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Contents

Pollution, Infection and High Flow

High-flow nasal cannula (HFNC) is a safe and well-tolerated noninvasive therapy in neonates and young children who required respiratory support not severe enough for mechanical ventilation. In this issue, Franklin and Schibler provided an excellent review of the mechanisms and rationale of HFNC.[1] Promotion of this patient-friendly respiratory support would help improve service delivery in children with respiratory distress, acute, or otherwise.

Traffic-related pollution has been found to be related with the development of asthma and exacerbation.[2,3] Siu *et al*. studied the risk factors of preschool children with wheeze in Hong Kong such as environmental nitrogen dioxide concentration, sulfur dioxide, particulate matter, and preterm delivery rate of gestational age <36 weeks.[4] In the report, they found that the annual average NO_2 concentration was the only independent factor associated with preschool wheeze admission using the multivariable regression analysis model. This finding suggests that environmental control is crucial for respiratory health in children with underlying diseases and clean air campaign should be targeted to ensure a decline in the admission of preschool wheeze in the forthcoming years.

Mycoplasma pneumoniae accounted for 7%–40% of all community-acquired pneumonia in children between 3 and 15 years of age.[5] Early targeted antibiotic therapy obviates unnecessary and overuse of antibiotics. The use of polymerase chain reaction may help early detection of *M. Pneumoniae;* however, it is not readily available, especially in resource-poor facilities; other alternative rapid diagnostic tests would be desirable. Liu *et al*. used the BioCard *Mycoplasma* IgM for the early diagnosis of *Mycoplasma pneumonia* in children comparing with standard IgM titers, they reported a sensitivity of 62.2% and specificity of 100%.[6] Despite the availability of BioCard test, it must be remember that a positive IgM titer may persist for up to 6 months after acute infections.[7]

I wish to take this opportunity to wish all readers a Happy Easter.

Kin-Sun Wong

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Review Article

Nasal High-flow Therapy in Infants and Children

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Abstract

This review highlights and summarizes the current evidence and knowledge of nasal high flow therapy management in infants and children. This review outlines the distinct differences in the use of NHF therapy between children and adults. A comprehensive literature review has been performed reviewing the relevant physiological studies and current evidence of support measures in these children. Despite the quick uptake of nasal high flow therapy in the clinical area there has been limited high-grade evidence, with new studies showing beneficial results with the use of nasal high flow therapy in acute respiratory disease and children.

Keywords: Acute respiratory distress, bronchiolitis, high flow, non-invasive respiratory support, pediatrics

Introduction

Of the 6.3 million children under the age of 5 years worldwide who died in 2013, over 1 million deaths were caused by respiratory infections.[1] While the mortality of respiratory infections has decreased in high-income countries, acute hypoxic respiratory failure (AHRF) is the most frequent cause of hospital admission resulting in major consumption of health-care resources.[2-4] Asthma, pneumonia, and bronchiolitis hospitalization in children in the USA are estimated to account for over US $3 billion/year.[5,6] In contrast, children in under-resourced countries presenting to hospitals with severe hypoxemic respiratory failure have a mortality rate between 13% and 28%.[7] There is an emerging trend to improve respiratory gas exchange with methods other than oxygen, particularly in the early stage of the disease process aiming to prevent the progression of the disease.[8] 'Furthermore, to date, the provision of positive pressure ventilation has been restricted to intensive care, which remains costly and requires a high level of skill. In view of the global burden of respiratory disease, the development of low cost and low technology interventions is urgently needed, such as nasal high flow (NHF) therapy, that can reduce health-care costs,[2,9] both in the first world and assist in reducing the burden of this disease in under-resourced countries.

Current treatment options for acute hypoxic respiratory failure

Oxygen

The main goal of respiratory support in AHRF is the prevention of severe hypoxemia to protect cerebral function and reduce end-organ failure.[10] Yet the danger of excessive use of oxygen (O_2) has been recognized, with toxicity being related to the concentration and length of exposure.[11-13] Oxygen causes tracheobronchial irritation and reduced mucociliary function (even in healthy volunteers exposed to 90% - 95% oxygen for 3 hours) and eventually, atelectasis, decreased vital capacity and changes similar to adult-type respiratory distress syndrome (RDS). For these reasons, other than emergency usage of 100% O_2, it is recommended that inspired oxygen concentration (FiO_2) should be carefully titrated against arterial hemoglobin saturation (SpO_2 or if available SaO_2). In neonates, use of 100% O_2 during resuscitation increases mortality, myocardial injury and renal injury[14] and in newborn infants, following an asphyxiating perinatal event, it is thought to increase the risk of cerebral damage.[15] A systematic review in children with chronic or recurrent hypoxia indicated that high level or prolonged use of O_2 caused adverse effects on development, behavior, and academic achievement; however, most studies did not stratify by SaO_2.[16] Therefore, a more controlled application of O_2 is desirable.

Noninvasive and invasive mechanical ventilation

Noninvasive ventilation (NIV) and mechanical ventilation (MV) deliver both an O_2/air mix and positive

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pressure through a face-mask or endotracheal tube. Both improve lung function and gas exchange.[8,17,18] Children require high levels of sedation to tolerate NIV or MV, which have been shown to carry inherent risks for long-term neurodevelopment, and which often prolong hospital stay due to related side effects.[19-22] Systems for NIV/MV are expensive, only applicable in Intensive Care Units (ICUs), and require high levels of expertise.

Nasal high-flow therapy

Historically, NHF therapy has been first introduced by a paper published in 1986 in the lancet by Klein and Reynolds.[23] In this study, children with severe upper airway obstruction were exposed to continuous fresh gas flow, which was humidified and heated. The authors showed a significant reduction in the work of breathing of these children while on NHF therapy. Others have shown that high fresh gas flow delivered through nasal cannula generates some positive airway pressure.[24] In preterm infants, NHF therapy rapidly became a common respiratory support mechanism, particularly in the postextubation phase. In pediatric critical care, high flow has first been used in infants with bronchiolitis and children with AHRF to prevent invasive ventilation. This review highlights the current evidence to use NHF therapy in children and explore some distinct differences in the use of NHF therapy between children and adults.

Neonatal High Flow

Preterm infants are at risk to develop respiratory distress resulting from surfactant deficiency, which is often required immediately after delivery intubation and MV. Exposure to endotracheal positive pressure ventilation is a risk factor for bronchopulmonary dysplasia, an important morbidity in preterm infants with potentially serious sequelae. This has led clinicians to explore alternative and less invasive respiratory support methods such as nasal continuous positive airway pressure (CPAP). NHF therapy was first introduced in neonatal nurseries in 2002 as an alternative to nasal CPAP, and its main indication was for apnea of prematurity and then later for respiratory support postextubation in preterm infants with RDS.[25] NHF systems have since increased in popularity, as they are less bulky and less cumbersome to be placed on an infant's face than standard nasal CPAP systems. Since the introduction of NHF therapy, several well-performed physiological studies were completed, and many randomized controlled trials were performed comparing NHF therapy with standard nasal CPAP.

Physiological evidence of high flow in neonates

Early studies in preterm infants showed that relatively small flow rates of 2 L/min can generate positive distending pressure of 4–5 cm H_2O and produced distending pressure showed to be dependent on both the flow and weight for the infant in addition to the size of the nasal cannula applied.[26] With the mouth open the effect of distending pressure can get lost and have no effect. Aside from the physiological effect, it is the infant's tolerance level and the high acceptance of high flow by the staff and parents that makes high flow in many neonatal units the preferred option for "CPAP" treatment. Despite the good tolerance, there remains from a clinical point of view some concerns regarding the risk of pneumothorax and gastric distension.

Evidence-based efficacy of nasal high-flow therapy in premature infants

A recently published large randomized controlled trial (RCT) in premature infants with RDS showed that NHF therapy can be successfully used as a primary respiratory support mode but CPAP remains the gold standard in these patients in regards to efficacy, particularly in very young preterm babies.[27] NHF therapy was used successfully in several large RCTs in premature infants postextubation and the failure rate (measured in reintubation rate) was similar to conventional nasal CPAP.[28,29] The weaning of respiratory support is a less well-investigated topic in preterm infants. Following the introduction of NHF therapy, clinicians soon began to explore the option to use it as a weaning therapy to come off nasal CPAP. The question still remains as to whether this practice is associated with increased length of oxygen therapy and respiratory support. The safety aspect of NHF therapy in premature infants remains a topic of debate because delivered airway pressures cannot be measured and there are concerns for potential excessive airway pressures. With more than 1000 studied infants on NHF therapy in large RCTs there is no obvious trend toward any specific side effect. There is also no evidence that NHF treatment is associated with any of the significant outcomes such as death or bipulmonary dysplasia. For safety measures the use of NHF therapy requires a selection of appropriate nasal cannula-to-nares ratio to enable adequate gas leak (approximately 50% of the area of the aperture of the nares). The flow rates used in preterm infants is relatively high compared to adults. The currently accepted and well-tolerated flow range is 2–8 L/min (translated in flow rates up to 8 L/kg/min).

Pediatric High Flow

Definition of high flow in pediatric respiratory disease

The definition of high flow remains vague and is commonly described as flow rates delivered of equal or more than 1 L/kg/min in infants with bronchiolitis.[30] A more precise (and the authors' preferred definition) could be: NHF therapy is an accurate oxygen delivery and estimate of the required inspired oxygen fraction (FiO_2) with fresh gas flow rates that exceed the inspiratory demand of the patient through nasal cannula using heated, humidified, and blended gas with a mixture of oxygen and air.

The physiological effects of high flow are based on the CO_2 washout effect of the nasopharyngeal dead space and on the support of the inspiratory and expiratory effort. During the expiratory phase, there is positive airway pressures while exhaling against the flow into the nasopharynx. This positive end-expiratory pressure effect is commonly described

in the range of 4–6 cm H_2O.[24] During the inspiratory phase, the inspiratory demand of the patient ideally should be matched by the delivered high flow. If the correct flow rate is applied, patients are experiencing a facilitated inspiration (inspiratory aid). If the inspiratory demand increases such as during respiratory distress, the high flow rate applied needs to be increased to prevent room air entrapment around the nasal cannula and hence reducing the inspired oxygen fraction (FiO_2) [Figure 1].

Physiological effects of nasal high flow

The physiological effects of NHF therapy in children are summarized as follows:

- Washout of nasopharyngeal dead space resulting in increased fraction of oxygen and decreased carbon dioxide for the following inspiration and the alveoli[30,31]
- Reduction of inspiratory resistance (mainly upper airway) and work of breathing by providing adequate flow if matched with inspiratory demand[24,32]
- Improvement of airway conductance and pulmonary compliance by reducing the effect of cold air; an *in vitro* study has shown that inspired gas with low humidity even for short periods may result in worsened function of human airway epithelial cells inflammatory indices[30,33]
- Reduction of the metabolic cost of gas conditions by providing air with 100% relative humidity[30]
- Providing an end-distending pressure to the lungs.[24,34]

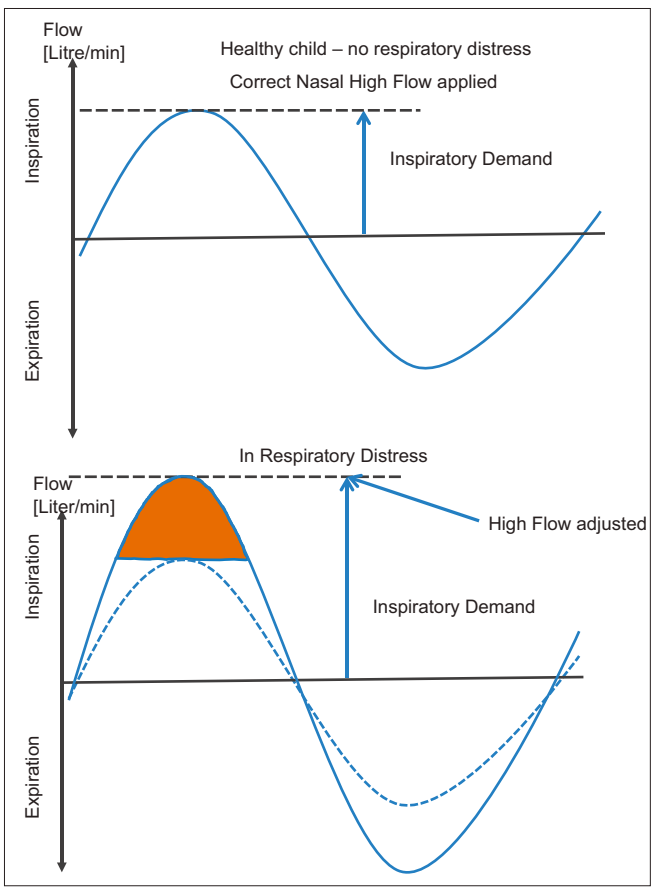

Figure 1: Flow rate versus respiration

In comparison to adults, infants break the expiratory phase using active innervation of the diaphragm to prevent the lung from partial collapse as infants are breathing near the closing volume of the lung. In the presence of respiratory distress, the expiratory phase can become active with the use of auxiliary, abdominal and intercostal muscles. To overcome and compensate for increased expiratory resistance, children and infants tend to increase their functional residual capacity. This not only allows distension of the airways but also provides a higher recoil pressure to work against airway resistance. Most of the studies investigating the physiological impact of NHF therapy were completed in infants with bronchiolitis. The estimated positive airway pressure using 2 L/kg/min in infants <12 months is approximately 4–6 cm H_2O.[34] In the absence of robust measurement techniques, the work of breathing is commonly assessed with clinical scoring systems, which are subjective and based on the clinical experience of the observer.[35] Using the directly measured electrical signal of the diaphragm muscle it has been shown that the workload of the diaphragm is significantly reduced in infants with bronchiolitis who are treated with high flow [Figure 2].[32]

Clinical evidence in pediatric respiratory disease

Despite the current widespread use of NHF therapy in children, the current pediatric clinical evidence for NHF therapy has been obtained mostly from infants with bronchiolitis. Two recent retrospective studies showed that after the introduction of NHF therapy as the standard approach for oxygen therapy in infants admitted to intensive care for bronchiolitis the intubation rates decreased to <10% from originally >30%.[36,37] With the introduction of NHF therapy in the emergency department (ED) a significant reduction in the odds of intubation in ED occurred suggesting the early use of NHF therapy may prevent escalation of therapy.[38] Similarly, an improved effectiveness of NHF therapy was demonstrated once introduced across the hospital and in the general pediatric ward.[39] The use of NHF therapy during pediatric transportation of children <2 years of age of which approximately 51%–57% were infants with bronchiolitis showed a high safety profile of NHF therapy and no impact on intubation rates subsequently after admission to pediatric ICU.[40]

A recent Australian single-center RCT in infants with bronchiolitis compared standard stand oxygen therapy with NHF therapy and showed no difference in the length of oxygen therapy (primary outcome) but showed a significantly reduced failure rate defined as intensive care admission in the NHF therapy group.[41] This study suggested

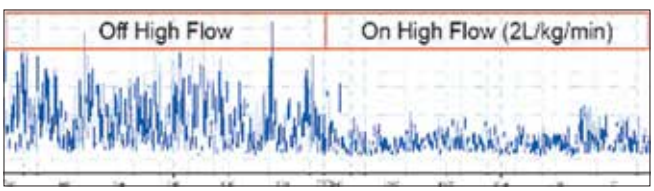

Figure 2: Diaphragmatic electrical activity off and on nasal high flow therapy in an infant with bronchiolitis.

that early use of NHF therapy does not modify the underlying disease process in moderately severe bronchiolitis, but NHF therapy may have a role as a rescue therapy to reduce the proportion of children requiring high-cost intensive care. The investigators used flow rates of 1 L/kg/min, which may be for some of these infants inadequate flow rates to fully support the inspiratory demand. A similar large RCT is currently completed in Australia and New Zealand and awaiting the outcome results. A recent well-conducted French multi-center study conducted in intensive care compared the use of NHF therapy and CPAP in infants with bronchiolitis.[42] The authors showed that NHF therapy had a proportionally greater failure rate than CPAP (NHF failure was rescued with CPAP), however, infants in both intervention groups had a similar intubation rate. A recent trial in limited resource settings compared Standard oxygen therapy (SOT), NHF therapy and bubble CPAP.[9] This study enrolled children up to 5 years of age with acute respiratory failure, of which approximately 10%–15% had bronchiolitis. The authors showed that the use of bubble CPAP reduced the mortality in comparison to SOT, but no difference between NHF therapy and bubble CPAP could be found.

Authors recommendation

A recent large RCT investigating the efficacy of NHF therapy in 1400 infants <12 months of age with bronchiolitis has been completed, and the results are currently pending and eagerly awaited to inform clinical practice.[43] The safety and quality aspect of this trial was high (personal communication). The trial used 2 L/kg/min of NHF in a general pediatric ward setting with a standard nursing ratio of 1:4. We have recently completed a pilot study in 460 children with AHRF and have demonstrated that NHF therapy is safe and likely superior to standard oxygen therapy (unpublished own data). The following flow rates (based on the age and weight adjusted minute ventilation) were tested in this pilot trial in Table 1. The use of NHF therapy however in this age group >1 year still needs to be further investigated.

Table 1: Nasal high flow rates as part of the clinical guidelines used at the Lady Cilento Children's Hospital, Brisbane, Queensland, Australia

Weight	High flow rates
0-12 kg	2 L/kg/min Maximum 25 L/min
13-15 kg	30 L/min
16-30 kg	35 L/min
31-50 kg	40 L/min
>50 kg	50 L/min

Conclusion

The use of NHF therapy in infants with bronchiolitis has been well accepted in intensive care settings as well as in general pediatric wards. More detailed evidence, however, is needed to fully establish its use in these settings. The use of NHF therapy in older children with hypoxic respiratory failure seems a plausible therapy based on evidence obtained in adults and infants, but high-grade evidence is still required.

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Conflicts of interest

There are no conflicts of interest.

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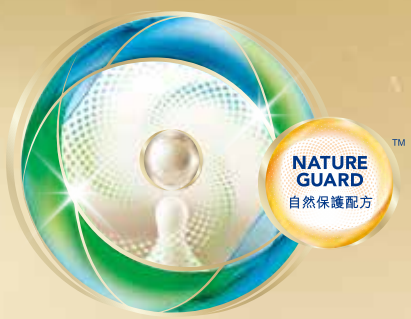

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Role of BioCard *Mycoplasma* Immunoglobulin M Rapid Test in the Diagnosis of *Mycoplasma pneumoniae* Infection

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Abstract

Background: *Mycoplasma pneumoniae* is an important pathogenic bacterium that causes community-acquired pneumonia in children. Rapid and dependable laboratory diagnosis of *M. pneumoniae* infection is important for starting an appropriate antibiotic treatment. Currently, the serological testing for detection of *M. pneumoniae* immunoglobulin M (IgM) has been used to determine the presence of an acute infection, the results of which, depending on the laboratory facility, are not available immediately. Therefore, an optimal and instant detection method is needed to facilitate a more accurate diagnosis, which leads to the appropriate treatment of patients with *M. pneumoniae*-related pneumonia and reduces rates of resistance to antibiotics because of their misuse. **Aims:** Here, we investigated the clinical diagnostic value of a rapid detection kit for *M. pneumoniae*-specific IgM antibody, the BioCard *Mycoplasma* IgM rapid test, in the detection of a *Mycoplasma* infection in children. **Material and Method:** 44 pediatric patients with clinically suspected *Mycoplasma* infection were enrolled for study. **Result:** Among 82 *Mycoplasma* IgM-positive samples, 51 samples were detected to be positive using the BioCard rapid test. The sensitivity and specifi city of the kit were 62.20% (51/82) and 100% (16/16), respectively. The positive and negative predictive values were 100% (51/51) and 34.04% (16/47), respectively. **Conslusion:** In conclusion, the BioCard *Mycoplasma* IgM rapid test provides an accurate point-of-care diagnosis for *M. pneumonia* infection.

Keywords: Child, immunoglobulin M, *Mycoplasma pneumoniae*, pneumonia, rapid test

Introduction

Mycoplasma pneumoniae is a common pathogen that causes community-acquired pneumonia (CAP), particularly in school-aged children and adolescents.[1-4] *M. pneumoniae* was discovered in 30% of pediatric CAP and >50% among children aged 5 years or older.[3,5] *M. pneumoniae*-associated pneumonia occurs in all seasons, though more common in the spring and autumn. Although significant cough without rhinorrhea is the classic manifestation, the symptoms include that of severe pneumonia.[1,6] Furthermore, many patients with bronchopneumonia, whether viral or bacterial, often have a co-infection with *M. pneumoniae*.[7,8] Therefore, an optimal detection method is needed to facilitate a more accurate diagnosis.

The identification of *M. pneumoniae* is difficult because it is hard to culture and has a very low growth rate; thus, culture-based approaches are commonly not helpful clinically. Polymerase chain reaction (PCR) assays for the diagnosis of *M. pneumoniae* are time-consuming and their availability is limited. Serological testing is now a major diagnostic method for the detection of *M. pneumoniae* infection. The detection of *M. pneumoniae* immunoglobulin M (IgM) has been used to determine the presence of an acute infection.

We evaluated the utility of a rapid detection kit for *M. pneumoniae*-specific IgM antibody, BioCard *Mycoplasma* IgM rapid test, in the diagnosis of *M. pneumoniae* in children.

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Patients and Methods

Patients

We enrolled patients aged 1.5–14 years who were admitted at Kaohsiung Chang Gung Memorial Hospital. We obtained 98 samples (42 whole blood, 29 sera, and 27 plasma samples) from 44 pediatric patients with clinically suspected *Mycoplasma* infection. All patients had pneumonia confirmed by chest X-ray. Fever was defined as a body temperature of ≥38.0°C, which was measured using infrared tympanic membrane thermometers. The Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital approved the collection of data from the patients' medical records (103-7061A3).

Methods

Mycoplasma infection was diagnosed using *M. pneumoniae*-specific IgM enzyme immunoassay test (ELISA ImmunoWELL kits, Ben-Bio, San Diego, CA, USA). The kit colorization was always interpreted with direct visual observation by the same pediatrician. The results of BioCard *Mycoplasma* IgM rapid test (Ani Biotech Oy, Vantaa, Finland) were classified into four color grades [Figure 1]. The results were graded based on the positive line. Grades 0, 1, 2, and 3 represent negative and weakly positive, moderately positive, and strongly positive results, respectively. We also measured complete blood counts (CBCs), C-reactive protein (CRP), alanine aminotransferase, aspartate aminotransferase levels, total duration of fever, total length of hospitalization, and test after illness onset. Demographic characteristics were collected from patient records. Continuous variables were expressed as means ± standard errors. All statistical tests were performed using SPSS software version 19.0 for Windows (SPSS, Inc., Chicago, IL, USA). $P < 0.05$ was taken to indicate statistical significance.

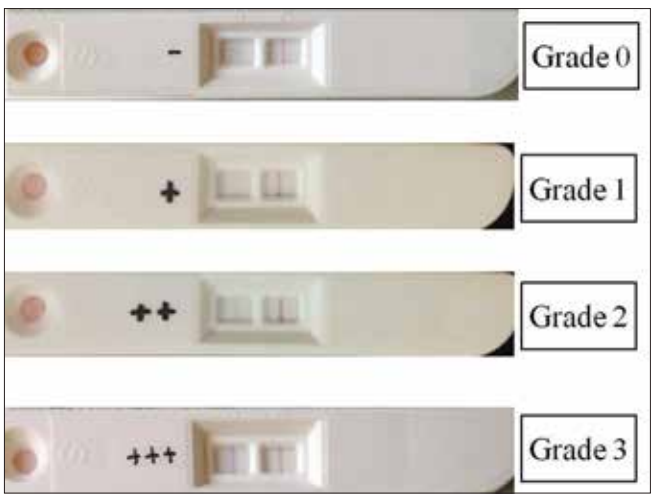

Figure 1: The results of BioCard test are classified into four colorization grades. The right and left lines of the BioCard test represent the control line and result of the patient, respectively.

Results

Clinical characteristics of enrolled patients

We obtained 98 samples (42 whole blood, 29 sera, and 27 plasma samples) from 44 patients with clinically suspected *Mycoplasma* infection. Of these 98 samples, 82 and 16 were detected to be *Mycoplasma* IgM positive and *Mycoplasma* IgM negative, respectively, using *M. pneumoniae*-specific IgM enzyme immunoassay test. The clinical characteristics of the 44 patients, including age, duration of fever, length of hospital stay, and laboratory analysis of blood, liver enzymes, and CRP, are summarized in Table 1.

Using Spearman's rank correlation, a highly monotonic relationship was observed in the association among whole blood, serum, and plasma samples (CBC and serum, $r = 0.929$; CBC and plasma, $r = 0.900$; and serum and plasma, $r = 0.903$) [Table 2].

Table 1: Clinical characteristics of the 44 patients with clinically suspected *Mycoplasma* infection

Clinical characteristics	Total cases
Age (years)	5.8±3.0
Sex (male:female)	19:25
Total fever duration (days)	5.2±3.4
Hospital stay (days)	5.9±2.8
Test after illness onset (days)	6.0±5.2
Red blood cell (million/μL)	4.7±0.4
Hemoglobin (g/dL)	12.7±0.9
Platelet (1000/μL)	294.2±78.4
White blood cell (1000/μL)	9.6±4.4
Segment (%)	60.3±16.9
Lymphocyte (%)	30.1±15.4
Eosinophil (%)	2.1±2.6
Basophil (%)	0.3±0.3
Monocyte (%)	6.5±2.6
AST (u/L)	34.2±11.6
ALT (u/L)	18.7±10.9
CRP (mg/L)	25.0±0.7

Data are presented as mean±SE. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, SE: Standard error

Table 2: Spearman's rank correlation to test the association between complete blood count, serum, and plasma

	CBC	Serum	Plasma
CBC			
r		0.929	0.900
P		<0.001	<0.001
Serum			
r	0.929		0.903
P	<0.001		<0.001
Plasma			
r	0.900	0.903	
P	<0.001	<0.001	

CBC: Complete blood count

High correlation between grades of *Mycoplasma* immunoglobulin M rapid test and titers of *Mycoplasma* immunoglobulin M for whole blood samples

Due to the unnecessary centrifugation of blood samples, whole blood acts as a more convenient sample for testing *Mycoplasma* IgM rapid test kits. Hence, we compared BioCard *Mycoplasma* IgM rapid test and serum *Mycoplasma* IgM only for whole blood samples. Of the 42 whole blood rapid test samples, 17, 13, 6, and 6 samples were graded 0, 1, 2, and 3, respectively.

Using one-way analysis of variance (ANOVA), a statistically significant relationship was found between BioCard *Mycoplasma* IgM rapid test for whole blood samples and the distribution of *Mycoplasma* IgM titer ($r = 0.885$, $P < 0.001$) [Figure 2].

Mycoplasma immunoglobulin M titers were significantly different among the four grades of BioCard *Mycoplasma* immunoglobulin M rapid test using whole blood samples

Using ANOVA Tukey's method, 42 whole blood samples were analyzed. Serum *Mycoplasma* IgM titers were significantly different among the four grades of the rapid test group [Table 3]. Among 42 whole blood samples, the minimum and maximum serum IgM titers were 127.5 U/mL and 6007.1 U/mL for Grades 0 and 3, respectively. The *Mycoplasma* serum IgM level was 1029.0 U/mL, which was interpreted as the weakest positive result of the rapid test.

Clinical application value of BioCard *Mycoplasma* immunoglobulin M rapid test

Among 82 *Mycoplasma* IgM-positive samples, 51 samples were detected to be positive using BioCard *Mycoplasma* IgM rapid test. The sensitivity and specificity of BioCard *Mycoplasma* IgM rapid test were 62.20% (51/82) and 100% (16/16), respectively, when using *Mycoplasma* IgM ELISA as the gold standard. The positive and negative predictive values were 100% (51/51) and 34.04% (16/47), respectively [Table 4].

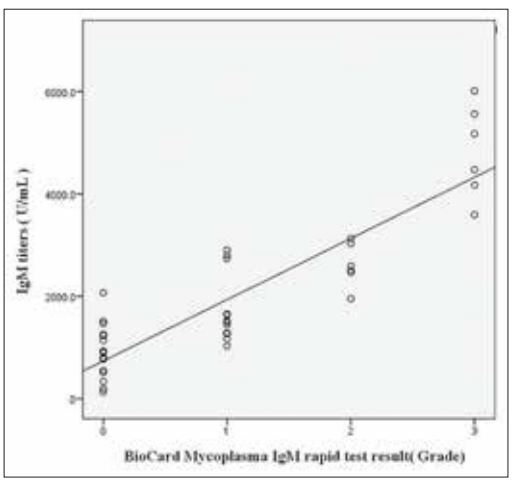

Figure 2: The relationship between the BioCard *Mycoplasma* immunoglobulin M rapid test and the distribution of *Mycoplasma* immunoglobulin M titer by using analysis of variance.

Discussion

In this study, we investigated the utility of a rapid detection kit for *M. pneumoniae*-specific IgM antibody, the BioCard *Mycoplasma* IgM rapid test, in the diagnosis of *Mycoplasma* infection in children. The kit was highly accurate and showed good sensitivity, specificity, and consistency. Point-of-care testing (POCT), known as bedside testing, is defined as a medical diagnostic testing at or near the point of care. Most importantly, POCT is simple to be used at the primary care level and in remote settings without laboratory infrastructures.[9]

POCT using BioCard *Mycoplasma* IgM rapid test helps facilitate the immediate diagnosis of *M. pneumonia* infection at bedside using whole blood. Therefore, with this optimal detection method, the appropriate treatment of patients with *M. pneumoniae*-associated pneumonia could be started, reducing the misuse of antibiotics.

The progression of *M. pneumonia* infection is often gradual and slow and, in adults, the illness is usually present for more than 1 week before the patient seeks medical assistance.[10] However, our results showed that children with pneumonia caused by *M. pneumoniae* were mostly admitted to hospital within the 1st week of infection.[1] This may be because fever is the major symptom in children rather than the prolonged

Table 3: *Mycoplasma* immunoglobulin M titer among the four grades of the rapid test group

Rapid test grade	Sample number	IgM titer (U/mL)*	Minimum IgM titer (U/mL)	Maximum IgM titer (U/mL)
0	17	912.8±122.7	127.5	2070.4
1	13	1710.8±181.3	1029.0	2902.4
2	6	2612.7±174.5	1954.8	3133.4
3	6	4830.2±370.8	3592.7	6007.1

*IgM titer data are presented as the mean±SD or SE. SD: Standard deviation, SE: Standard error, IgM: Immunoglobulin M

Table 4: Sensitivity, specificity, positive predictive value, and negative predictive value between *Mycoplasma* immunoglobulin M (immunoWELL) positive samples and BioCard *Mycoplasma* immunoglobulin M rapid test

	ImmunoWELL positive ($n=82$)	ImmunoWELL negative ($n=16$)
BioCard rapid test positive (n=51)	51[A]	0[B]
BioCard rapid test negative (n=47)	31[C]	16[D]

Sensitivity: A/(A+C)×100=51/(51+31)×100=51/82×100=62.20%. Specificity: D/(D+B)×100=16/(16+0)×100=16/16×100=100%. Positive predictive value: A/(A+B)×100=51/(51+0)×100=51/51×100=100%. Negative predictive value: D/(D+C)×100=16/(16+31)×100= 16/47×100= 34.04%. IgM: Immunoglobulin M

cough typically seen in adults infected with *M. pneumoniae*. Children are therefore brought to the hospital sooner than adults due to the concerns of the caregiver. In a previous study, we reported the initial positivity rate for *M. pneumoniae* IgM ELISA detection to be about 60%.[1] Many cases of *Mycoplasma* infection were *Mycoplasma* IgM negative upon admission. Hence, BioCard *Mycoplasma* IgM rapid test has the same limitation like *M. pneumoniae* IgM ELISA. Hence, repeated test is necessary for a more accurate diagnosis for highly suspected condition in clinic.

In addition to using *M. pneumoniae*-specific IgM antibody for the diagnosis of *M. pneumoniae* infection, *M. pneumoniae* rapid antigen test is also used for the detection of *M. pneumoniae*. Recently, Miyashita *et al*. reported a commercial rapid antigen kit (Asahi Kasei Pharma Co., Tokyo, Japan) for the detection of *M. pneumoniae* ribosomal protein L7/L12 using an immunochromatographic antigen assay. The sensitivity and specificity of this rapid antigen test were 57.6% and 91.6%, respectively, as compared to PCR assay.[11] In our study, the sensitivity and specificity of BioCard *Mycoplasma* IgM rapid test were 62.20% and 100%, respectively, compared with ELISA assay. Therefore, both IgM and antigen can be used for the rapid detection of *M. pneumoniae* infection.

This study has two limitations. First, the sample size was small. Second, different patients had different blood sampling time in the course of disease. Therefore, some selection bias may be present.

Conclusion

The present study is the first report that showed BioCard *Mycoplasma* IgM rapid test as a useful POCT diagnostic tool for *M. pneumonia* infection, to investigate the utility of a rapid detection kit for *M. pneumoniae*-specific IgM antibody. The positive rapid test result confirms *Mycoplasma* infection; however, a negative result cannot exclude *Mycoplasma* infection. Repeated test may be needed if *Mycoplasma* infection is highly suspected.

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Conflicts of interest

There are no conflicts of interest.

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Air Pollution as a Risk Factor for Increasing Hospitalizations of Preschool Wheeze in Hong Kong

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Abstract

Background: Wheeze has been reported to affect one-third of preschoolchildren. While different wheeze patterns have been shown to predict future asthma risk, limited data are available on the risk factors for preschool wheeze in Asia. **Methods:** Preschool children admitted to hospitals through emergency departments for wheeze, from 2004 to 2015 in Hong Kong, were retrospectively identified. Potential risk factors for admissions over the same period were retrieved (i.e., air pollutants, preterm delivery, and maternal age). **Results:** A total of 46,258 patients meeting the inclusion criteria were identified during the 12-year period. The preschool wheeze admission rate increased by 34% over the past 12 years, with an average year-on-year rise of 4.2%. Environmental nitrogen dioxide (NO_2) concentration was significantly associated with an increase in admission for preschool wheeze ($r = 0.63$, $P = 0.028$). Univariate regression analysis was performed on potential risk factors. Annual average NO_2 concentration ($P = 0.007$) and maternal age more than 40 years ($P = 0.012$) were significant risk factors. For multivariable regression analysis, annual average NO_2 concentration ($\beta = 0.18$, 95% confidence interval = 0.06–0.30) was the only independent factor associated with preschool wheeze admission. **Conclusions:** The increase of NO_2 concentration is a significant risk factor for the increase in hospitalizations for preschool wheeze in Hong Kong.

Keywords: Bronchiolitis, pollutants, wheezing

Introduction

Preschool wheeze in children aged 6 years or below is a heterogeneous disorder, including asthma, acute bronchitis, and acute bronchiolitis. It was reported to occur in one-third of all preschoolchildren,[1] and there was a rising trend in different countries.[2,3] Several birth cohort studies classified wheeze by temporal phenotypes.[4-6]

In 2008, the European Respiratory Society Task Force[1] proposed classifying wheeze by symptoms into episodic viral wheeze (EVW) and multiple triggered wheeze (MTW). In EVW, the child wheezes only at the time of viral upper respiratory tract infection and is symptom free between viral colds. In MTW, the child wheezes at the time of viral colds, also between colds, for example, with excitement, aeroallergen, cold, and smoke exposure. Different patterns of preschool wheeze may have long-term implications on lung function and development of asthma.[7-9]

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Preschool wheeze in children was reported to occur in 33% of children aged 1–6 years.[1] In the UK, Kuehni *et al*.[10] reported a significant increase in wheeze admission from 1990 (6%) to 1998 (10%), while Green *et al*.[11] reported an average of 1.8% per year rise for bronchiolitis in infants from 2005 to 2014.

Various risk factors were reported to be associated with preschool wheeze in previous studies, including climate factors such as temperature, rainfall, relative humidity,[12] air pollution index,[13,14] frequency of preterm deliveries,[15] and maternal age.[16]

Prematurity was investigated in a recent meta-analysis of 147,000 European children, investigating the association

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of gestational age (<37 weeks), birth weight (<2500 g), and infant weight gain with childhood asthma outcomes.[15] It was shown that preterm births were largely associated with preschool wheeze and asthma.[15] Another known risk factor for preterm birth, advanced maternal age, was also studied, as preterm births are more likely among teen mothers and mothers ≥40 years of age. In 2013, 16% of preterm births were from mothers aged 40 to 44 years and 25% of preterm births were from mothers ≥45 years old.[16] Particulate matter (PM_{10}) and nitrogen dioxide (NO_2) were reported to be associated with wheeze/asthma in children aged 2–18 years.[17]

The aim of this study was to investigate the trend of preschool wheeze requiring hospitalization and to identify the significant risk factors.

Methods

Study design and patients

This was a retrospective review that utilized data from the Clinical Data Analysis and Reporting System (CDARS), an information system with analytical and reporting capacities, to support the analysis of clinical data for research in the Hong Kong Hospital Authority. It incorporated data including diagnoses, procedures performed, and drug data for all patients admitted to public hospitals, which accounted for 80% of hospital admissions in Hong Kong.[18] Patients aged 0–6 years, with diagnoses of bronchiolitis, asthma, bronchitis, or wheeze, were included in the study from 2004 to 2015.

Search strategy

Since there is no International Classification of Diseases, Ninth Revision (ICD-9) code for preschool wheeze, admission data for children aged 0–6 years, with bronchiolitis (ICD-9 code 466), asthma (ICD-9 code 493), bronchitis (ICD-9 code 490, 491.20, 491.21), and wheeze (ICD-9 code 786.07), were retrieved for the study period from 2004 to 2015 from CDARS. For comparison, data for febrile convulsion admission during the study period were also retrieved to see if there was any change in admission policy.

The total number of admissions and the yearly admission rate per 1000 preschoolchildren were retrieved. Trend of hospital admissions for preschool wheeze was studied against potential risk factors, i.e., NO_2, sulfur dioxide (SO_2), PM_{10}, maternal age, and preterm delivery, in Hong Kong from 2004 to 2015.

Data on preterm deliveries (gestation <36 weeks) were obtained from the Annual Obstetric Reports of the Hong Kong Hospital Authority. Data on maternal age were obtained from the Hong Kong Census and Statistics Department. Pollutants' data, i.e., the yearly average of NO_2, SO_2, and PM_{10}, were obtained from Hong Kong Environmental Protection Department.[19] Pollutants' data were obtained from three roadside monitoring stations throughout Hong Kong. The monitoring technique was certified by the Hong Kong Laboratory Accreditation Scheme.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Inc., Armonk, NY, USA). The annual number of patients admitted for preschool wheeze was reported. Linear regression analysis was used for analyzing the trend of significance. Univariate linear regression analysis was performed to identify the potential risk factors for preschool wheeze emergency admission. Multivariable linear regression analysis was performed to identify the independent risk factors that had $P < 0.2$ in the univariate analysis. Variables were selected for inclusion in the final models with the use of a step-wise selection process. The data were used to investigate the correlation between each of the pollutants and emergency admissions using bivariate correlation. For all analyses, $P < 0.05$ was considered statistically significant.

Results

A total of 46,258 patients meeting the inclusion criteria were identified during the 12-year period. Admission for preschool wheeze rose significantly from 9.9/1000 preschoolchildren in 2004 to 19.1/1000 preschoolchildren in 2013, an increase of 93%. The average year-on-year rise was 6.2%. This was a significant rising trend, $P = 0.001$ [Figure 1]. Admissions for preschool wheeze fell from 2013 to 2015 from 19.1 to 13.3/1000 preschoolchildren. Overall, the preschool wheeze admission rate increased by 34% over the past 12 years, with an average year-on-year rise of 4.2%.

In comparison, febrile convulsion admission over the same period (2004–2015) in the same age group showed no significant change in trend ($P = 0.797$). Univariate regression analysis was performed on potential risk factors [Table 1]. Annual average NO_2 concentration ($P = 0.007$) and maternal age more than 40 years ($P = 0.012$) were significant risk factors. For multivariable regression analysis, annual average NO_2 concentration ($\beta = 0.18$, 95% confidence interval [CI] = 0.06–0.30) was the only independent factor associated with preschool wheeze admission [Table 1]. The correlation between NO_2 and preschool wheeze emergency admission was significant, $r = 0.63$, $P = 0.028$ [Figure 2]. The rise and fall of preschool wheeze admission mirrored that of NO_2 [Figure 1].

Discussion

This study looked at the risk factors for the increase in hospital admission for preschool wheeze in Hong Kong. Compared with other countries, the preschool wheeze admission rate in Hong Kong at 13.3/1000 children was lower than that in Canada (23–42/1000).[2] This could be related to ethnic differences. A study performed in the United States showed that ethnic minority children (Blacks, Hispanics) with preschool asthma were twice as likely to have wheeze compared with Caucasian after controlling for disease severity, access to care, and environmental factors.[20] The difference in ethnic origin may account for the difference in admission rates between Hong Kong and North America. Other possible

Table 1: Risk factors for emergency preschool wheeze admission by linear regression analysis

	Univariate analysis			Multivariable analysis		
	β	95% CI	*P*	β	95% CI	*P*
NO_2	0.18	0.06-0.30	0.007*	0.18	0.06-0.30	0.007*
SO_2	−0.23	−0.48-0.02	0.063	-	-	-
PM_{10}	−0.13	−0.27-0.02	0.085	-	-	-
Preterm delivery rate (gestation <36 weeks)	4.44	−0.29-9.16	0.063	-	-	-
Maternal age ≥40/1000 babies	0.53	0.15-0.92	0.012*	-	-	-

*P<0.05. NO_2: Nitrogen dioxide, SO_2: Sulfur dioxide, PM_{10}: Particulate matter, CI: Confidence interval

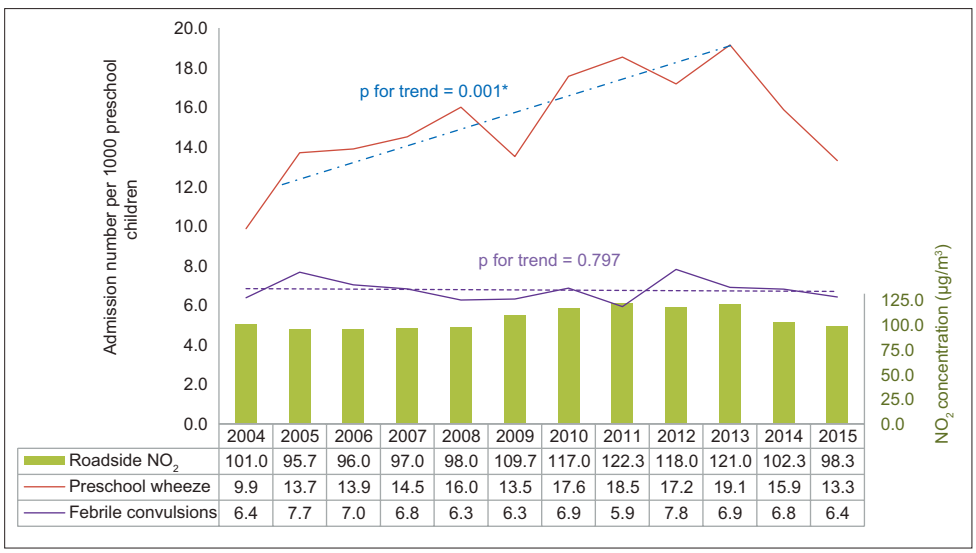

Figure 1: Emergency admission rate for preschool and febrile convulsion versus NO_2. *P < 0.05.

factors accounting the differences included socioeconomic status,[21] household smoking,[22] allergens' exposure,[9] and damp housing.[23] These factors could not be identified in our study due to its retrospective design. Our study demonstrated a significant rising trend of preschool wheeze admission in Hong Kong. Preschool wheeze hospitalizations increased significantly from 9.9/1000 in 2004 to 19.1/1000 in 2013 and fell to 13.3/1000 in 2015. The only risk factor identified was environmental NO_2. There was biological explanation for our findings. NO_2 was demonstrated to cause formation of excessive amount of reactive oxygen species in airways and in experimental animals, leading to tissue inflammation and cell death.[24] Oxidative stress has been linked to clinical phenotypes such as asthma and atherosclerosis.[25]

Several studies demonstrated the effect of NO_2 on childhood respiratory diseases. NO_2 exposure was associated with lifetime asthma and wheeze among children with allergic disease in Toronto.[26] A dose–response association was observed between asthma symptoms and self-reported exposure to truck traffic in the Phase 3 International Study of Asthma and Allergies in Childhood, representing more than 500,000 children across the globe.[27] In addition, high traffic-related air pollution exposure at birth was significantly associated with both transient and persistent wheezing phenotypes (adjusted odds ratio [aOR] =1.64; 95% CI = 1.04–2.57 and aOR = 2.31; 95% CI = 1.28–4.15, respectively); exposure from birth to 1 year and 1–2 years was also associated with persistent wheeze in birth cohort of 762 children in Greater Cincinnati, Ohio, United States.[28] Outdoor concentrations of traffic-related air pollutants (NO_2, $PM_{2.5}$, and soot) were found to be associated with asthmatic symptoms during the first 4 years of life in a birth cohort study of 4000 children.[29] There was also a consistent positive association between PM_{10} and SO_2 with the prevalence of wheeze and bronchodilator use in children aged 6–12.[30] Our study demonstrated NO_2 to be positively associated with preschool wheeze hospitalization in Hong Kong. During the study period, the Government of Hong Kong initiated a program of low sulfur fuel for vehicles and ships since 2008 and 2015, respectively, which resulted in a significant drop of NO_2 since 2013.[31]

Contrary to the literature,[15] the current study did not show prematurity as a risk factor for preschool wheeze and it might be due to the fact that preterm delivery was also related to NO_2.[32] In view of the significant rising trend of preschool wheeze hospitalization and its significant association with higher NO_2 levels, it seems to be reasonable for government to continue targeting NO_2 in the next phase of clean air campaign in Hong Kong. For example, the UK Government will end the sale of all new conventional petrol and diesel cars and vans by 2040, in order to cut NO_2 emission.[33] Preschool wheeze was

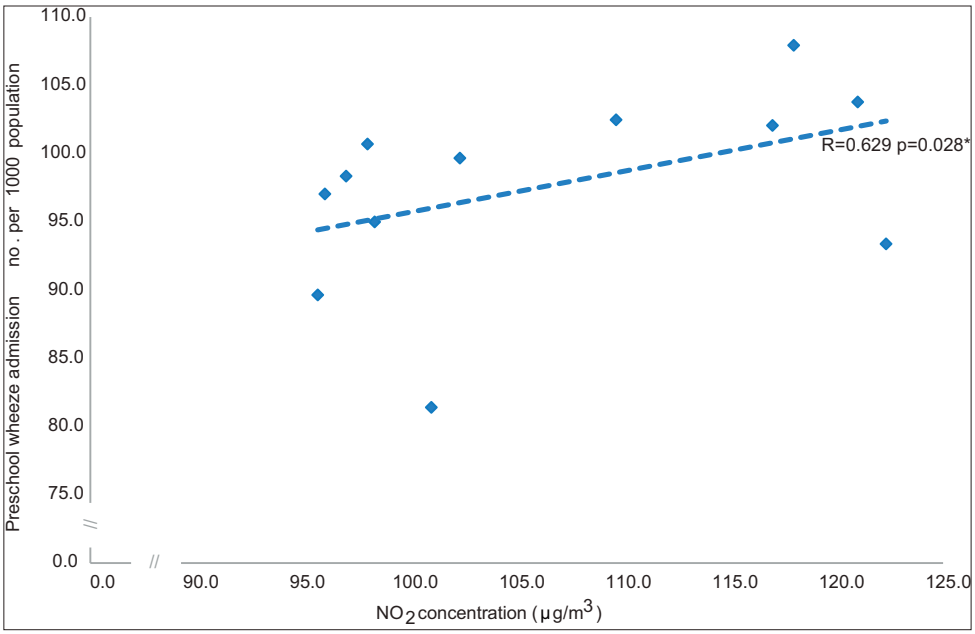

Figure 2: Correlation between preschool wheeze admission rate and NO_2 (2004–2015), *$P < 0.05$.

reported to be associated with emergency asthma admission for the school-age group,[34] and the current results might predict a subsequent surge in asthma admission for school-age children when the preschool wheeze children got older if the current downward trend for NO_2 did not continue.[34] More importantly, the current study predicted a similar increase for preschool wheeze in China in the following year because China witnessed a fourfold increase in car ownership in the past decade.[35]

This study had two limitations. First, we only included patients with wheeze severe enough to be admitted to public hospitals in Hong Kong. Patients who attended private hospitals for wheeze could not be traced and children with wheeze managed in the outpatient setting were not included. Second, this was a retrospective study and only limited number of risk factors for wheeze could be obtained. Further prospective studies are warranted to assess the relationships of preschool wheeze and other risk factors, i.e., presence of older siblings, day-care attendance, family history of atopy, maternal smoking, environment tobacco exposure, viral infection, and incense burning.

Conclusions

There was a 93% increase of emergency preschool wheeze admission from 2004 to 2013. The increase of NO_2 concentration is the significant risk factor for this increase. Therefore NO_2 should remain the main target of the clean air campaign in Hong Kong so as to ensure a continuous decline in preschool wheeze admission.

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Conflicts of interest

There are no conflicts of interest.

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Erratum: Airway Disease and Environmental Aeroallergens in Eczematics Approaching Adulthood

In the article titled "Airway Disease and Environmental Aeroallergens in Eczematics Approaching Adulthood", published on pages 81-85, Issue 4, Volume 1 of Pediatric Respirology and Critical Care Medicine,[1] the name of the first author is written incorrectly as Ellis Kam Lun Hon instead of Kam Lun Hon.

The "How to cite this article" section should read correctly as Hon KL, Liu M, Zee B. Airway disease and environmental aeroallergens in eczematics approaching adulthood. Pediatr Respirol Crit Care Med 2017;1:81-5.

Reference

1. Lun Hon EK, Liu M, Zee B. Airway disease and environmental aeroallergens in eczematics approaching adulthood. Pediatr Respirol Crit Care Med 2017;1:81-5.

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