IMPACT OF INTERCURRENT RESPIRATORY INFECTIONS ON LUNG HEALTH IN INFANTS BORN < 29 WEEKS WITH BPD

BY

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Abstract:

Objective: To assess the impact of intercurrent respiratory infections on infants born <29 weeks gestation with bronchopulmonary dysplasia (BPD).

Study Design: A retrospective cohort study was conducted on 111 infants born <29 weeks gestation with BPD in one academic center from 2008-2010.

Results: Backward stepwise logistic regression showed viral infections significantly increased oxygen use with an OR of 15.5 [CI 3.4, 71.3]. Stratified bivariate Cochran-Mantel-Hansel chi-square analysis showed both viral and bacterial infections affected oxygen use (9% vs. 47%, p<0.0002 and 8% vs. 24%, p =0.02) with viral infections maintaining significance in the no/mild and severe BPD groups (2% vs. 40% p=0.02 and 26% vs. 83% p=0.02). Both viral and bacterial infections were associated with increased steroid use (11% to 29%, P=0.01 and 9% to 22%, p=0.03) but only viral infections were associated with an increased diuretic use in the combined BPD groups and no/mild BPD group (32% to 57%, P=0.02 and 10% to 50%, p=0.03). The Cochran-Armitage trend test showed that an increasing number of viral infections is associated with increased oxygen use (OR [95% CI] = 6.4 [2.3-17.4]), diuretic use (OR [95% CI] = 2.4 [1.1 – 5.2], p=0.02) and inhaled steroid use (OR [95% CI] = 2.2[1.003 – 5.2], p=0.049).

Conclusions: Viral infections caused more long term pulmonary morbidity/mortality than bacterial infections on premature lung health over the first year of life.

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Introduction:

Each year 1 out of 8 infants are born premature in the United States, costing approximately $26.2 billion dollars a year ($51,600 per infant) on their medical care (1, 2) . Infants born in the United States before 28 weeks gestation now have a 90% survival rate (3) and chronic respiratory morbidity is the most common and costly adverse outcome for these infants (4-6).

Premature infants' arrested lung development places them at risk for respiratory complications in the first year of life. A "new" form of BPD has developed that is primarily due to arrested lung development which involves less inflammation and fibrosis of the airways but has increased structural abnormalities (6, 7). 77% of infants born before 30 weeks gestation develop BPD (4) and can initially have mild respiratory problems that deteriorate over the first year of life (6). These pulmonary abnormalities are not always associated with the infants' presenting level of BPD or respiratory support in the Neonatal Intensive Care Unit (NICU) (8).

Currently the cause of this unexpected deterioration in lung function is unknown; however, other literature has established that respiratory infections in this group has increased morbidity associated with it and premature infants have a 73% chance of readmission to the hospital for respiratory infections in the first two years of life (9). Respiratory Syncytial Virus (RSV) is the most common cause for readmission (10); however, Rhinovirus, the most common viral pathogen in childhood, can also cause severe respiratory infections in premature infants (11-13).

BPD, in combination with respiratory infections, may be creating the conditions for an epidemic of severe morbidity and deaths among premature infants who appeared to be developing successfully. Recent literature has indicated that even infants with milder BPD may be at risk for increased pulmonary morbidity over time but the exact cause of this increased morbidity is unclear (6). The objective of this study was to evaluate the impact of both intercurrent bacterial and viral respiratory infections on a cohort of extremely premature infants' pulmonary health over the first year of life past NICU discharge.

METHODS:

Data Repository: The data repository of the Center for Infant Pulmonary Disorders is located at Children's Mercy Hospitals and Clinics and provided de-identified data for this study according to the process approved by the IRB at Children's Mercy Hospitals and Clinics (CMH). Infants hospitalized at CMH were included in the data repository if they were born less than 29 weeks gestational age, born within 2008-2010, born on-sight or transferred to CMH within 24 hours of life and had no history of congenital heart disease or structural airway abnormalities. The data repository collects information on the cohort from birth thru five years of live.

Determination of BPD: Classification of BPD was performed at 36 weeks gestational age and used the criteria outlined by Ehrenkranz et al in 2005 for infants born less than 32 weeks gestation (5). An infant had no BPD if he/she was on room air at 36 weeks or upon discharge from the NICU (whichever came first) or if the child was on supplemental oxygen for less than 28 days. A diagnosis of BPD was given if the patient was on supplemental oxygen for at least 28 days. Infants were classified as: mild BPD, included patients who were on supplemental

oxygen for greater than 28 days but were on room air by discharge or at 36 weeks gestation; moderate BPD, if they were on less than 30% supplemental oxygen at 36 weeks gestational age or upon discharge; or severe BPD, if they were on 30% or more supplemental oxygen at 36 weeks gestation/discharge or were on positive pressure ventilation at 36 weeks. The confounding variable of BPD severity was controlled for by stratifying our cohort into three groups according to their BPD classification: none/mild, moderate and severe.

Definition of Infection: A bacterial infection was identified in the NICU when the patient was clinically symptomatic, there was supporting clinical and/or laboratory/radiographic evidence for infection, a bacterial isolate consistent with a respiratory pathogen was obtained from a tracheal aspirate, sputum sample or nasal aspirate, and the patient required more than 7 days of antibiotic therapy. Patients who were discharged from the NICU were considered to have a bacterial infection if they were given the diagnosis of a bacterial pneumonia/bronchitis from an emergency room (ER) physician, pediatrician or hospitalist (with or without supporting laboratory data) and prescribed antibiotics for > 7 days. A viral infection was identified in the NICU when the patient was clinically symptomatic and had a virus isolated from a viral PCR/culture. Patients who were discharged from the NICU were considered to have a viral infection if they were given the diagnosis of a viral respiratory infection from an ER physician, pediatrician or hospitalist (with or without supporting laboratory data). The patient charts were analyzed for evidence of intercurrent respiratory infections by trained data abstractors up to one year post NICU discharge. Medical record reviews included evaluation of the discharge summary, 6mo and 12mo follow up visits in the special care NICU clinic, ER notes and hospital discharge notes.

Study Population: We included all infants enrolled in the data repository between the dates of 01/01/2008 thru 12/31/2010 who were less than 29 weeks gestational age at birth and admitted to CMH within 24 hours of birth. We excluded infants who died before 36 weeks corrected gestational age, were over 29 weeks gestational age at birth or had significant congenital heart disease or structural airway abnormalities. Out of the 157 infants in the data repository, 15 infants died before 36 weeks corrected gestational age leaving a total of 142 infants met criteria for entry into the study.

Study Design: A retrospective (historical) cohort design was used to evaluate the impact of intercurrent respiratory infections on lung health in extremely premature infants up to one year of age.

Data Analysis: Statistical analysis used the SAS programming version 9.2 software package. We first performed bivariate analysis between risk factors (BPD, viral infection and bacterial infection) and outcome variables (oxygen use, diuretics use and inhaled steroid) using either the Chi-square test and/or Fisher's exact test. A stratified analysis was then used to assess the impact of intercurrent bacterial and viral respiratory infections on the entire cohort and on each individual BPD group. The 2-sided trend t-test was used to evaluate data that did not reach statistical significance but appeared to be trending towards significance. The Cochran-Armitage trend test was used to evaluate the impact of multiple infections on outcome variables. A secondary outcome variable of death after NICU discharge was also evaluated. We developed a multivariable model using backwardstepwise logistic regression. In the multivariate analysis, we considered gestational age, gender, severity of BPD, viral infection, bacterial infection, viral/bacterial interaction, BPD/viral interaction, BPD/bacterial interactions and birth weight on their association with the outcome variables. Odds ratio (OR) and 95% confidence interval (CI)

of OR were reported. To keep model parsimony, non-significant factors are removed from the multivariate models. Statistical significance were claimed with $p<0.05$.

RESULTS:

Basic demographic information on gender, gestational age and birth weight was collected on the 111 infant cohort (Table 1).

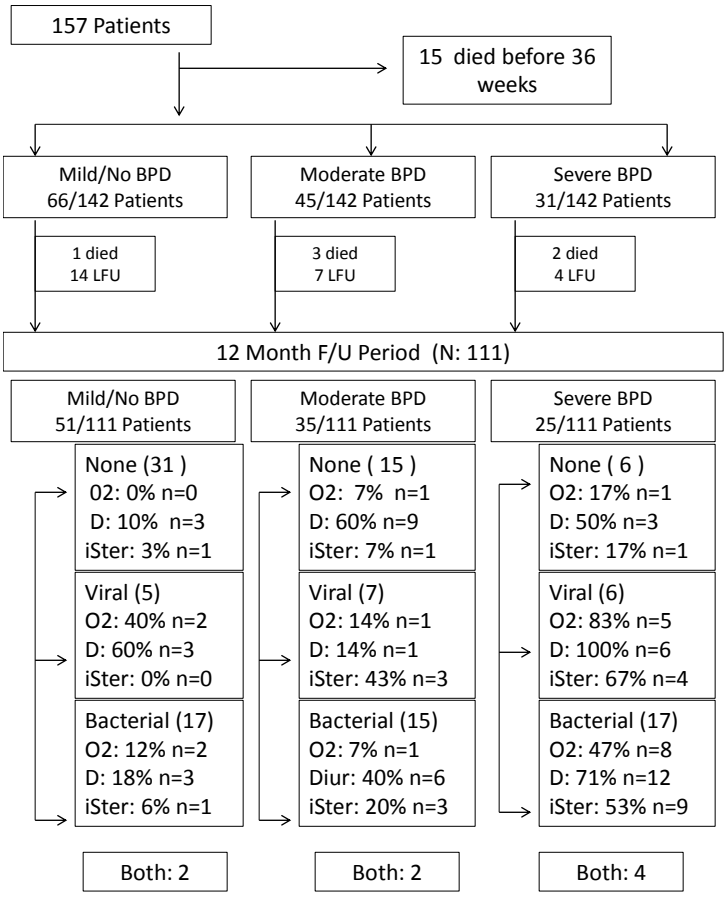
Table 1: Patient demographic information.

	Mild/no BPD (n=66, 46%)	moderate BPD (n=45, 32%)	Severe BPD (n=31, 22%)	p-value
Gender (F/M)	25/41 (38%/62%)	20/25 (44%/56%)	9/22 (29%/71%)	0.40
Gestational Age (week)	26.9 ± 1.2	25.9 ± 1.5	25.3 ± 1.5	<0.0001
Birth Weight (g)	1017 ± 220	847 ± 207	781 ± 175	<0.0001
Subjects died after NICU discharge	1 (1.5%)	3 (6.7%)	2 (6.5%)	0.35

Out of the initial 157 infants, 15 died before 36 weeks corrected gestational age (Figure 1). This left a sample size of 142 patients that underwent BPD classification using the Ehrenkranz model (5). These infants were then separated into three groups for our study which included no/mild BPD (66/142), moderate BPD (45/142) and severe BPD (31/142). Of the 142 children, 31 patients died or were LFU including 14 patients LFU and 1 death in the no/mild BPD group, 7 patients LFU and 3 deaths in the moderate BPD group and 4 LFU and 2 deaths in the severe BPD group. Complete data was available on 51 patients in the no/mild BPD group, 35 patients in the moderate BPD group and 25 patients in the severe BPD group. Of the 35 patients in the mild/no BPD group there were 17 bacterial infections and 5 viral infections identified; 2 patients had overlapping infections identified. Of the 35 patients in the moderate

BPD group there were 15 bacterial infections and 7 viral infections identified; 2 patients had overlapping infections identified. Of the 25 patients in the severe BPD group there were 17 bacterial infections and 6 viral infections identified; 4 patients had overlapping infections identified. Increasing BPD severity was associated with increasing oxygen, diuretic and inhaled steroid use among patients with no/mild, moderate and severe BPD respectively (P<0.0003, P<0.0001 and P<0.0001). Oxygen use was 6%, 11%, and 40%, increasing inhaled steroid use was 3%, 16% and 39%, and increasing diuretic use was 14%, 44%, and 71%.

Figure 1: Patient flow diagram over the 12 month study period.



To evaluate the impact of intercurrent respiratory tract infections on three primary outcome variables (oxygen use, inhaled steroid use and diuretic use at 12 months) in each BPD group, we then used a stratified bivariate analysis using the Cochran-Mantel Haenszel chi-square modeling to assess the impact of both bacterial and viral infections on our outcome variables in each of the defined BPD groups. A logarithmic regression model showed that there was not significant interaction between the viral and bacterial infections (OR[95%]=2.1[0.1, 38.3], p=0.61).

Intercurrent bacterial and viral infections were associated with significantly higher oxygen use when all BPD groups were combined with a significantly greater impact seen in the viral group (8% vs 24%, p=0.02 and 9% vs 47%, p<0.0002 respectively)(Table 2). Bacterial infections did not statistically influence the oxygen use in any of the three BPD sub-groups; however, intercurrent viral infections did statistically increase oxygen use at 12 months post NICU discharge: 2% vs. 40% O2 use in the no/mild BPD (p: 0.02) and 26% vs. 83% in the severe BPD group (p:0.02)(Table 2). The intercurrent bacterial infections did not show a statistically significant change in oxygen use; however, there did seem to be a trend towards significance so the trend t-test was used to see if a statistically significant trend was seen in the bacterial infection cohort and a z score of 0.0963 did show a marginally significant trend towards increased oxygen use in this cohort.

Table 2: CMH chi-square analysis comparing bacterial and viral impact on three outcome variables (oxygen use, diuretic use and inhaled steroid use) in infants with mild, moderate and severe BPD.

	No Bacterial Infection	Bacterial Infection	P-value	No Viral Infection	Viral Infection	P-value
Oxygen use at 12 months						
Mild/no BPD	3%	12%	0.25	2%	40%	0.02
Moderate BPD	10%	13%	1	7%	25%	0.21
Severe BPD	25%	47%	0.40	26%	83%	0.02
All subjects	8%	24%	0.02	9%	47%	0.0002
Total diuretics at 12 months						
Mild/no BPD	12%	17%	0.71	10%	50%	0.03
Moderate BPD	46%	42%	1	49%	30%	0.47
Severe BPD	70%	71%	1	63%	100%	0.08
All subjects	30%	43%	0.12	32%	57%	0.02
Inhaled Steroid use at 12 months						
Mild/no BPD	2%	4%	1	3%	0%	1
Moderate BPD	15%	16%	1	11%	30%	0.17
Severe BPD	20%	48%	0.23	33%	57%	0.38
All subjects	9%	22%	0.03	11%	29%	0.01

The intercurrent bacterial and viral infections were associated with increased inhaled steroid use in the combined BPD groups, but not in any individual BPD groupings. Bacterial

infections increased the use from 9% to 22% (p=0.03) and viral infections increased the use from 11% to 29% (p=0.01)(Table 2).

The intercurrent respiratory infections were associated with increased diuretic use in the viral group only. The viral impact on the combined BPD group analysis was 32% vs. 57% (p=0.02). When the BPD subgroups were broken apart, the no/mild BPD group continued to show a significant increase in diuretic use (10% vs. 50%, p=0.03) (Table 2).

The data was then analyzed, using the Cochran-Armitage trend test, to see if an increasing number of viral or bacterial infections impacted the three primary outcome variables. We first looked at the impact of increasing viral infections on oxygen use. Increasing number of viral infections was noted to cause a greater impact on oxygen use (OR [95% CI] = 6.4 [2.3 – 17.4], p=0.0003): at baseline 9% of the cohort required oxygen which increased with increasing number of viral infections to 44% with 1 viral infection and 67% with 2 viral infections. Increasing number of viral infections also caused a moderate impact on diuretic use (OR [95% CI] = 2.4 [1.1 – 5.2], p=0.02): at baseline 32% of the cohort required diuretics which increased with increasing number of viral infections to 53% with 1 viral infection and 75% with 2 viral infections. Increasing number of viral infections also caused a slight impact on the inhaled steroid use (OR [95% CI] = 2.2[1.003 – 5.2], p=0.049): at baseline 12% of the cohort required inhaled steroids which increased with increasing number of viral infections to 32% with 1 viral infection and 25% with 2 viral infections. With increasing bacterial infections we saw an increase in oxygen use from 8% at baseline to 24% with 1 infection, 29% with 2 infections (p=0.05), an increase in diuretics use from 31% at baseline to 41% with 1 infection, 50% with 2 infections (p=0.07), and an increase in oxygen use from 9% at baseline to 22% with 1 infection, 25% with 2 infections (p=0.07), but they are not statistically significant.

Three separate logistic regression models were created for each of our three primary outcome variables. We forced the following variables into each model: gestational age, BPD class, viral infection and bacterial infection). We originally included the variables gender and viral*bacterial variables but these were excluded after backwardstepwise regression. Viral infections were shown to increase oxygen use (OR[95%]=15.57 [3.4, 71.28], p=0.0004)(Table 3). The model had 89.3% prediction accuracy. There was no significant interaction between viral and bacterial infections (OR[95%]=2.1[0.1, 38.3], p=0.61).

Table 3: Logistic regression models for the three outcome variables of oxygen use, inhaled steroid use and diuretic use.

3A) Oxygen Use (prediction accuracy =89.3%).			
Effect	β Estimate	p-value	odds ratio (95% CI)
Intercept	9.7 ± 6.2	0.12	
Gestational Age (per 1 week increase)	-0.5 ± 0.2	0.03	0.6 (0.4 – 0.95)
BPD Moderate BPD vs. No/Mild BPD Severe BPD vs. No/Mild BPD	 0.006 ± 0.9 1.8 ± 0.9	0.04 0.99 0.04	 1.0 (0.2 – 6.1) 6.1 (1.1 – 35.0)
Viral (Yes vs. No)	2.7 ± 0.8	0.0004	15.6 (3.4 – 71.5)
Bacterial (Yes vs. No)	0.8 ± 0.7	0.26	2.3 (0.5 – 9.6)
3B) Diuretics Use (prediction accuracy =82.2%).			
Effect	β Estimate	p-value	odds ratio (95% CI)
Intercept	10.9 ± 4.0	0.01	
Gestational Age (per 1 week increase)	-0.5 ± 0.2	0.001	0.6 (0.5 – 0.8)
BPD Moderate BPD vs. No/Mild BPD Severe BPD vs. No/Mild BPD	 1.2 ± 0.5 2.2 ± 0.6	0.0006 0.02 0.0001	 3.4 (1.2 – 9.0) 9.1 (2.9 – 28.4)
Viral (Yes vs. No)	0.7 ± 0.5	0.18	2.0 (0.7 – 5.8)
Bacterial (Yes vs. No)	-0.2 ± 0.4	0.66	0.8 (0.3 – 2.0)
3C) Steroid Use (prediction accuracy =82.5%).			
Effect	β Estimate	p-value	odds ratio (95% CI)
Intercept	-0.3 ± 5.0	0.95	
Gestational Age (per 1 week increase)	-0.1 ± 0.2	0.45	0.9 (0.6 – 1.2)
BPD Moderate BPD vs. No/Mild BPD Severe BPD vs. No/Mild BPD	 1.6 ± 0.9 2.5 ± 0.9	0.01 0.07 0.003	 4.7 (0.9 – 25.2) 12.4 (2.3 – 66.6)
Viral (Yes vs. No)	1.0 ± 0.6	0.10	2.7 (0.8 – 8.9)
Bacterial (Yes vs. No)	0.5 ± 0.6	0.35	1.7 (0.6 – 5.3)

Finally, the secondary outcome variable of death after NICU discharge was evaluated using bivariate analysis. Seven infants were identified (5% of the cohort) who died after NICU discharge. 6/7 infants had recent or ongoing viral infections at the time of their death ($p<0.0001$). One had mild BPD, three had moderate BPD and two had severe BPD. These deaths do not appear to correlate with the 36 week BPD severity assessment. 3/6 infants had a history of adrenal insufficiency during their NICU stay and 4/6 infants had a history of transient pulmonary hypertension in the NICU; however, the sample size for these observations were too small to draw any meaningful conclusions.

DISCUSSION:

This study evaluated the impact of both bacterial and viral infections on the same cohort of extremely premature infants at the same time. We demonstrated that viral infections had a significantly greater impact on premature lung health over time compared to bacterial infections. Increasing number of viral infections also had a significant impact on premature infant lung morbidity while increasing number of bacterial infections did not.

To understand why viral infections appear to affect BPD lung physiology differently than bacterial infections it is important to understand how BPD lung structure differs from a full term infants lung physiology. BPD lung structure consists of a simplified alveolar architecture (7, 15) with less alveolar area for ventilation as well as a decreased intravascular pulmonary network that affects the perfusion to the lung (16-18). In the short term, this leads to less baseline pulmonary reserve which is further compromised by infection mediated inflammation in the lungs causing more V/Q mismatch.

Viral infections have been shown to remain in lung tissue for over a month after the acute infection has resolved, causing prolonged abnormal inflammatory responses (19, 20). Viral infections have also been linked to development of airway hyper reactivity and asthma in later life (21) which further demonstrates the long lasting impact of viral infections on the pulmonary physiology. Since viruses persist in the lung longer than bacteria, it is not surprising that our cohort had worse pulmonary outcomes at one year with a history of viral as opposed to bacterial intercurrent lung infections. Also, recent animal studies have indicated that supplemental oxygen increases an animal's sensitivity to influenza infection through altered inflammatory pathways (22)which adds biologic plausibility to our clinical findings linking greater lung morbidity in premature infants at a year of age who have had intercurrent viral infections. It is

surprising to see how much more striking the increased morbidity is with the viral as opposed to bacterial infections.

There were several limitations in our study design that must be considered when evaluating these results. All of these infants were from one center and our findings may not be generalizable to the population at large. Also, obtaining long-term data on NICU infants can be challenging, especially when the NICU cares for infants who are born over 100 miles away. Therefore, some infants were LFU up after NICU discharge. Some of these infants could have moved out of state and died in another center or have significant pulmonary morbidity that was being managed at another location. Another limitation was our definition of infections. While the patients were in the NICU we had better control over management; however, once the patients were in the community the type of work-up they obtained varied and did not always include the same supporting laboratory/radiographic studies. They were also not being evaluated on a daily basis and it is likely that minor infections, both bacterial/viral, went unnoticed by care givers.

There were several strengths in our study design. We evaluated infants that were born recently (2008-2010) and had been hospitalized within the same hospital within 24 hours of birth. This study design minimized the variability of ventilatory strategies used on this cohort since they were managed by the same group of physicians incorporating the goal of quick transition from invasive to non-invasive ventilatory support. Since our cohort was born recently and only spans over three years, the impact of changing technology and medical therapies over time was minimized. Also, our study required access to medical records for this cohort past NICU discharge with special interest being placed on ER, hospital and primary care provider records. Since this center is the only tertiary referral center for complex children in this

geographic region, we hospitalize over 86% of pediatric cases (unpublished CMH demographic data) and closer to 100% of high risk pediatric cases which this cohort falls into. The NICU also has a multispecialty clinic (the special care clinic) that follows the NICU graduates over time with outside pediatrician support and access to their outside records. They see the patients frequently for at least a year past NICU discharge and the CMH-DR has permission to collect information on participants up to five years post NICU discharge.

In general, there has been variability between post-NICU discharge management for this patient population and literature on long-term pulmonary outcomes in this population has only recently become available. Current post-NICU BPD management focuses mainly on nutrition, growth and neurological outcome. Several studies on home oxygen therapy and weaning strategies have been proposed(14, 23, 24); however, there still remains a wide variability in practice in the pediatric providers(25). Even the efficacy of reducing healthcare expenditures in this patient population with outpatient pulmonary follow-up is unclear. However, recent literature has shown that pulmonary follow-up keeps the ER visits and hospitalization rates between mild and severe BPD patients stable (26) when normally more severe BPD patients have increased sequelae. Previous recommendations for evaluation of sleep disordered breathing in this population was focused on infants with severe BPD; however, recent studies have shown that daytime oxygen saturations and respiratory rates did not predict instability seen on sleep studies (27). A recent study performing serial infant pulmonary function tests did not demonstrate any "catch up" lung growth in the BPD infants in the first year of life (28). Longer term studies that looked at lung health in teenagers/adults with a history of BPD showed persistent abnormalities in lung function as seen by increased air trapping, increased residual volume, increased incidence of airway hyper reactivity and a faster decline in lung function in

adulthood compared with controls (29-31). While the longer term pulmonary outcomes were preformed on groups of infants that fell into both the "old" and "new" definitions of BPD, these findings still have significant implications for the type of long term pulmonary follow up these patients should be receiving. Not all BPD patients are followed by multi-specialty clinics with pediatric pulmonology support and even between pediatric pulmonologists there is significant variability among management. Our study suggests that a wider range of extremely premature infants may be at risk of significant pulmonary sequelae from intercurrent infections and warrant closer observation in not just long-term pulmonary follow up but also shorter-term management as well. Patients with a history of extreme prematurity with mild/moderate BPD with an acute viral URI who are mildly hypoxic should be monitored closely and physicians may need to have a low threshold for obtaining a cardiac echo to evaluate for transient pulmonary hypertension and consideration of hospitalization for observation. This population also warrants closer observation for sleep disordered breathing and patients with mild/moderate BPD may benefit from screening for sleep disordered breathing before they leave the NICU. There should be a low provider threshold for obtaining a sleep study if abnormalities are suspected in clinical history despite reassuring pulse oximetry and respiratory rates obtained in clinic.

Finally, our cohort had 7 individuals (6%) die post NICU discharge and six were associated with acute viral infections. The sample size was not large enough to draw any statistically significant conclusions from; however, it was noted that 3/7 infants had adrenal insufficiency and 4/7 infants had transient pulmonary hypertension while in the NICU. Some of these patients, and other cohort participants who did not die, were noted to have pulmonary hypertension with hospitalizations secondary to viral illnesses which was not noted on NICU discharge cardiac ECHO. We hypothesize that there may be an increased risk for developing

transient pulmonary HTN in this population with intercurrent viral illnesses after NICU discharge and larger studies will have to be performed to corroborate this clinical observation and determine potential risk factors for this outcome. The other possibility is that our cardiac echo technique does not allow us to adequately evaluate this population for very mild persistent pulmonary hypertension and other markers will need to be developed to detect pulmonary hypertension in this patient population. Larger studies with national datasets should also be performed to determine if this trend seen in our patient population can be generalized to the larger US population of premature infants.

References:

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012 Jun 9;379(9832):2162-72.

2. Morken NH. Preterm birth: new data on a global health priority. Lancet. 2012 Jun 9;379(9832):2128-30.

3. Bick D. Born too soon: the global issue of preterm birth. Midwifery. 2012 Aug;28(4):341-2.

4. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. N Engl J Med. 2008 Jul 17;359(3):262-73.

5. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005 Dec;116(6):1353-60.

6. Greenough A. Long term respiratory outcomes of very premature birth (<32 weeks). Semin Fetal Neonatal Med. 2012 Apr;17(2):73-6.

7. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001 Jun;163(7):1723-9.

8. Anand D, Stevenson CJ, West CR, Pharoah PO. Lung function and respiratory health in adolescents of very low birth weight. Arch Dis Child. 2003 Feb;88(2):135-8.

9. Greenough A, Cox S, Alexander J, Lenney W, Turnbull F, Burgess S, et al. Health care utilisation of infants with chronic lung disease, related to hospitalisation for RSV infection. Arch Dis Child. 2001 Dec;85(6):463-8.

10. Drysdale SB, Wilson T, Alcazar M, Broughton S, Zuckerman M, Smith M, et al. Lung function prior to viral lower respiratory tract infections in prematurely born infants. Thorax. 2011 Jun;66(6):468-73.

11. Bennett NJ, Tabarani CM, Bartholoma NM, Wang D, Huang D, Riddell SW, et al. Unrecognized viral respiratory tract infections in premature infants during their birth hospitalization: a prospective surveillance study in two neonatal intensive care units. J Pediatr. 2012 Nov;161(5):814-8.

12. Linder JE, Kraft DC, Mohamed Y, Lu Z, Heil L, Tollefson S, et al. Human rhinovirus C: Age, season, and lower respiratory illness over the past 3 decades. J Allergy Clin Immunol. 2013 Jan;131(1):69-77 e1-6.

13. Regamey N, Kaiser L. Rhinovirus infections in infants: is respiratory syncytial virus ready for the challenge? Eur Respir J. 2008 Aug;32(2):249-51.

14. Groothuis JR, Makari D. Definition and outpatient management of the very low-birth-weight infant with bronchopulmonary dysplasia. Adv Ther. 2012 Apr;29(4):297-311.

15. Reyburn B, Martin RJ, Prakash YS, MacFarlane PM. Mechanisms of injury to the preterm lung and airway: implications for long-term pulmonary outcome. Neonatology. 2012;101(4):345-52.

16. Kunig AM, Balasubramaniam V, Markham NE, Morgan D, Montgomery G, Grover TR, et al. Recombinant human VEGF treatment enhances alveolarization after hyperoxic lung injury in neonatal rats. Am J Physiol Lung Cell Mol Physiol. 2005 Oct;289(4):L529-35.

17. Balinotti JE, Chakr VC, Tiller C, Kimmel R, Coates C, Kisling J, et al. Growth of lung parenchyma in infants and toddlers with chronic lung disease of infancy. Am J Respir Crit Care Med. 2010 May 15;181(10):1093-7.

18. Mourani PM, Ivy DD, Gao D, Abman SH. Pulmonary vascular effects of inhaled nitric oxide and oxygen tension in bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2004 Nov 1;170(9):1006-13.

19. Hegele RG, Hayashi S, Bramley AM, Hogg JC. Persistence of respiratory syncytial virus genome and protein after acute bronchiolitis in guinea pigs. Chest. 1994 Jun;105(6):1848-54.

20. Estripeaut D, Torres JP, Somers CS, Tagliabue C, Khokhar S, Bhoj VG, et al. Respiratory syncytial virus persistence in the lungs correlates with airway hyperreactivity in the mouse model. J Infect Dis. 2008 Nov 15;198(10):1435-43.

21. Bacharier LB, Cohen R, Schweiger T, Yin-Declue H, Christie C, Zheng J, et al. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol. 2012 Jul;130(1):91-100 e3.

22. O'Reilly MA, Yee M, Buczynski BW, Vitiello PF, Keng PC, Welle SL, et al. Neonatal oxygen increases sensitivity to influenza A virus infection in adult mice by suppressing epithelial expression of Ear1. Am J Pathol. 2012 Aug;181(2):441-51.

23. Abman SH, Groothius JR. Pathophysiology and treatment of bronchopulmonary dysplasia. Current issues. Pediatr Clin North Am. 1994 Apr;41(2):277-315.

24. Ellsbury DL, Acarregui MJ, McGuinness GA, Eastman DL, Klein JM. Controversy surrounding the use of home oxygen for premature infants with bronchopulmonary dysplasia. J Perinatol. 2004 Jan;24(1):36-40.

25. Palm K, Simoneau T, Sawicki G, Rhein L. Assessment of current strategies for weaning premature infants from supplemental oxygen in the outpatient setting. Adv Neonatal Care. 2011 Oct;11(5):349-56.

26. Rhein LM, Konnikova L, McGeachey A, Pruchniewski M, Smith VC. The role of pulmonary follow-up in reducing health care utilization in infants with bronchopulmonary dysplasia. Clin Pediatr (Phila). 2012 Jul;51(7):645-50.

27. McGrath-Morrow SA, Ryan T, McGinley BM, Okelo SO, Sterni LM, Collaco JM. Polysomnography in preterm infants and children with chronic lung disease. Pediatr Pulmonol. 2012 Feb;47(2):172-9.

28. Schmalisch G, Wilitzki S, Roehr CC, Proquitte H, Buhrer C. Development of lung function in very low birth weight infants with or without bronchopulmonary dysplasia: longitudinal assessment during the first 15 months of corrected age. BMC Pediatr. 2012;12:37.

29. Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. Pediatrics. 2006 Jul;118(1):108-13.

30. Vrijlandt EJ, Gerritsen J, Boezen HM, Grevink RG, Duiverman EJ. Lung function and exercise capacity in young adults born prematurely. Am J Respir Crit Care Med. 2006 Apr 15;173(8):890-6.

31. Halvorsen T, Skadberg BT, Eide GE, Roksund OD, Carlsen KH, Bakke P. Pulmonary outcome in adolescents of extreme preterm birth: a regional cohort study. Acta Paediatr. 2004 Oct;93(10):1294-300.