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Early inspired oxygen and intermittent hypoxemic events in extremely premature infants are associated with asthma medication use at two years of age

Juliann M. Di Fiore, BSEE[1], **Andrew M. Dylag, MD**[2], **Ryan D. Honomichl, PhD**[3], **Anna Maria Hibbs, MD, MSCE**[1], **Richard J. Martin, MD**[1], **Curtis Tatsuoka, PhD**[3], and **Thomas M. Raffay, MD**[1]

[1]Division of Neonatology, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

[2]Division of Neonatology, Golisano Children's Hospital, University of Rochester, Rochester, NY

[3]Division of Neurology, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, OH

Abstract

Objective: Extremely premature infants are at risk for childhood wheezing. Early respiratory support and intermittent hypoxemia (IH) events may be associated with adverse breathing outcomes.

Study Design: A single-center retrospective cohort study of 137 premature infants <28 weeks gestational age characterized the associations of cumulative oxygen, cumulative mean airway pressure, IH, and oxygen saturation (SpO_2) on the primary outcome of prescription asthma medication use at 2 year follow-up. Relative risk was calculated by generalized estimating equations.

Results: Reported asthma medication use was 46%. At 1–3 days of age, elevated cumulative oxygen exposure, increased daily IH, and lower mean SpO_2 (adjusted for gestational age and sex) and increased cumulative mean airway pressure exposure (unadjusted) were associated with asthma medication use.

Conclusion: Increased oxygen and frequent IH events during just the first three days of age may help identify extremely premature newborns at risk for symptomatic childhood wheezing requiring prescription asthma medications.

Address for Correspondence: Thomas Raffay, Division of Neonatology, Rainbow Babies & Children's Hospital, Department of Pediatrics, Case Western Reserve University, 11100 Euclid Avenue, Cleveland, OH 44106, Phone (216) 844-3387, Fax (216) 844-3380, tmr12@case.edu.

Conflict of Interest

The authors have no conflict of interest to disclose

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Keywords

Hypoxia; intermittent hypoxemia; wheezing; preterm infants; oxygen

Introduction:

Wheezing disorders and asthma-like symptoms are among the most common childhood pulmonary sequelae of premature birth. In the US, one in twelve children is diagnosed with asthma [1] but in preterm infants childhood wheezing may be higher than one in three [2, 3, 4]. Extremely premature infants, <28 weeks gestational age (GA), display the highest risk of both childhood wheezing [2, 5] and obstructive lung disease [6, 7].

In preterm infants, an immature respiratory drive often leads to apnea or uncoordinated breathing [8, 9] with accompanying decreases in oxygen saturations (SpO_2) and intermittent hypoxemic (IH) events [10, 11]. These IH events progressively increase during the first month of age [11, 12] and have been associated with multiple morbidities including retinopathy of prematurity [11, 13], neurodevelopmental impairment [13], septicemia [14], and mortality [13, 15].

Because of their immature lungs and high incidence of IH during early postnatal life, premature newborns often require supplemental oxygen and invasive or non-invasive positive pressure support. However, these life-saving neonatal interventions may themselves increase risk for future wheezing and abnormal spirometry [4, 6, 16, 17]. Therefore, we aimed to identify whether clinical markers of neonatal respiratory disease (inspired oxygen and mean airway pressure) and oxygen saturation levels (SpO_2 and IH) were associated with prescription asthma medication use and wheezing problems in early childhood.

Subjects and Methods:

Population

A retrospective cohort of 137 preterm infants (24 0/7 wks – 27 6/7 wks GA) from 2005–2009 at Rainbow Babies & Children's Hospital in Cleveland, Ohio were reviewed for birth, hospital, and respiratory follow-up data. All infants that completed a respiratory health questionnaire at their 2 year follow-up visit and had continuous oxygen saturation waveforms recorded through four weeks of age were included in the analysis.

Institutional IRB approval was obtained for the study which included a waiver of consent to collect continuous oxygen saturation waveforms from the bedside pulse oximeter during the initial hospital stay. Parents provided written consent prior to completing the respiratory questionnaire at the 2 year follow-up visit.

Data Collection and Analysis

Hospital charts were reviewed for birth history and hospital course. Daily levels of respiratory support with their associated mode, pressure, and fraction of inspired oxygen (FiO_2) were recorded from the respiratory flowsheets. Gestational age was calculated by the obstetrical estimated date of delivery. Severity of illness was calculated by Score for

Neonatal Acute Physiology-Perinatal Extension-II (SNAPPE-II) at 24 hours of life [18]. Sepsis was defined as culture-positive bacteremia or fungemia. Bronchopulmonary dysplasia was diagnosed by the National Institutes of Health (NIH) physiologic definition at 36 weeks post-menstrual age [19]. Severe intraventricular hemorrhage (IVH) was made by radiologic diagnosis of a Grade 3 or 4 IVH by head ultrasound during hospitalization. Necrotizing enterocolitis is reported as ≥ stage 2 by Bell's criteria [20]. Any breastmilk feeds were noted at discharge.

Oxygen exposure was recorded as the FiO_2 at the end of defined 6 hour intervals (0000, 0600, 1200 and 1800 hours) and the maximum level for that day. For infants on nasal cannula, effective FiO_2 was estimated using the previously published equations of the STOP-ROP trial to account for cannula flow and infant body weight [21]. A daily effective FiO_2 exposure was then calculated by the weighted mean of the effective FiO_2 time points (Eff_{0000}, Eff_{0600}, Eff_{1200}, and Eff_{1800}) with an adjustment for the maximum effective FiO_2 exposure (Eff_{max}) documented that day, as described by Stevens *et al.* [16]:

$$\text{Daily Effective } FiO_2 = \left[\left(22 \text{ x } (Eff_{0000} + Eff_{0600} + Eff_{1200} + Eff_{1800}\right)/4\right) + \left(2 \text{ x } Eff_{max}\right)]/24$$

Mean airway pressure (MAP) was recorded as the highest documented exposure for each day [16, 22]. MAP estimates of nasal cannula flow were calculated using the formulae published by Wilkinson *et al.* [23]. Cumulative effective FiO_2 and cumulative MAP exposures were then integrated over the first 3, 7, and 28 days of age and presented as an area under the curve (AUC) [16, 22]:

$$FiO_{2AUC} = \text{ Daily Effective } FiO_2(\%) \text{ x exposure duration (days)}$$

$$MAP_{AUC} = \text{ Daily MAP } \left(\text{cm } H_2O\right) \text{ x exposure duration (days)}$$

Oxygen saturation (SpO_2) was continuously recorded over the first 4 weeks of age with a 2 second averaging time and 0.5 Hz sample rate (Radical; Masimo, Irvine, CA, USA). During this time period, SpO_2 targets were historically between 85–95%, and there was not a hospital policy to adjust targets before 4 weeks of postnatal age. Intermittent hypoxemia (IH) events were defined as an SpO_2 ≤80% for ≥10 sec and ≤180 sec, as previously described [24].

The primary outcome, asthma medication, was operationalized as parental reported prescription asthma medication use in the last 6 months (rescue inhalers/nebulizers, inhaled or systemic steroids, and/or leukotriene antagonists) from respiratory questionnaires obtained at 2 year follow-up [25, 26]. Secondary outcomes from the respiratory questionnaire included, in the last 6 months 1) wheezing or whistling in the chest more than two times in a week; 2) visit to doctor, emergency room, or hospital due to wheezing or breathing problems; and 3) change in family plans due to child's breathing problems [27, 28,

29]. Environmental exposures to pets or tobacco smokers in the child's home were also noted at the 2 year follow-up visit.

Statistics

Twenty-three of the 137 cases were the result of multiple births (10 sets of twins and 1 set of triplets). Because of the correlated nature of these observations, generalized estimating equations (GEE) for Poisson regression models with a log link were used with same family exchangeable correlation (SAS PROC GENMOD; SAS Inc, Cary, NC). Using Poisson GEE regression, unadjusted estimated relative risks are reported in Tables 1, 2, and 3. Additionally, multivariate-adjusted relative risks were estimated after controlling for GA and sex. Two-sided Type I error level is 0.05 for the primary outcome related to asthma medication, and for the secondary outcomes.

Results:

Characteristics of the study population are shown in Table 1. In this retrospective cohort study of extremely premature survivors, the overall reported use of prescription asthma medication at 2 year follow-up was 46%. Maternal asthma was significantly increased among the group of children who had received asthma medication compared to those who had not. Bronchopulmonary dysplasia (BPD), defined as need for supplemental oxygen or positive pressure at 36 weeks postmenstrual age, was also positively associated with asthma medication use at 2 year follow-up. Other patient characteristics did not significantly differ. Durations of hospitalization, days of supplemental oxygen, days of both invasive and noninvasive positive pressure, breastmilk feeds at discharge, pets in home, and exposure to tobacco smoke were not significantly different between groups.

Early neonatal respiratory exposures (FiO_{2AUC} and MAP_{AUC}) and saturation parameters (daily IH and mean SpO_2) were associated with childhood respiratory outcomes reported on the health questionnaire (Tables 2 and 3). During the first 3 and 7 days of age, infants that had received childhood asthma medications were exposed to higher cumulative oxygen (FiO_{2AUC}), received greater cumulative mean airway pressure (MAP_{AUC}), had more frequent IH events, and a lower mean SpO_2. When adjusted for GA and sex, FiO_{2AUC}, IH events, and mean SpO_2 remained significantly different between groups; MAP_{AUC} was no longer statistically significant after adjustment. At 4 weeks of age, respiratory exposures and saturation parameters were no longer significantly different between groups.

Secondary outcomes from the respiratory health questionnaire also revealed associations with early neonatal respiratory exposures and saturation parameters (Table 3). Parental reports of wheezing or whistling in the chest of their child >2 days/week in the last 6 months (31% of cohort) were associated with increased IH events during the first 3 and 7 days of age. FiO_{2AUC} during the first 4 weeks of age was increased in children identified as wheezing by their parents, but the correlation was no longer significant when adjusted for GA and sex. Forty-four percent of parents reported doctor, emergency room, and/or hospital visits due to wheezing or breathing problems in their child in the past 6 months. Reported health care visits for wheezing or breathing problems were associated with increased IH events during the first 3 and 7 days of age after adjustment for GA and sex. Finally, 16% of

parents reported needing to change family plans due to their child's breathing problems during the previous 6 months. When adjusted for GA and sex, this was associated with increased FiO_{2AUC} during the first 3 days of age, increased IH events and lower SpO_2 during the first 7 days of age, and a higher average SpO_2 at 4 weeks of age.

Discussion:

Childhood wheezing is a substantial long-term respiratory sequelae in former preterm infants. This study maintains that symptomatic wheezing continues to be a major problem facing children born prematurely, with nearly half of our cohort receiving prescription asthma medications at 2 years of age. We observed that an increased relative risk of asthma medication use was associated with elevated inspired oxygen and early postnatal patterns of oxygenation, including a higher number of daily intermittent hypoxemia events and a lower mean SpO_2, during the first 3 and 7 days of age.

It has been well documented that premature infants are at increased risk for developing wheezing disorders during childhood, with more premature infants showing the greatest childhood risk [2, 3, 30]. Previous studies have suggested causal pathway models encompassing genetic and environmental factors and preterm birth [17, 31, 32, 33]. While often diagnosed and treated as asthmatics, the wheezing of premature infants may be unique in that patients often display less pronounced airway reversibility, less atopy/allergy, with decreased inflammation and exhaled nitric oxide than childhood asthmatics [34].

Childhood wheezing disorders in these preterm infants have traditionally been associated with prolonged courses of supplemental oxygen and/or mechanical ventilation and the diagnosis of BPD [4, 17]. Yet, Doyle *et al.* has reported that measurements of childhood airflow obstruction have increased in recent preterm cohorts despite less invasive ventilation and consistent monitoring by pulse oximetry [6]. In this study, we chose to concentrate on the associations between early postnatal parameters on later respiratory outcomes, isolated from intermediate diagnoses such as BPD and allergy which may be part of the causal pathway. Stevens *et al.* investigated the newborn and childhood exposures of premature infants without BPD that went on to have symptomatic airway dysfunction, finding strong associations with cumulative supplemental oxygen exposures in just the first few days of age [16]. Use of asthma medication in our cohort was also associated with elevated FiO_{2AUC} during the first 3 and 7 days of age, even when controlling for GA and sex. We found an increased prevalence of BPD in the 2 year old children who had received asthma medication (43% compared to 27%), but contrary to previous reports [4, 17], the duration of supplemental oxygen through hospitalization and the duration of both invasive and noninvasive pressure support did not have an apparent association on the primary outcome.

A large retrospective analysis of very low birthweight infants enrolled in the Canadian Oxygen Trial (COT) revealed an association between increased time spent in hypoxemia and multiple morbidities including neurodevelopmental impairment and ROP [13]. In a more detailed analysis of transient patterns of IH we have previously shown that the frequency of IH events progressively increases during the first postnatal month and that a sustained increase in IH events after 5 weeks of age was associated with morbidity [11]. In contrast,

our current study showed that longer-term respiratory morbidity may be influenced by early patterns of IH during the first 3 and 7 days of age, where the incidence of IH was relatively low. This may be reflective of an early postnatal window of vulnerability where an increase in both IH and oxygen exposure predisposes the infant to longer term airway hyperreactivity. In adults, obstructive sleep apnea IH induces airway inflammation and oxidative stress [35, 36] but data describing the relationship between IH and inflammation/oxidative stress in infants is severely limited [8, 37, 38]. In animal models, exposure to intermittent hypoxia induces a proinflammatory response [39, 40] and reactive oxygen species generation [41, 42, 43], suggesting multiple causal pathways that may induce a pathological cascade leading to lung injury and childhood wheezing [32].

Supplemental oxygen has been used in various newborn animal models to induce airway hyperreactivity [44, 45, 46]. Additionally, newborn hyperoxic animal models have suggested that the addition of recurrent postnatal hypoxia events may contribute to longer-term pulmonary changes [44, 47, 48, 49]. Specifically, airway reactivity studies in recovered rodents exposed to frequent intermittent hypoxia in the setting of underlying hyperoxia during the first week of age show juvenile airway hyperreactivity to methacholine challenge when compared to room air controls [44], suggesting that exposure to recurrent desaturation events treated with supplemental oxygen may contribute to longer-term wheezing. Importantly, this animal study also indicated that intermittent hypoxia alone does not increase airway hyperreactivity and corresponds to the current study findings of both increased IH and increased oxygen exposure predisposing infants to long term respiratory morbidity.

The Surfactant Positive Pressure and Oximetry Randomized Trial (SUPPORT) randomly assigned extremely premature infants to mandatory intubation and surfactant versus continuous positive airway pressure (CPAP) in the delivery room [50]. At 6–22 months corrected age, less respiratory morbidity was observed among infants initially randomized to receive CPAP and a limited ventilation strategy [29], although subanalyses of the delivered level and duration of positive pressure were not reported. We did not observe significant associations between modes of ventilation nor cumulative mean airway pressure exposures (after adjusting for GA and sex) on the various childhood wheezing outcomes, which is congruent with the previous MAP_{AUC} data of Stevens *et al.* [16]. We speculate that infants in our cohort having frequent IH events and a lower mean SpO_2 during the first week of age are preferentially treated with increased supplemental oxygen and secondarily with modestly elevated positive airway pressure in attempts to alleviate IH episodes.

At 2 year follow-up, approximately a third of our cohort had recurrent wheezing and nearly half reported healthcare visits for wheezing or breathing problems in the past six months. These secondary respiratory health outcomes were also associated with early increases in IH frequency. Despite the relatively high incidence of doctor, emergency room, or hospital visits, only 16% of parents reported changing family plans due to their child’s breathing problem. Change in family plans was associated with increased IH events and lower SpO_2 during the first 7 days of age, and an unexpected higher SpO_2 at 4 weeks of age. The higher SpO_2 is most likely a result of the increased oxygen exposure at 4 weeks of age.

The strengths of this study include the continuous recordings of oxygen saturation during the first month of age, the daily documentation of inspired oxygen and mean airway pressure, and the use of prescribed asthma medications to substantiate respiratory morbidity by a clinical care provider. Our primary outcome of prescription asthma medication has been previously used in follow-up studies of preterm populations [25, 26] and reflects a need for medical treatment due to breathing problems as evaluated by a physician and the child's caregiver. The respiratory questionnaire was structured similar to the Tucson Asthma Study previously validated in a term cohort [27] and used in the SUPPORT preterm infant follow-up study [29]. Additionally, parental questionnaire reports of wheezing or whistling in the chest in a preterm population have shown test-retest reliability and convergence with other respiratory outcomes, including inhaled medications and oral steroids [28].

Among potential limitations of this retrospective cohort study, only parent-child dyads that returned for follow-up were included and their respiratory outcomes were reported by parental questionnaires, which may be predisposed to selection and recall biases for all outcomes. Given the study design, we cannot attribute causality nor exclude the possibility that more critically-ill infants required increased inspired oxygen, had increased IH events, lower SpO_2, and were more likely to be on asthma medications as children. While a history of maternal asthma was notably increased in subjects receiving asthma medications, the adjustment models failed to converge when maternal asthma was included as a covariate, likely due to inadequate sample size (10 of the 137 infant cohort). Future cohort studies of childhood wheezing would benefit from more detailed accounting of family medical histories and postnatal exposures as they pertain to allergy or asthma.

In summary, cumulative inspired oxygen exposure and frequent IH events during just the first 3 and 7 days of age in extremely premature newborns were associated with childhood use of prescription asthma medications. Increased neonatal IH events were also associated with wheezing and substantial demands on the healthcare system and families. Risk for childhood wheezing disorders remain high despite efforts to decrease early exposures to excessive hyperoxia and invasive ventilation. Early recognition of premature infants prone to developing symptomatic wheezing has the potential to enhance patient care by allowing targeted surveillance and intervention, family education, and preventative measures against environmental triggers.

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Table 1:

Patient Characteristics.

Mean (with standard deviation) or percentage of population by perinatal characteristics, hospitalization characteristics, and respiratory exposures through hospital discharge and in home. Relative Risk (95% Confidence Intervals) and p-values reported for variable's association with reported prescription asthma medication use within the past 6 months of child's two year follow-up visit by generalized estimating equations for Poisson regression models with clustering of twins or triplets within one mother. SNAPPE-II (Score for Neonatal Acute Physiology-Perinatal Extension-II)

mean(SD)	Population (N=137)	Prescription Asthma Medication (N=63)	No Respiratory Medications (N=74)	Relative Risk (95% Confidence Intervals)	p-value
Perinatal Characteristics					
Gestational Age (weeks completed)	26.2(1.1)	26.1(1.0)	26.3(1.1)	0.92 (0.77, 1.09)	0.34
Birth Weight (g)	839(179)	836(166)	840(190)	0.82 (0.28, 2.37)	0.71
Multiple Pregnancy	17%	13%	20%	0.75 (0.36, 1.56)	0.44
Female	49%	40%	57%	0.73 (0.53, 1.02)	0.07
Race (Black)	58%	63%	53%	1.31 (0.87, 1.96)	0.19
SNAPPE-II	38.9(17.5)	41.3(18.6)	36.9(16.3)	1.01 (1.00, 1.01)	0.23
Maternal Asthma	7%	13%	1%	1.99 (1.44, 2.75)	0.0001
Hospitalization Characteristics					
Duration of Hospitalization (days)	97(36)	97(28)	97(41)	1.00 (1.00, 1.01)	0.90
Sepsis	24%	22%	26%	0.90 (0.63, 1.29)	0.57
Bronchopulmonary Dysplasia	34%	43%	27%	1.59 (1.09, 2.31)	0.02
Intraventricular Hemorrhage (Grade 3 or 4)	8%	8%	8%	0.85 (0.39, 1.85)	0.69
Necrotizing Enterocolitis	9%	10%	9%	0.98 (0.53, 1.82)	0.95
Hospitalization Respiratory Exposures					
Duration of Supplemental Oxygen (days)	61(45)	64(41)	58(49)	1.00 (1.00, 1.01)	0.33
Duration of Positive Pressure (days)	69(41)	71(36)	67(45)	1.00 (1.00, 1.01)	0.38
Mechanical Ventilation	19(20)	20(19)	18(21)	1.00 (0.94, 1.01)	0.41
Nasal CPAP/BiPhasic	27(13)	27(13)	27(13)	0.98 (0.63, 1.08)	0.95
Nasal Cannula	23(22)	25(18)	21(25)	1.01 (1.00, 1.01)	0.20
Post-Discharge Characteristics					
Breastmilk at Discharge	27%	24%	30%	0.89 (0.59, 1.34)	0.32
Pets in Home	39%	35%	42%	0.85 (0.57, 1.27)	0.42
Tobacco Exposure in Home	37%	37%	38%	0.95 (0.65, 1.40)	0.81

Table 2:

Respiratory Parameters and Prescription Asthma Medication.

Mean (standard deviation) of cumulative inspired oxygen exposure (FiO_{2AUC}), cumulative mean airway pressure (MAP_{AUC}), intermittent hypoxemia events per day, and mean oxygen saturation (SpO_2) at Days 1–3, 1–7, and 1–28 of postnatal age. Relative Risk (95% Confidence Intervals) and p-values reported for variable's association with reported prescription asthma medication (Yes) or no respiratory medications (No) within the past 6 months of child's two year follow-up visit by generalized estimating equations (GEE) for Poisson regression models with clustering of twins or triplets within one mother. Adjusted for gestational age (weeks completed) and sex. GEE iteration limit exceeded for adjusted RR of Day 1–28 cumulative oxygen exposure and asthma medication outcome.

In Last 6 Months, Any Prescription Asthma Medication Used																		
mean(SD)	**Day 1–3**		**RR (95% CI)**	**p**	**Adjusted RR (95% CI)**	**p**	**Day 1–7**		**RR (95% CI)**	**p**	**Adjusted RR (95% CI)**	**p**	**Day 1–28**		**RR (95% CI)**	**p**	**Adjusted RR (95% CI)**	**p**
	Yes	**No**					**Yes**	**No**					**Yes**	**No**				
FiO_{2AUC} (% × day)	96.4 (31.1)	87.7 (21.6)	1.01 (1.001, 1.01)	.02	1.01 (1.0003, 1.01)	.04	202.5 (50.2)	186.4 (33.9)	1.004 (1.001, 1.01)	.009	1.004 (1.001,1.01)	.02	920.2 (271.6)	865.2 (241.8)	1.00 (1.00,1.00)	.10	No estimates: Iteration limit exceeded	-
MAP_{AUC} (cm H_2O × day)	19.7 (5.7)	18.0 (4.1)	1.03 (1.01, 1.06)	.02	1.03 (0.99, 1.06)	.052	42.9 (16.7)	38.3 (12.9)	1.01 (1.0004, 1.02)	.04	1.01 (0.99,1.02)	.09	169.0 (74.4)	157.2 (72.2)	1.00 (1.00, 1.00)	.28	1.00 (1.00,1.01)	.41
Intermittent Hypoxemia (per day)	33 (33)	21 (17)	1.01 (1.004,1.01)	.0002	1.01 (1.004, 1.01)	<.0001	31 (24)	21 (15)	1.01 (1.01,1.02)	<.0001	1.01 (1.01,1.02)	.0005	98 (58)	83 (51)	1.00 (1.00, 1.01)	.09	1.00 (1.00, 1.00)	.28
Mean SpO_2 (%)	93.5 (2.5)	94.5 (2.2)	0.92 (0.87, 0.98)	.005	0.93 (0.88,0.98)	.005	93.7 (2.3)	94.5 (1.9)	0.91 (0.85,0.98)	.01	0.91 (0.86,0.99)	.02	92.7 (2.3)	93.3 (2.4)	0.94 (0.88,1.00)	.06	0.94 (0.88,1.01)	.09

Table 3:

Respiratory Parameters and Secondary Respiratory Health Outcomes.

Mean (standard deviation) of cumulative inspired oxygen exposure (FiO_{2AUC}), cumulative mean airway pressure (MAP_{AUC}), intermittent hypoxemia events per day, and mean oxygen saturation (SpO_2) at Days 1–3, 1–7, and 1–28 of postnatal age. Relative Risk (95% Confidence Intervals) and p-values reported for variable's association with parental reported respiratory outcomes (Yes or No) within the past 6 months of child's two year follow-up visit by generalized estimating equations for Poisson regression models with clustering of twins or triplets within one mother. Adjusted for gestational age (weeks completed) and sex.

In Last 6 Months, Wheezing or Whistling in the Chest >2 Days/Week																	
mean(SD)	Day 1–3		RR (95% CI)	p	Adjusted RR (95% CI)	p	Day 1–7		RR (95% CI)	p	Adjusted RR (95% CI)	p	Day 1–28		RR (95% CI)	p	Adjusted RR (95% CI)	p
	Yes	No					Yes	No					Yes	No				
FiO_{2AUC} (% × day)	96.0 (33.1)	89.8 (23.2)	1.01 (1.00,1.01)	.13	1.01 (1.00,1.01)	.18	202.5 (51.4)	190.0 (38.0)	1.00 (1.00,1.01)	.07	1.00 (1.00,1.01)	.20	955.1 (269.3)	861.9 (246.6)	1.001 (1.00,1.002)	.02	1.00 (1.00,1.00)	.30
MAP_{AUC} (cm H_2O × day)	19.4 (5.4)	18.6 (4.8)	1.02 (0.98,1.07)	.30	1.02 (0.97,1.08)	.50	41.1 (16.4)	40.1 (14.2)	1.00 (0.99,1.02)	.70	1.00 (0.98,1.02)	.89	166.5 (74.8)	161.0 (72.8)	1.00 (1.00,1.00)	.69	1.00 (0.99,1.00)	.38
Intermittent Hypoxemia (per day)	34 (35)	23 (20)	1.01 (1.004,1.01)	.0005	1.01 (1.004,1.02)	.0002	30 (25)	23 (18)	1.01 (1.003,1.02)	.01	1.01 (1.002,1.02)	.02	96 (57)	87 (54)	1.00 (0.98,1.01)	.34	1.00 (0.96,1.01)	.93
Mean SpO_2 (%)	93.8 (2.3)	94.2 (2.4)	0.95 (0.86,1.04)	.27	0.96 (0.87,1.07)	.46	93.8 (2.1)	94.2 (2.1)	0.93 (0.83,1.04)	.21	0.96 (0.85,1.08)	.49	92.6 (2.1)	93.2 (2.5)	0.93 (0.84,1.02)	.12	0.97 (0.88,1.07)	.58
In Last 6 Months, Visit to Doctor, Emergency Room, or Hospital Due To Wheezing/Breathing Problems																		
mean(SD)	Day 1–3		RR (95% CI)	p	Adjusted RR (95% CI)	p	Day 1–7		RR (95% CI)	p	Adjusted RR (95% CI)	p	Day 1–28		RR (95% CI)	p	Adjusted RR (95% CI)	p
	Yes	No					Yes	No					Yes	No				
FiO_{2AUC} (% × day)	93.8 (32.1)	90.1 (21.5)	1.00 (1.00,1.01)	.14	1.01 (1.00,1.01)	.05	195.2 (47.8)	192.7 (38.6)	1.00 (1.00,1.01)	.34	1.01 (1.00,1.01)	.07	867.6 (224.0)	908.3 (279.2)	1.00 (1.00,1.00)	.34	1.00 (1.00,1.00	.11
MAP_{AUC} (cm H_2O × day)	18.9 (5.6)	18.7 (4.4)	1.01 (0.97,1.04)	.66	1.01 (0.98,1.05)	.47	39.8 (16.3)	40.8 (13.7)	0.99 (0.99,1.01)	.70	1.00 (0.98,1.01)	.70	155.2 (66.8)	168.5 (77.7)	1.00 (1.00,1.00)	.28	1.00 (0.99,1.00)	.07
Intermittent Hypoxemia (per day)	31 (33)	23 (18)	1.01 (1.002,1.01)	.002	1.01 (1.003,1.01)	.002	29 (24)	23 (16)	1.01 (1.003,1.02)	.003	1.01 (1.004,1.02)	.002	94 (55)	87 (54)	1.00 (0.98,1.00)	.64	1.00 (0.97,1.00)	.92
Mean SpO_2 (%)	93.8 (26)	94.2 (2.2)	0.97 (0.91,1.03)	.28	0.97 (0.93,1.03)	.39	94.0 (2.3)	94.2 (2.0)	.099 (0.92,1.06)	.73	1.00 (0.93,1.07)	.96	93.0 (2.2)	93.1 (2.5)	0.98 (0.93,1.06)	.73	1.00 (0.94,1.06)	.93
In Last 6 Months, Had to Change Family Plans Due To Child's Breathing Problems																		
mean(SD)	Day 1–3		RR (95% CI)	p	Adjusted RR (95% CI)	p	Day 1–7		RR (95% CI)	p	Adjusted RR (95% CI)	p	Day 1–28		RR (95% CI)	p	Adjusted RR (95% CI)	p
	Yes	No					Yes	No					Yes	No				
FiO_{2AUC} (% × day)	102.6 (37.1)	89.6 (23.8)	1.01 (1.003,1.02)	.008	1.01 (1.001,1.02)	.03	213.5 (54.1)	190.0 (39.4)	1.01 (1.003,1.01)	.003	1.01 (0.99,1.01)	.05	1009.7 (264.8)	867.7 (249.5)	1.001 (1.0004,1.002)	.008	1.00 (1.00,1.00)	.18
MAP_{AUC} (cm H_2O × day)	20.1 (5.1)	18.6 (4.9)	1.05 (0.98,1.12)	.13	1.04 (0.96,1.13)	.32	43.0 (13.0)	39.9 (15.2)	1.01 (0.99,1.03)	.27	1.00 (0.98,1.03)	.78	186.0 (74.5)	158.2 (72.4)	1.00 (1.00,1.01)	.07	1.002 (1.00,1.01)	.66
Intermittent Hypoxemia (per day)	31 (23)	25 (27)	1.01 (0.96,1.02)	.26	1.01 (0.98,1.02)	.13	33 (24)	24 (20)	1.02 (1.001,1.03)	.03	1.02 (1.002,1.03)	.02	97 (48)	89 (56)	1.00 (0.97,1.01)	.44	0.99 (0.93,1.01)	.79
Mean SpO_2 (%)	93.3 (2.0)	94.2 (2.4)	0.87 (0.77,0.99)	.04	0.88 (0.77,1.02)	.08	93.1 (2.1)	94.3 (2.1)	0.81 (0.69,0.94)	.007	0.84 (0.71,0.99)	.04	93.3 (2.3)	91.9 (2.2)	0.82 (0.72,0.94)	.004	0.85 (0.74,0.98)	.03