HHS Public Access

Author manuscript

Pediatr Pulmonol. Author manuscript; available in PMC 2019 June 10.

Published in final edited form as:

Pediatr Pulmonol. 2019 May ; 54(5): 581–586. doi:10.1002/ppul.24261.

Pulmonary findings in infants with cystic fibrosis during the first year of life: results from the Baby Observational and Nutrition Study (BONUS) cohort study.

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Abstract

Importance—Treatment recommendations for infants with CF standardize care, but most surveillance or treatment guidance of pulmonary manifestations are consensus-based due to sparse evidence.

Objective—To report observations about pulmonary correlates of growth and other clinical features in infants with CF.

Methods—We analyzed data from the prospective Baby Observational and Nutrition Study conducted in 28 centers across the US, including clinical features, medications, guardian diaries of respiratory symptoms, oropharyngeal swab cultures and chest radiographs (CXR) collected over the first year of life.

Results—Cough was reported in 84% of infants in the first year. Up to 30% had clinically important cough but only 6.3% had crackles; 16.5% had wheeze. Wisconsin CXR score was above 5 in 23% (normal=0; maximum score=100). *Pseudomonas* was recovered from at least one respiratory culture in 24% of infants and was associated with crackles/wheezes and use of proton pump inhibitors (PPI) (OR=5.47; 95% CI=1.36, 21.92; p=0.02) or PPI plus histamine-2 (H2) blocker (OR=8.2; 95% CI= 2.41, 27.93; p=0.001), but not H2 blocker alone. Hospitalization for

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respiratory indications occurred in 18% of infants and was associated with crackles/wheeze and abnormal CXR but not low weight, *Pseudomonas* or use of acid blockade.

Conclusions—Cough is common in infants with CF, but few present with crackles/wheeze or CXR changes. *Pseudomonas* is associated with use of PPI or PPI plus H2 blocker, but not with respiratory hospitalization. These observations cannot prove cause and effect but add to our understanding of pulmonary manifestations of CF in infants.

Trial registration—United Sttes ClinicalTrials.Gov registry NCT01424696 (clinicaltrials.gov).

Keywords

Cystic fibrosis; CF; Pulmonary outcomes; Nutrition

INTRODUCTION

Newborn screening for cystic fibrosis (CF) over the last 20 years has contributed to improved weight and stature in children with CF in the United States, particularly in the first year of life[1,2]. CF pulmonary disease begins early, with inflammation and infection leading to bronchiectasis in up to 80% of children age 5 years and above[1]. Structural lung disease can be present even in children with normal lung function. Lung disease in infants can be progressive and can progress rapidly if not identified early. Recommendations for treatment of lung disease in the first year of life have helped to standardize care in CF, but most recommendations for surveillance or treatment of pulmonary disease are based on expert consensus as the evidence is sparse[1]. Identifying factors associated with the early onset of clinical lung disease may enable us to develop effective monitoring strategies. Enhanced surveillance in the routine clinical setting is essential for improved pulmonary outcomes in CF.

The Baby Observational and Nutrition Study (BONUS) was a prospective multi-center study of infants with CF with the primary aim of examining the current state of weight gain and linear growth in the first year of life. Its secondary aim was to prospectively explore concurrent nutritional, metabolic, respiratory, infectious, and inflammatory characteristics associated with early CF anthropometric measurements. Previous publications have reported on the correlations of clinical parameters such as *Pseudomonas aeruginosa* (*Pa*), pancreatic insufficiency and growth factor levels with weight and length in the first year of life[2], as well as the lack of pancreatic enzyme dose effect on growth[5]. This current clinical report summarizes the pulmonary findings in the BONUS CF infants, including symptoms of cough, wheeze, crackles and chest x-ray (CXR) abnormalities, frequency of cultures for CF specific organisms, as well as the relationship of pulmonary findings to acid suppression medications.

METHODS

Patients and Study Design

The Baby Observational and Nutrition Study (BONUS) was a prospective cohort study conducted at 28 US Cystic Fibrosis Foundation (CFF) accredited care centers within the

CFF Therapeutic Development Network, with methods previously described[2]. Length, weight, and occipital frontal circumference (OFC) were performed at each visit by trained and certified staff[6,1]. Prior to each study visit, participant guardians completed various diaries, including an assessment of frequency and severity of cough[7]. Cough was classified by participant guardians into four categories based on the Wisconsin Neonatal Screening project's work in CF: 0, no cough; 1, rare cough; 2, cough in the morning or with postural drainage; or 3, frequent (>10 times per day), productive or paroxysmal cough[7]. Blood was collected at enrollment, 6, and 12 months; urine and fecal samples were collected at enrollment and at each visit; respiratory tract cultures and CXRs were performed per CF Care Guidelines[4]. Respiratory tract cultures and other samples were banked for later analyses if consent was given. The 12-month CXR was scored[8]centrally by two independent readers using the Wisconsin scale[8]. Written informed consent was obtained from all participating parents/guardians, and all participating sites received Institutional Review Board approval. The study was registered at ClinicalTrials.gov (NCT01424696).

Definitions and Statistics

Attained weight, length, and OFC for age z-scores were calculated using WHO standard growth curves.[9, 10] Infants were denoted as having a severe phenotype if both *CFTR* alleles were classes I-III[11]. Infants were categorized as being *Pseudomonas aeruginosa* (*Pa*) positive if *Pa* was recovered on at least one oropharyngeal (OP) swab, collected clinically, during the year of observation[2]. We used the Wisconsin score to assess chest radiographs (CXR). A score of 0 indicates a normal chest radiograph and a score of 100 indicates the most severe lung disease[12]. A score of less than 5 was chosen as the upper limit for very mild, reversible abnormalities based on the Wisconsin Neonatal Screening Trial[8].

Summary statistics including means, medians, standard deviations [SD], ranges, and 95% confidence intervals (CI) are reported when appropriate. In the current analysis, crackles and wheezing were evaluated together. Differences and comparisons were made with one and two-sample t-tests, Fisher's exact test for categorical data, or Pearson's correlation coefficient. Univariate and multivariable logistic regression was used to assess whether the odds of the outcomes were associated with the risk factors. The association between risk factors and mean respiratory and total hospital days was assessed using gamma regression with a log link function; all model parameters have been exponentiated to reflect risk ratios, such that a value greater than one indicates that the given risk factor is associated with a greater number of hospital days, while a value less than one indicates the risk factor is associated with fewer hospital days. For all multivariable models, variables with a univariate p-value <0.25 were initially considered, and stepwise selection was used to produce the final models. 95% confidence intervals (CIs) were calculated and all p-values were two-sided ($p<0.05$ significant).

RESULTS

BONUS enrolled 231 infants with CF (48% female, 57% Phe508del homozygous, 84.4% severe mutations, 91% pancreatic insufficient). A description of the cohort and associations between clinical characteristics and growth have been reported previously, including the

association of weight and length with pulmonary features such as *Pa* growth[2]. For example, it was previously reported that wheezing was associated with an increased risk for low length and the presence of *Pa* on respiratory tract cultures at any time in the first year of life was associated with low weight. This current publication focuses on the pulmonary status of the infants including pulmonary symptoms, CXR and oropharyngeal swab findings, and relationship to acid suppression medications.

Pulmonary Status

New analysis of the BONUS data showed that thirty-eight babies out of 231 (16.5%) had wheeze: 9 of those had crackles with wheeze (3.9%), while 29 babies had wheeze alone (12.6%). Participant guardians reported cough in 81.6%, 83.7% and 67.4% of infants at ages 3, 6, and 12 months, respectively. A clinically important cough was defined as “coughed a lot, more than 10 times a day, was productive, or in spasms”; this was reported in 21.9%, 30.2%, and 26.9% of infants at 3, 6, and 12 months, respectively. Despite the frequency of reported cough, only 6.3% of BONUS infants with cough were found to have crackles on physical exam.

Dornase alfa and hypertonic saline were prescribed on > 1 occasion in 32.1% and 15.8% of infants, respectively in the first year of life. Inhaled tobramycin was used in 23.5%. *Pa* was recovered in 24.9% of infants; 27% of those with severe mutations were positive for *Pa* compared to 10% of those with mild mutations were positive for *Pa* (p=0.17). Patients with *Pa* were significantly more likely than those without *Pa* to have crackles and/or wheezing (29% versus 15%, p=0.03).. Staphylococcus aureus (MSSA) was cultured in 58% (130/231) of infants but not associated with any clinical or radiologic pulmonary findings; respiratory MRSA was cultured in only 14 infants (6%). Among the 193 infants (84%) who grew a CF specific pathogen (*Pa*, MSSA, MRSA, Hemophilus influenza, Stenotrophomonas maltophila, Achromobacter or aspergillus), 150 (77.7%) had significant cough. The incidence of significant cough (73%) did not differ in the 37 infants who never grew one of these organisms. The frequency of CF pathogens is reported in Table 1.

More than 54% of infants had a CXR available for scoring. At one year of age, 9% (11/126) had a Wisconsin CXR score >5, with an overall median score of 2.5 (range: 0, 12.9). BONUS infants with CXR scores > 5 were less likely to have *Pa* infection than those with scores ≤ 5 (0% versus 27%, p=0.05).

Hospitalization for respiratory indications occurred in 17% (40/231) of infants in the BONUS cohort. The mean length of respiratory hospitalization was 11.3 ± 9.23 days and the median length of respiratory hospitalization was 9.5 days (3.5, 15). As previously reported, there was no association between respiratory hospitalization and growth parameters[2]. Hospitalized infants were more likely to have crackles and/or wheezes (p=0.009) and abnormal CXR score (p=0.0008), however there was no association between respiratory hospitalization and growth of *Pa* on OP culture.

Association between acid blockade and pulmonary outcomes

Acid suppression, either with histamine-2 blockers (H2 blocker), proton pump inhibitors (PPI) or use in combination was prescribed in 70% of infants during the first year of life.

Use of any acid suppression strategy was not associated with having a Wisconsin CXR score >5 and did not increase the odds of respiratory hospitalization.

Infants who were prescribed H2 blocker monotherapy did not have increased risk of crackles and/or wheezing and use was not associated with *Pa* growth. The 27% (11/40) of all hospitalized infants who were treated with H2 blocker alone had a two-fold increase in mean hospital days compared to those not on an acid blocker (RR 2.03; 1.17, 3.53, p =0.01). Infants taking PPI monotherapy were more likely to have crackles and/or wheezing than infants not treated with any acid blockade (OR=8.48 (1.47, 49.09), p=0.02, adjusted for sex, birth length, severe classification, and CXR score). They were more likely to be colonized with *Pa* (OR=5.47 (1.36, 21.92; p=0.02) and their odds of having MSSA were reduced (adjusted OR=0.24 (0.06, 0.89; p=0.03). There was no significant association of PPI monotherapy and mean days of hospitalization in the 22% (9/40) of all hospitalized infants who were treated with PPI alone.

Infants treated with a combination of H2 blocker and PPI had increased odds of crackles and/or wheezing (adjusted OR=4.2 (0.81, 21.92), but this did not reach statistical significance (p=0.09). Patients prescribed H2 blocker combined with PPI were more likely to have *Pa* (OR=8.2 (2.41, 27.93; p=0.001) and the 25% (10/40) of all hospitalized infants who were treated with this combination had an increased number of total respiratory hospital days compared to those not treated with any acid blockade (RR=2.73; 1.09, 6.81; p=0.03). The complex associations of low weight, adventitious sounds on examination of the chest, *Pa*, hospitalization and use of acid blockade are summarized in Table 2.

DISCUSSION

This study shows that cough was quite common in the first year of life in CF infants, but most infants with cough did not exhibit adventitious sounds on respiratory physical exam or have abnormal CXR findings. The presence of *Pa* on OP cultures at any time in the first year of life was associated with severe *CFTR* mutations and having been prescribed inhaled tobramycin or PPI alone or in combination with an H2 blocker. Surprisingly, hospitalized infants were unlikely to have *Pa* detected by OP swab but were likely to have crackles and/or wheezes and mildly abnormal Wisconsin CXR scores.

Cough was a common symptom in infants with CF, especially in the first 6 months of life. Frequent, productive, or spasms of cough were reported in up to 30% of infants. Cough can be common in infants in general in the first 6 months of life and conclusions are limited due to the lack of a control group of infants. Reasons for cough in infants outside of CF could include viral illness or passive tobacco smoke exposure, which were not quantitated in the BONUS study. Despite the high prevalence of cough, infants with CF in the BONUS study had very infrequent objective findings on physical exam. In addition, only 9% of 12-month old infants had Wisconsin CXR scores above 5 (mildly abnormal). In a previous study measuring lung function and radiograph findings in infants with CF across 10 centers, 23% of 141 CXRs done 12 months after enrollment had Wisconsin scores ≥ 5[12]. Children were older in the previous study compared to BONUS (could be enrolled up to 24 months of age with Wisconsin scores measured 12 months post enrollment); scores were thus higher in the

previous study as the children could be up to 3 years of age compared to 1 year of age in our study.

It is of interest that infants with mildly abnormal CXRs in our study were less likely to be colonized with *Pa*. The low incidence of abnormal findings on CXR and lack of association between CXR score and growth suggests the need for a more sensitive indicator of lung disease in these infants. High-resolution chest computed tomography (CT) and bronchoalveolar lavage (BAL) are more effective at detecting early lung disease but are more invasive[3]. The multiple breath washout technique has been used to calculate Lung Clearance Index (LCI), a measure of ventilation inhomogeneity. LCI was found to be elevated at least 1.64 z-score in 41% of a group of 100 infants with CF[14]. Chest CT, BAL, LCI, or magnetic resonance imaging might provide improved objective measures to identify which coughing infants have more severe early lung disease that warrants prompt treatment.

We recovered *Pa* by OP swab at least once in the first year of life in almost one quarter of this very young and healthy population. *Pa* was not associated with hospitalizations, although hospitalizations occurred in in almost 20% of BONUS infants. This suggests that either *Pa* is not reliably detected using oropharyngeal swabs or that *Pa* eradication regimens are effective in reducing colonization[15]. Notably, using a more sensitive detection method, the Australian AREST-CF studies of infants with CF detected *Pa* by BAL in 9.5% of infants at 1 year of age[16]. However, in our study the use of OP swabs enabled more frequent testing, which may account for the difference. Not surprisingly, the hospitalized BONUS infants were likely to have crackles and/or wheezing or abnormal CXR. It is possible that infants with CF may be hospitalized for viral illnesses such as bronchiolitis, which can lead to abnormal chest exam and CXR findings rather than being admitted for *Pa*-associated pulmonary exacerbations. This important observation suggests that either a more sensitive measure than OP swabs is needed to detect *Pa* during exacerbations or that factors which contribute to pulmonary disease in infants with CF may be evolving.

Treatment with PPI or the combination of an H2 blocker with PPI, but not H2 blocker alone, was associated with increased crackles and wheezing as well as *Pa* positive status. This could be an example of indication bias, in that those with *Pa* had lower weight and could have been placed on a PPI either as an adjunct to pancreatic enzyme replacement therapy or as a treatment for gastroesophageal reflux (GER). Infants in the BONUS cohort who were on PPI had higher weight z-score at 12 months compared to those on H2 blockers[5]. It has previously been reported that children and teenagers with CF who were *Pa* positive had a significantly higher total acid and non-acidic GER burden than those who were *Pa* negative[17]. In a recent retrospective study of 114 adults with CF, PPI use was associated with a higher prevalence of clinically-diagnosed GER and a higher mean number of hospitalizations for pulmonary exacerbations in both univariate and multivariate models; there was no difference in *Pa* colonization between those on PPI and those who were not[18]. In a Dutch CF registry study of patients aged 5–18 years, use of PPI was associated with an accelerated annual decline in FEV1% predicted (estimated pooled effect −0.69, 95% CI −1.26- −0.12) as well as increased risk of pulmonary exacerbations, adjusted for *Pa* colonization and other risk factors[19]. Another single site retrospective chart review of 126 CF patients on PPI for ≥ 6 months showed higher rates of at least one pulmonary

exacerbation (59.6%) compared to only 24.5% of the 49 CF patients not on PPI[20]. This contrasts with our infant study in which use of PPI or any acid blockade was not associated with respiratory hospitalization. One of the reasons for the discrepancies between the previously published studies and our study may be the older age of the patients and the longer use of PPI in prior studies; the Dutch study found that increasing PPI use duration was associated with increased annual decline and exacerbation rate[20]. The relationship of lung involvement and growth in infants with CF, GER, use of PPIs and *Pa* colonization requires future investigation.

The limitations of this study include its observational nature, lending it to indication bias. For example, in addition to the issues confounding treatment of infants with PPI described above, the study was not designed to answer associations between medication changes and symptoms or laboratory findings. Given the observational design of the study, it was not possible to examine the order of events, for example, whether or not cough led to treatment with PPIs, which led to *Pa* acquisition. Future interventional studies could be designed to specifically address this question. In addition, recommended clinical monitoring of early pulmonary disease in the US does not currently include BAL cultures and high-resolution CT scans. Thus, we may not have been able to detect lower airway bacterial infection or inflammation to adequately study other associated features. In addition, we did not test for respiratory viruses, or assess for tobacco smoke exposure, which could also adversely affect pulmonary function and lead to respiratory hospitalizations in infants. The role of respiratory viral illnesses or other contributors to CF pulmonary disease early in life is an area for further research.

In summary, parents report cough frequently in infants with CF in the first year of life, but most infants with cough did not exhibit adventitious sounds on respiratory physical exam. Infants with *Pa* on OP cultures at any time in the first year of life were more likely to have been prescribed PPI alone or in combination with an H2 blocker. Surprisingly, hospitalized infants were unlikely to have *Pa* detected by OP swab but were likely to have crackles and/or wheezes and mildly abnormal Wisconsin CXR scores. The BONUS biorepository may provide an opportunity to develop more sensitive measures of early airway involvement in infants with CF. Clinical observations in this large cohort of infants with CF in the first year of life provide data to aid in investigating new approaches to management of early pulmonary manifestations of CF and preventing their later consequences.

Acknowledgments

The authors acknowledge funding through CFFT (BONUS11KO) and NIH (R01DK095738 P30DK089507) and the following principal investigators and study site coordinators who participated in the Baby Observational and Nutrition Study (BONUS):

A Stecenko, M.Schechter, and E. Hunter (Emory University,Atlanta, Georgia);W. Hoover, H. Hathorne, and K.Brand (University of Alabama at Birmingham); A. Filbrun and M. Linn (University of Michigan, Ann Arbor); D. Borowitz and N. Caci (Women and Children's Hospital of Buffalo, Buffalo, New York); B. McWilliams and I. Brazil (Children's Medical Center of Central Texas, Austin); J. Heubi and M Bushman (Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio); S. McColley and A. Bowen (Chicago Lurie Children's Hospital, Chicago, Illinois); K. McCoy and K. Sakellaris (Nationwide Children's Hospital, Columbus, Ohio); P. Sharma, C. Cannon, and A. Hebert (University of Texas Southwestern Medical Center, Dallas); S. Sagel and M. Anthony (Children's Hospital Colorado, Denver); M. Dyson and H. Urbanek (Cook Children's Medical Center, Fort Worth, Texas); S. Millard and C. Gile (Helen DeVos Women and Children's Center, Grand Rapids, Michigan); G. Graff

and L. Allwein (Hershey Medical Center, Hershey, Pennsylvania); P. Hiatt and N. Schaap (Baylor College of Medicine, Houston, Texas); N. Krupp and L. Bendy (Riley Hospital for Children, Indianapolis, Indiana); R. Ahrens and M. Teresi (University of Iowa, Iowa City); A. Berlinski and L. L. Ramsey (Arkansas Children's Hospital, Little Rock); J. McNamara and M. Johnson (Minnesota Children's Hospital and Clinics, Minneapolis); R. Brown and P. Berry (Vanderbilt Children's Hospital, Nashville, Tennessee); N. Mehdi, J. Royall, and D. Thomas (Children's Hospital of Oklahoma, Oklahoma City); R. Rubenstein and E. Donnelly (Children's Hospital of Philadelphia, Philadelphia, Pennsylvania); D.Weiner, S. Hurban, and E. Hartigan (Children's Hospital of Pittsburgh and University of Pittsburgh, Pittsburgh, Pennsylvania); M. Powers and K. Simmons (Oregon Health & Sciences University, Portland); B. Chatfield and H. Oldroyd (University of Utah, Salt Lake City); L. Hoffman and S. McNamara (Seattle Children's Hospital, Seattle, Washington); J. Wooldridge and A. Cooper (Cardinal Glennon Children's Hospital and St Louis University, St Louis, Missouri); A. Faro and D. Rodgers (St Louis Children's Hospital, St Louis, Missouri); C. Fortner and V. Suttmore (SUNY Upstate Medical University, Syracuse); J. Hocevar-Trnka, M. Kloster,M. Skalland, and A. Fowler (Cystic Fibrosis Foundation Therapeutics Development Network Coordinating Center, Seattle Children's Research Institute, Seattle, Washington).

ABBREVIATIONS

CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
BONUS	Baby Observational and Nutrition Study
WHO	World Health Organization
PI	pancreatic insufficient
Pa	Pseudomonas aeruginosa
OFC	occipital head circumference
OP	oropharyngeal
CXR	chest radiograph
LCI	lung clearance index
CT	computed tomography
SD	standard deviation
CI	confidence interval
OR	odds ratio
PPI	proton pump inhibitor

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Table 1:

Frequency of Organisms Reported from oropharyngeal cultures in Infants with CF in the BONUS Study

Culture Result	Total Number of Subjects	Frequency
Methicillin Sensitive Staphylococcus aureus (MSSA)	130	56.3%
Methicillin Resistant Staphylococcus aureus (MRSA)	14	6%
Haemophilus influenza	80	34.6%
Pseudomonas aeruginosa (Pa)	56	24.2%
Burkholderia cepacia	0	0%
Stenotrophomonas maltophila	32	13.9%
Achromobacter	5	2.2%
Aspergillus	2	0.9%
None of the above organisms	37	16%

Table 2:

Association of various clinical factors, assessed using univariate comparisons, reflecting pulmonary health in infants with CF in the BONUS cohort. The + sign indicates $p < 0.05$

	Low weight	Wheezing/crackles	Pseudomonas	Hospitalization	Acid blockade
Low weight					
Wheezing/crackles	+				
Pseudomonas	+	+			
Hospitalization	−	+	−		
Acid blockade	−[1]	+[2]	+[2]	−	

[1] Infants in the BONUS cohort who were on PPI had higher weight z-score at 12 months compared to those on H2 blockers[5].

[2] PPI or PPI in combination with H2 blocker, but not H2 blocker alone