.3%)	1.45	0.65 - 3.25	0.07
< 2 months	23 (11.0%)	2 (28.6%)	3.23	0.59 - 17.64	0.19
< 3 months	40 (19.1%)	3 (42.8%)	3.17	0.68 - 14.72	0.14
Sex					
Boys	131 (62.7%)	4 (57.1%)	0.79	0.17 - 3.64	0.53
Girls	78 (37.3%)	3 (42.9%)	1.26	0.27 - 5.78	0.53
Ethnicity					
Malay	125 (59.8%)	5 (71.4%)	1.68	0.32 - 8.86	0.54
Chinese	44 (21.1%)	1 (14.3%)	0.63	0.07 - 5.33	0.55
Indian	40 (19.1%)	1 (14.3%)	0.70	0.08 - 6.01	0.60
Social class					
Class I	13 (6.0%)	0 (0%)	NA	NA	0.69
Class II	32 (15.4%)	0 (0%)	NA	NA	0.38
Class III	80 (38.5%)	3 (42.9%)	1.20	0.26 - 5.52	0.53
Class IV	77 (36.8%)	3 (42.9.%)	1.28	0.30 - 5.93	0.52
Class V	7 (3.3%)	1 (14.2%)	4.89	0.51 - 47.22	0.24
Failure to thrive	36 (17.2%)	4 (57.1%)	6.41	1.37 - 29.87	0.02[a]
Premature	21 (10.0%)	4 (57.1%)	11.94	2.50 - 56.99	<0.01[a]
Cardiac disease	15 (7.2%)	1 (14.3%)	2.16	0.24 - 19.09	0.42

NA = not available; [a]significant p value.

ture for a blood gas determination of hypoxemia. Even in poor developing nations, its use and importance appear to be increasingly recognized in identifying hypoxemia in children with respiratory infection (Duke *et al*, 2001).

Prematurity was found to be the most important risk factor for both hypoxemia and respiratory failure in our study population. This observation is consistent with the common finding that premature infants, despite being well are a more likely to develop severe respiratory distress with RSV bronchiolitis (Groothius *et al*, 1988; Meert *et al*, 1990). It is therefore reasonable to advocate that vigilance be exercised in assessing premature infants who present with RSV bronchiolitis and that early intervention, namely a lower threshold for hospital admission for this category of children, is probably warranted. Percutaneous pulse oxymetry should perhaps be a mandatory procedure in the assessment of premature infants who develop RSV bronchiolitis. The current evolution in high technology care and medical advances in managing very premature neonates will result in the survival of a significant number of premature infants at high risk of severe RSV bronchiolitis.

The hypoxemia of RSV bronchiolitis occurs as a result of abnormal distribution of ventilation relative to perfusion leading to intrapulmonary shunting and impairment of adequate oxygenation (Reynolds, 1963; Hall *et al*, 1979). Poor alveolar ventilation in RSV bronchiolitis is caused by widespread atelectasis and small airway obstruction that reduces the availability of air-flow into the alveoli for gas exchange. It is obvious that this pathological process will be exaggerated in premature infants with symptomatic chronic lung disease, in which the abnormal lung parenchyma main-

tains an already fragile balance of ventilation and perfusion exchange.

However, none of the 25 premature children in our study population had chronic lung disease that was associated with persistent respiratory symptoms or required home oxygen support. As prematurity alone appeared to be an independent factor for hypoxemia and respiratory failure in our study population, no subgroup analysis of chronic lung disease was conducted. Nonetheless, premature infants without chronic lung disease also remain at risk of severe RSV bronchiolitis (Law *et al*, 1998). This category of children who are premature has been documented to have smaller lung capacity, as shown by reduced FEV1 (forced expiratory volume in 1 second), FVC (forced vital capacity) and TLC (total lung capacity) compared with their full-term counterparts (Mansell *et al*, 1987; Galdes-Sebaldt *et al*, 1989). A smaller lung capacity with airway hyper-responsiveness is an important feature that renders this category of children more likely to have hypoxemia and respiratory failure in RSV bronchiolitis.

Hypoxemia is an important complication of RSV bronchiolitis that requires early recognition and is most likely to be encountered in premature infants. It is clear that measurement of the SpO_2 for premature infants with RSV bronchiolitis ought to be considered a mandatory aspect of clinical assessment.

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