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Risk Factors for Bronchiectasis in Children with Cystic Fibrosis

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ABSTRACT

BACKGROUND

Bronchiectasis develops early in the course of cystic fibrosis, being detectable in infants as young as 10 weeks of age, and is persistent and progressive. We sought to determine risk factors for the onset of bronchiectasis, using data collected by the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) intensive surveillance program.

METHODS

We examined data from 127 consecutive infants who received a diagnosis of cystic fibrosis after newborn screening. Chest computed tomography (CT) and bronchoalveolar lavage (BAL) were performed, while the children were in stable clinical condition, at 3 months and 1, 2, and 3 years of age. Longitudinal data were used to determine risk factors associated with the detection of bronchiectasis from 3 months to 3 years of age.

RESULTS

The point prevalence of bronchiectasis at each visit increased from 29.3% at 3 months of age to 61.5% at 3 years of age. In multivariate analyses, risk factors for bronchiectasis were presentation with meconium ileus (odds ratio, 3.17; 95% confidence interval [CI], 1.51 to 6.66; P=0.002), respiratory symptoms at the time of CT and BAL (odds ratio, 2.27; 95% CI, 1.24 to 4.14; P=0.008), free neutrophil elastase activity in BAL fluid (odds ratio, 3.02; 95% CI, 1.70 to 5.35; P<0.001), and gas trapping on expiratory CT (odds ratio, 2.05; 95% CI, 1.17 to 3.59; P=0.01). Free neutrophil elastase activity in BAL fluid at 3 months of age was associated with persistent bronchiectasis (present on two or more sequential scans), with the odds seven times as high at 12 months of age and four times as high at 3 years of age.

CONCLUSIONS

Neutrophil elastase activity in BAL fluid in early life was associated with early bronchiectasis in children with cystic fibrosis. (Funded by the National Health and Medical Research Council of Australia and Cystic Fibrosis Foundation Therapeutics.)

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Illness and death from cystic fibrosis are due primarily to progressively destructive lung disease resulting in bronchiectasis and respiratory failure. Computed tomography (CT) can detect changes in the lungs associated with bronchiectasis[1,2] and evidence of structural lung disease in children with cystic fibrosis as young as 10 weeks of age.[3-8] The true prevalence of bronchiectasis among children with cystic fibrosis is unknown; however, studies conducted by the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) and the Australasian Cystic Fibrosis Bronchoalveolar Lavage study group have shown that 50 to 70% of patients have CT-defined bronchiectasis by 3 to 5 years of age.[3,5,9] Once present, bronchiectasis persists and progresses in approximately 75% of young children,[3] despite receipt of the best current therapy.

A coordinated approach to early surveillance in young children with cystic fibrosis has been developed by the AREST CF, a collaborative program of the pediatric cystic fibrosis clinics at Princess Margaret Hospital for Children, Perth, and the Royal Children's Hospital, Melbourne. The clinics serve the entire populations of Western Australia and Victoria, respectively, apart from the southern metropolitan region of Melbourne. The program includes assessments soon after diagnosis (average age, 3 months) and annually until 6 years of age, encompassing clinical assessment, lung-function testing, chest CT with the use of a low-radiation protocol, bronchoalveolar lavage (BAL), and collection of blood and urine samples (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

Previous studies from the AREST CF, using largely cross-sectional data, have shown that neutrophilic inflammation (characterized by the presence of free neutrophil elastase activity in BAL fluid) and pulmonary infection (especially with *Pseudomonas aeruginosa*) are the major risk factors for early disease in cystic fibrosis, including the development and progression of bronchiectasis,[3-5] a reduction in the body-mass index,[10] and lung-function decline.[11] BAL-based studies have shown that lung disease begins early in life[4-6,12,13] and is associated with increased levels of proinflammatory cytokines, such as CXCL8 (interleukin-8),[4,14] and that more extensive inflammation is found in lung lobes with more severe bronchiectasis.[6] We conducted the current study to test the hypothesis that the risk of bronchiectasis, especially persistent bronchiectasis, could be accurately determined by measuring biomarkers of inflammation and infection in BAL fluid at 3 months of age.

Methods

Study Population

We examined data from 127 consecutive infants who received a diagnosis of cystic fibrosis on the basis of newborn screening and who were participants in the AREST CF surveillance program. Assessments were undertaken when the children were in stable clinical condition. We sought to determine whether pulmonary inflammation and infection detected in BAL fluid at 3 months and 1, 2, and 3 years of age were associated with the development of bronchiectasis by 3 years of age.

CT and BAL

Chest CT and BAL were performed while the infants were under general anesthesia.[3-5] Children were initially intubated with a cuffed tracheal tube; a standardized recruitment maneuver, consisting of 10 consecutive slow breaths up to total lung capacity (transrespiratory pressure [P_{RS}], 37 to 40 cm of water) over a positive end-expiratory pressure of 5 cm of water for 1 to 2 seconds after each inspiration, was used to reduce procedure-related atelectasis. A volume-controlled, limited-slice CT scan (initial scan at 3 months of age; see Table S1 in the Supplementary Appendix) was obtained, with three slices obtained at both end inspiration (P_{RS}, 25 cm of water) and end expiration (P_{RS}, 0 cm of water); a volume-controlled volumetric CT scan was obtained at end inspiration for older children (starting in 2007 in Perth and 2010 in Melbourne). Details of the scanners and settings used have been published previously.[3,15]

CT images were scored, as previously reported, with no knowledge of the child's clinical status or the results of any previous scans or tests to detect infection or inflammation.[3-5] Each scan was considered in six zones (upper, middle, and lower areas of the left and right lungs), and each zone was scored for the presence or absence and extent of bronchiectasis (on inspiratory scans) and gas trapping (on expiratory scans). Bronchiectasis was defined as a bronchus-to-artery ratio of more than 1.0 or the presence of a nontapering bronchus in the transverse plane.[3,5] To avoid overinterpretation of radiologically defined disease, especially from limited-slice scans in early life, we defined persistent bronchiectasis as bron-

chiectasis that was present on two successive scans, scored independently. This assessment was performed at 12 months and 3 years of age.

BAL was performed after CT, with the tracheal tube replaced by a laryngeal mask airway for passage of the bronchoscope. The right middle lobe was lavaged with three aliquots of warmed normal saline (1 ml per kilogram of body weight), with one additional aliquot lavaged into the lingua or the most affected lobe identified on CT.

PULMONARY INFLAMMATION AND INFECTION

The first aliquot from each lobe was processed for detection of bacteria, viruses, or fungi.[4] Pulmonary infection was determined as previously described,[16] with infection defined as a colony count for a specific organism (excluding mixed oral flora) of 10^5 colony-forming units per milliliter or more. In the case of *P. aeruginosa*, however, the criterion for infection was the presence of the organism in any density in BAL cultures. The second and third aliquots retrieved from the right middle lobe were pooled and used for analyses of inflammation, as previously described.[4] Total and differential cell counts were performed and free neutrophil elastase activity was determined; the lower limit of detection for neutrophil elastase activity was 200 ng per milliliter.[4]

STATISTICAL ANALYSIS

Logistic regression was performed to determine cross-sectional associations between inflammatory and infection variables assessed by means of BAL and the presence of bronchiectasis at 3 months of age. Longitudinal analyses were performed to determine the associations between inflammatory and infection variables and the presence or absence of bronchiectasis from 3 months to 3 years of age. Generalized estimating equations were used for up to four repeated measurements in each child. We assumed a binomial family, logit link, and first-order autoregressive correlation structure. We tested the significance of the interaction between each inflammatory and infection variable and the age at the time of the scan by adding the interaction term to a model containing both main effects and comparing it with the model containing only the main effects. In the absence of significant interactions, each variable of interest was examined univariately, and variables that were significant at the 0.20 level were included in a multivariable model. Variables were retained in the multivariable model if they were significant at the 0.05 level. Analyses were performed separately with bronchiectasis as the outcome and with persistent bronchiectasis as the outcome. The association between the presence of persistent bronchiectasis at 12 months and at 3 years of age and data collected at 3 months of age was examined with the use of logistic regression. Further details of the analyses and the data sets used are shown in Table S1 in the Supplementary Appendix.

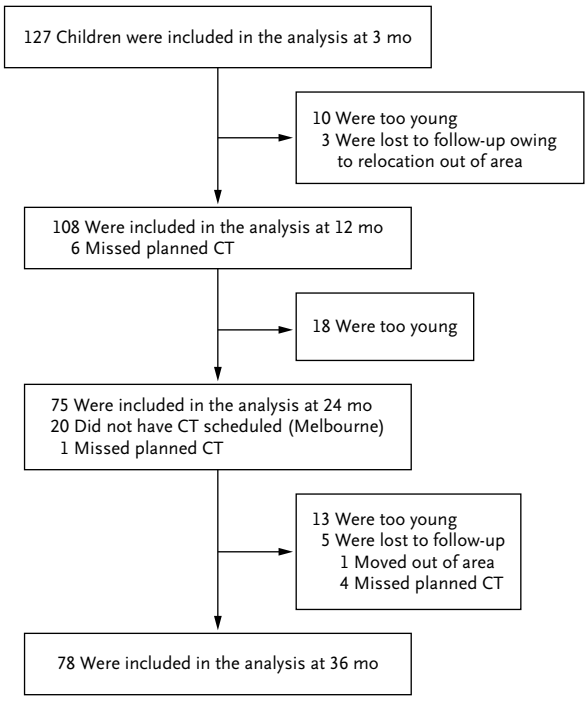

Figure 1. Children Included in the Analyses at 3, 12, 24, and 36 Months.
Four children were lost to follow-up because they moved from the study area. Eleven children missed a planned CT study at an annual review but continued in the study. During the study period, the Melbourne site stopped performing the 24-month CT study, meaning that a CT scan at 24 months of age was not scheduled for 20 children. Children were considered to be too young if they had not reached the assessment age by the end of the data-collection period.

RESULTS

CHARACTERISTICS OF THE STUDY PARTICIPANTS

Longitudinal data were available from 3 months of age for 127 children with cystic fibrosis, with 127 assessed at a mean (±SD) age of 0.35±0.12 years, 109 assessed at 1.17±0.20 years, 92 assessed at 2.17±0.23 years, and 81 assessed at 3.20±0.22 years. The primary reason for the

Table 1. Demographic and Clinical Characteristics of the Study Population, According to Time of Assessment.*

Characteristic	3 Months (N=127)	1 Year (N=109)	2 Years (N=92)	3 Years (N=81)
Age	0.35±0.12	1.17±0.20	2.17±0.23	3.20±0.22
Sex — no. (%)				
Male	64 (50)	55 (50)	48 (52)	43 (53)
Female	63 (50)	54 (50)	44 (48)	38 (47)
BMI z score†	−1.34±1.19	−0.42±1.26	−0.16±1.46	0.22±0.96
CT performed — no.	126‡	108	74§	78
BAL performed — no.	125	109	92	81
Positive for neutrophil elastase activity — no./total no. (%)¶	28/120 (23.3)	19/105 (18.1)	20/92 (21.7)	19/76 (25.0)
Neutrophil count — $\times 10^{-3}$ cells/ml of fluid retrieved	416±810	482±761	1441±2822	2334±5618
Infection — no./total no. (%)				
Any‖	28/125 (22.4)	23/109 (21.1)	37/92 (40.2)	38/81 (46.9)
Staphylococcus aureus	8/125 (6.4)	6/109 (5.5)	10/92 (10.9)	18/81 (22.2)
Pseudomonas aeruginosa	7/125 (5.6)	9/109 (8.3)	5/92 (5.4)	8/81 (9.9)
Bronchiectasis**				
Point prevalence — no./total no. (%)††	36/123 (29.3)	34/108 (31.5)	33/75 (44.0)	48/78 (61.5)
Incidence rate — no./total no. (%)‡‡	36/123 (29.3)	19/81 (23.5)	13/53 (24.5)	19/36 (52.8)
Ever present — no./total no. (%)§§	36/123 (29.3)	55/118 (46.6)	68/108 (63.0)	87/104 (83.7)
Extent¶¶	0.54±1.01	0.64±1.28	1.42±2.43	2.30±2.84
Gas trapping				
Point prevalence — no./total no. (%)††	85/125 (68.0)	74/108 (68.5)	53/74 (71.6)	54/78 (69.2)
Incidence rate — no./total no. (%)‡‡	85/126 (67.5)	16/35 (45.7)	4/11 (36.4)	3/7 (42.9)
Extent‖‖	2.59±2.68	2.54±2.52	2.90±2.92	3.35±3.32

* Plus–minus values are means ±SD. BAL denotes bronchoalveolar lavage.
† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
‡ Bronchiectasis could not be assessed on three CT scans owing to procedure-related atelectasis.
§ Fewer scans were performed at 2 years of age in Melbourne as part of the clinic policy.
¶ Positive neutrophil elastase activity was defined as activity detected above the limit of detection of the assay (200 ng per milliliter).
‖ Any infection was defined as the presence of any organism detected in BAL fluid at a density of 10^5 colony-forming units per milliliter or more, except that the presence of *P. aeruginosa* at any density was classified as infection. The presence of mixed oral flora, regardless of the density, was not classified as infection. Data on infecting organisms other than *S. aureus* and *P. aeruginosa* are available in the Supplementary Appendix.
** Bronchiectasis was defined as a bronchus-to-artery ratio of more than 1.0 or the presence of a nontapering bronchus in the transverse plane.
†† The point prevalence of bronchiectasis or gas trapping was calculated from scans obtained at the designated visit only.
‡‡ The incidence rate of bronchiectasis or gas trapping was calculated as new cases occurring at that visit divided by the number of scans performed at that age (previous cases were not included).
§§ This variable was defined as bronchiectasis at any time up to and including the current period (see the sensitivity-analysis data set in Table S1 in the Supplementary Appendix).
¶¶ The extent of bronchiectasis in each lung zone was scored as 0 (not detected), 1 (affecting ≤50% of the airways), or 2 (affecting >50% of the airways). The overall score was calculated by adding the values for the six zones, with a maximum score of 12.
‖‖ The extent of gas trapping in each lung zone was scored as 0 (not detected), 1 (affecting ≤50% of the lung field), or 2 (affecting >50% of the lung field). The overall score was calculated by adding the values for the six zones, with a maximum score of 12.

smaller numbers of children with increasing age was that the children had not yet reached the assessment age by the end of the data-collection period (Fig. 1). Demographic and clinical data are shown in Table 1. The point prevalence of bronchiectasis increased from 29.3% at 3 months of age to 61.5% at 3 years of age (P<0.001) (Table 1). The cumulative prevalence of bronchiectasis reached 83.7% by 3 years of age. The point prevalence of CT-defined gas trapping at each visit was 68.0% at 3 months, 68.5% at 1 year, 71.6% at 2 years, and 69.2% at 3 years (Table 1).

Table 2. Characteristics of the Study Participants at the 3-Month Assessment, According to Status with Respect to Neutrophil Elastase Activity and Bronchiectasis at That Time.*

Characteristic	Neutrophil Elastase Activity			Bronchiectasis		
	Positive (N=28)	Negative (N=92)	P Value	Present (N=36)	Not Present (N=91)†	P Value
Sex — no.			0.82			0.12
Male	15	47		15	48	
Female	13	45		21	40	
Severe genotype — no./ total no. (%)‡	25/25 (100)	69/78 (88.5)	0.11	29/29 (100)	69/78 (88.5)	0.11
BMI z score§	−1.45±0.84	−1.33±1.23	0.66	−1.34±1.05	−1.33±1.25	0.98
Respiratory symptoms — no./total no. (%)	10/28 (35.7)	9/84 (10.7)	0.007	11/33 (33.3)	10/83 (12.0)	0.01
Meconium ileus — no./total no. (%)	7/27 (25.9)	14/79 (17.7)	0.40	12/30 (40.0)	10/81 (12.3)	0.002
Pancreatic insufficiency — no./total no. (%)	26/26 (100)	61/78 (78.2)	0.006	27/29 (93.1)	63/80 (78.8)	0.09
Infection — no./total no. (%)						
Any	11/28 (39.3)	16/92 (17.4)	0.02	12/35 (34.3)	14/90 (15.6)	0.03
Staphylococcus aureus	3/28 (10.7)	4/92 (4.3)	0.35	3/35 (8.6)	5/90 (5.6)	0.69
Pseudomonas aeruginosa	3/28 (10.7)	3/92 (3.3)	0.14	5/35 (14.3)	2/90 (2.2)	0.02

* Fisher's exact test was used for all analyses, unless otherwise noted.
† Bronchiectasis could not be assessed on three CT scans owing to procedure-related atelectasis, and these scans were considered to be negative.
‡ Severe genotype was defined as a lack of predicted function of residual cystic fibrosis transmembrane conductance regulator (*CFTR*) on the basis of mutation class.
§ Plus–minus values are means ±SD. Analysis of variance was used for the comparisons.

At the initial assessment, at 3 months of age, 28 of 120 children (23.3%) had detectable neutrophil elastase activity in BAL fluid, and 36 of 123 (29.3%) had bronchiectasis on the chest CT scan. Demographic and clinical data stratified according to status with respect to neutrophil elastase activity and bronchiectasis at the initial assessment are shown in Table 2. Neutrophil elastase activity in BAL fluid was associated with the presence of respiratory symptoms at the time of BAL (P=0.007), pancreatic insufficiency (P=0.006), and pulmonary infection (P=0.02). Bronchiectasis on the initial CT scan was associated with respiratory symptoms (P=0.01), meconium ileus at presentation (P=0.002), and any pulmonary infection (P=0.03) or infection with *P. aeruginosa* (P=0.02) (Table 2).

RISK FACTORS FOR BRONCHIECTASIS

Risk factors associated with the development of bronchiectasis from 3 months to 3 years of age are shown in Table 3. Risk factors for bronchiectasis on multivariate analysis were meconium ileus at presentation (odds ratio, 3.17; 95% confidence interval [CI], 1.51 to 6.66; P=0.002), respiratory symptoms at the time of CT and BAL (odds ratio, 2.27; 95% CI, 1.24 to 4.14; P=0.008), neutrophil elastase activity in BAL fluid (odds ratio, 3.02; 95% CI, 1.70 to 5.35; P<0.001), and gas trapping on expiratory CT (odds ratio, 2.05; 95% CI, 1.17 to 3.59; P=0.01). There were no significant interactions between any of the risk factors and the age at which BAL was performed. A sensitivity analysis, with the assumption that once bronchiectasis was detected, all subsequent scans would be positive, had similar results (Table S2 in the Supplementary Appendix), with the presence of neutrophil elastase activity in BAL fluid and initial presentation with meconium ileus as significant predictors in multivariate analyses.

RISK FACTORS FOR PERSISTENT BRONCHIECTASIS

Persistent bronchiectasis was observed in 15 of 104 children (14.4%) at 12 months of age and in 25 of 78 children (32.1%) at 3 years of age. Risk

Table 3. Longitudinal Analyses of Risk Factors for Bronchiectasis from 3 Months to 3 Years of Age.*

Risk Factor	Odds Ratio (95% CI)	P Value
Univariate analyses		
BMI z score	1.02 (0.82–1.27)	0.85
Male sex	1.23 (0.67–1.90)	0.65
Meconium ileus at presentation	3.13 (1.68–5.82)	<0.001
Pancreatic insufficiency	1.91 (1.05–3.48)	0.03
Severe genotype	2.54 (1.57–4.11)	<0.001
Respiratory symptoms at time of CT and BAL	2.57 (1.50–4.39)	<0.001
Positive for neutrophil elastase activity	3.74 (2.21–6.32)	<0.001
Infection		
Any	2.00 (1.24–3.21)	0.004
Staphylococcus aureus	1.38 (0.68–2.81)	0.37
Pseudomonas aeruginosa	3.12 (1.55–6.27)	0.001
Gas trapping	2.15 (1.38–3.35)	<0.001
Multivariate analysis		
Meconium ileus at presentation	3.17 (1.51–6.66)	0.002
Respiratory symptoms at time of CT and BAL	2.27 (1.24–4.14)	0.008
Positive for neutrophil elastase activity	3.02 (1.70–5.35)	<0.001
Gas trapping	2.05 (1.17–3.59)	0.01

* Analyses were conducted with the use of a generalized estimating equation with a binomial family, logit link, and first-order autoregressive correlation structure. The original data set was used for these analyses (i.e., the presence or absence of bronchiectasis on each CT scan was used as the outcome for analyses).

factors for persistent bronchiectasis at these ages are shown in Table 4. Neutrophil elastase activity in BAL fluid at 3 months of age was the major predictor of persistent bronchiectasis at both 12 months of age (odds ratio, 7.20; 95% CI, 2.14 to 24.28; P<0.001) and 3 years of age (odds ratio, 4.21; 95% CI, 1.45 to 12.21; P=0.008).

DISCUSSION

Bronchiectasis develops early in infants with cystic fibrosis. In our study, risk factors at 3 months of age for detection of bronchiectasis included meconium ileus on presentation, respiratory symptoms, pulmonary infection (especially with *P. aeruginosa*), and gas trapping on the CT scan. Free neutrophil elastase activity in BAL fluid at 3 months of age was associated with increased odds of persistent bronchiectasis; the odds were seven times as high at 12 months of age and four times as high at 3 years of age.

The results of this longitudinal study are consistent with those of our previous studies, which showed that free neutrophil elastase activity in BAL fluid and pulmonary infection were risk factors for both the development and progression of bronchiectasis.[3-5] What this study adds is evidence that free neutrophil elastase activity at 3 months of age increases the odds of persistent bronchiectasis at both 12 months and 3 years of age. Gas trapping on expiratory CT was also a risk factor for bronchiectasis, and although this may represent early-onset peripheral lung disease, the precise relationship between gas trapping and bronchiectasis requires clarification.

Cystic fibrosis is characterized by extensive and chronic neutrophilic inflammation of the airways. Neutrophils play a major part in antibacterial defense through the release and activation of enzymes, including peroxidases (e.g., myeloperoxidase) and proteases (including neutrophil elastase).[17,18] The primary lung defense against neutrophil elastase is α_1-antitrypsin,[17] which binds extracellular neutrophil elastase. Bound neutrophil elastase cannot digest elastin. Extracellular or surface-associated neutrophil elastase[19] that exceeds antiprotease-binding capacity will be active and capable of elastin digestion, which is presumed to underlie the development of bronchiectasis. The presence of free neutrophil elastase activity in the lung is associated with active neutrophilic inflammation and, although such activity was seen in a minority of children at each BAL performed in this study (Table 1), it is a potent risk factor for bronchiectasis.

Several limitations of this study need to be acknowledged. In the AREST CF program, chest CT and BAL are performed when the child is in stable clinical condition and is fit for anesthesia. Thus, we cannot comment on the role of respiratory viral infections in the development of bronchiectasis. In addition, our data do not reflect the situation during an acute respiratory exacerbation, when viral and bacterial infections are more likely to be found.[9] Finally, there is controversy about whether early radiologic detection of dilated airways represents the onset of the destructive process resulting in bronchiectasis. We have reported that when CT scans are obtained 12 months apart, dilatation of the airways persists on the later scan in approximately 75% of children.[3] In the present study, 31 children had apparent "resolution" of bronchiectasis (Table S1

in the Supplementary Appendix). This could be a particular problem in interpreting dilated airways on limited-slice scans obtained at an early age. To overcome this limitation, we have introduced the term "persistent bronchiectasis" for the detection of dilated airways on two or more sequential scans. In addition, we have conservatively defined dilated airways as those with a bronchus-to-artery ratio of more than 1.0.[3-5] Kapur et al.[20] reported a mean ratio of 0.63 (95% CI, 0.60 to 0.65) in 41 children without apparent pulmonary pathologic features and suggested that a ratio of more than 1.0 underestimates the prevalence of early disease. Thus, the prevalence of bronchiectasis in our study may underestimate the true prevalence.

The AREST CF surveillance program has practical limitations; it provides a "once-a-year snapshot," arguably not at the most informative time. Our data do suggest that noninvasive or minimally invasive assessment of activated neutrophils is needed to show the true role of pulmonary free neutrophil elastase activity in the development and persistence of bronchiectasis. Unfortunately, such biomarkers have not been studied in infants with cystic fibrosis. Potential biomarkers studied in adults and older children include urinary desmosines,[21] α_1-antitrypsin:CD16b complex,[22] and YKL-40.[23] None of them have been validated in infants or in early disease.

Data from the present study suggest that treatment that targets activated neutrophils or that inhibits neutrophil elastase activity could be a logical strategy for preventing bronchiectasis. Such therapies are available or are under investigation in clinical trials,[24-26] highlighting the relevance of understanding the role that neutrophil elastase may play in disease initiation and progression. Studies of ibuprofen in older children and adults have shown a delayed decrease in lung function and improved maintenance of weight, with these findings attributed to antiinflammatory activity.[27,28] However, ibuprofen is not used widely and has not been tested in appropriate trials involving infants. Our data showing the association of free neutrophil elastase activity in BAL fluid at 3 months of age with persistent bronchiectasis at both 12 months and 3 years of age suggest that free neutrophil activity could be used as a criterion to select high-risk infants for clinical trials. The antiinflammatory properties of neutrophil elastase inhibitors are well established,[26] and at least one such agent has shown promise in early trials involving adults with cystic fibrosis.[24]

Table 4. Risk Factors at 3 Months for Persistent Bronchiectasis at 12 Months of Age and at 3 Years of Age.*

Risk Factor	Odds Ratio (95% CI)	P Value
Persistent bronchiectasis at 12 mo of age		
Univariate analyses		
BMI z score	1.10 (0.65–1.88)	0.72
Male sex	0.89 (0.30–2.68)	0.84
Meconium ileus at presentation	2.74 (0.80–9.41)	0.11
Pancreatic insufficiency	2.52 (0.30–20.99)	0.39
Respiratory symptoms at time of CT and BAL	3.38 (1.04–11.02)	0.04
Positive for neutrophil elastase activity	7.2 (2.14–24.28)	<0.001
Infection		
Any	4.87 (1.49–15.93)	0.009
Staphylococcus aureus	2.77 (0.48–15.89)	0.25
Pseudomonas aeruginosa	7.17 (0.92–55.72)	0.06
Multivariate analysis: positive for neutrophil elastase activity	7.20 (2.14–24.28)	<0.001
Persistent bronchiectasis at 3 yr of age		
Univariate analyses		
BMI z score	1.13 (0.73–1.74)	0.58
Male sex	1.04 (0.40–2.70)	0.93
Meconium ileus at presentation	2.97 (0.81–10.90)	0.10
Respiratory symptoms at time of CT and BAL	3.87 (0.98–15.24)	0.053
Positive for neutrophil elastase activity	4.21 (1.45–12.21)	0.008
Infection		
Any	1.88 (0.66–5.31)	0.24
S. aureus	0.93 (0.04–3.54)	0.40
P. aeruginosa	1.42 (0.98–2.04)	0.06
Multivariate analysis: positive for neutrophil elastase activity	4.21 (1.45–12.21)	0.008

* Persistent bronchiectasis was observed in 15 of 104 children (14.4%) at 12 months of age and in 25 of 78 children (32.1%) at 3 years of age.

In conclusion, free neutrophil elastase activity in the lung at 3 months of age was associated with increased odds of persistent bronchiectasis at 12 months and at 3 years of age. This observation sets the stage for trials of treatments that target activated neutrophils or inhibit neutrophil elastase activity in order to prevent or delay the onset of bronchiectasis in patients with cystic fibrosis.

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