Effect of Bronchoalveolar Lavage–Directed Therapy on Pseudomonas aeruginosa Infection and Structural Lung Injury in Children With Cystic Fibrosis
A Randomized Trial

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EARLY PULMONARY INFECTION IN children with cystic fibrosis, particularly with Pseudomonas aeruginosa, is associated with increased morbidity and mortality. However, diagnosing P. aeruginosa infection accurately in nonexpectorating patients with cystic fibrosis can be difficult. Although oropharyngeal cultures are used widely, they have limited sensitivity and variable specificity for predicting the presence of lower airway pathogens. Bronchoalveolar lavage (BAL) is an alternative diagnostic tool when young children with cystic fibrosis cannot provide sputum. However, its role in the cystic fibrosis clinic is still to be determined and will depend on its safety and evidence of clear clinical benefit.

A prospective, longitudinal BAL-based study conducted in the 1990s in preschool children with cystic fibrosis from Melbourne, Australia, reported that 30% had P. aeruginosa infection by age 5 years. Cumulative P. aeruginosa infection rates continue to increase throughout childhood, and by adulthood 80% of patients with cystic fibrosis are affected. Early strains are usu-
ally susceptible to antipseudomonal antibiotics and are often eradicated if treated promptly. However, once established, \textit{P} \textit{aeruginosa} infection is rarely eliminated, leading to lung injury with deteriorating pulmonary function and increased treatment requirements. Thus, early detection and treatment offer the greatest opportunity for preventing or delaying chronic \textit{P} \textit{aeruginosa} infection.

We undertook the Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) trial to determine, following the newborn diagnosis of cystic fibrosis, whether BAL-directed therapy for pulmonary exacerbations in the first 5 years of life reduced \textit{P} \textit{aeruginosa} infection and structural lung injury at age 5 years compared with standard management based on clinical features and oropharyngeal culture results.

**METHODS**

**Design and Participants**

Our multicenter, randomized, parallel-group trial recruited infants diagnosed with cystic fibrosis through newborn-screening programs in 8 cystic fibrosis centers in Australia (states of New South Wales, Queensland, South Australia, and Victoria) and New Zealand between June 1, 1999, and April 30, 2005, with completion of final outcomes on December 31, 2009. Eligible infants were younger than 6 months, with a confirmed diagnosis of classic cystic fibrosis (2 of the following: 2 cystic fibrosis mutations, sweat chloride level >60 mEq/L, pancreatic insufficiency, or meconium ileus).

Ethics committees at each participating center approved the trial, and written informed consent was obtained from parents or caregivers. Infants were randomly assigned in a 1:1 ratio to receive either BAL-directed therapy or standard therapy, with Stratification by state (Australian state or New Zealand) and sex. Randomization was by a centralized computer-generated schedule with allocation revealed by telephone after confirmed recruitment. Although group allocation was not blinded, microbiologic assessment of BAL and scoring of high-resolution chest computed tomography (CT) scans at final outcome were performed by observers blinded to treatment allocation.

**Protocol**

At each center, participants were treated according to best available practice (eSupplement, available at http://www.jama.com). Infants recruited in 3 centers received oral flucloxacinil as antistaphylococcal prophylaxis until their first birthday. Participants were seen every 3 months from enrollment until completion at age 5 years, whereupon each underwent anthropometric assessments, BAL, high-resolution chest CT scan, and pulmonary function testing. These tests were conducted within 2 weeks of one another, when each child was judged to be clinically stable. Visits for illness were scheduled as needed. A prospective health economic analysis was also undertaken, and the results will be reported separately.

Infants randomized to the BAL-directed therapy group also underwent BAL (1) before age 6 months when well, (2) when hospitalized for pulmonary exacerbations, (3) if \textit{P} \textit{aeruginosa} was cultured from oropharyngeal specimens, and (4) following \textit{P} \textit{aeruginosa} eradication therapy.

Pulmonary exacerbations were defined as any change in respiratory symptoms from baseline. When a child was unwell with upper respiratory symptoms, increased cough, or wheeze, an oropharyngeal specimen was obtained by clinic staff and oral antipseudomonal antibiotics commenced. Hospitalization for exacerbations occurred if oropharyngeal specimens grew \textit{P} \textit{aeruginosa} or the treating physician judged hospitalization was warranted because of symptom severity or failure to improve after 6 weeks of ambulatory treatment.

Hospitalized children in both study groups initially received intravenous tobramycin and ticarcillin-clavulanate or ceftazidime followed by 2 months of tobramycin inhalation solution and 1 month of oral ciprofloxacin. Children with fewer than 10^3 CFU/mL of \textit{P} \textit{aeruginosa} in their BAL fluid cultures were offered 2 weeks of parenteral antipseudomonal antibiotics but not the full eradication course, because although these low counts were likely to result from the upper airway contamination, they may have also represented early infection.

At end of treatment, another BAL was performed (BAL-directed therapy group) or an oropharyngeal swab was obtained (standard therapy group) to determine clearance. If \textit{P} \textit{aeruginosa} persisted, the eradication protocol was repeated. After the second cycle, repeat testing determined either successful clearance or presence of chronic infection. Successful clearance meant future positive cultures were treated as new isolations, while children with chronic \textit{P} \textit{aeruginosa} infection received inhaled and oral antipseudo-
monal antibiotics for respiratory exacerbations not requiring hospitalization.

**BAL and Oropharyngeal Specimen Collection**

Standardized BAL was performed in all centers according to a standard operating procedure under general anesthesia using a laryngeal mask. Suction channel use was avoided until the bronchoscope tip extended beyond the carina. A single BAL (1 mL/kg; maximum, 20 mL of sterile saline) was conducted sequentially in the right middle and lingula lobes or in areas identified as abnormal on radiography or at bronchoscopy. BAL fluid was pooled and placed on ice.

Oropharyngeal specimens were obtained by sweeping a cotton-tipped swab over the posterior oropharynx and tonsillar fauces or by using a suction catheter while the child was coughing. BAL samples, suction specimens, and oropharyngeal swabs in transport media were sent immediately to the laboratory for processing.

**Sample Processing**

As described previously, BAL and oropharyngeal specimens were plated onto selective and nonselective media for counting and identifying respiratory pathogens by standard microbiologic techniques. BAL fluid total and differential cell counts were determined using a hemocytometer; interleukin 8 levels were determined by enzyme-linked immunoassay (Medgenix Diagnostics, Fleurus, Belgium).

**High-Resolution Chest CT Scans**

A low-dose high-resolution chest CT scan (1-mm collimation scans at 10-mm intervals, 120 kVp, 50 mA, 1.0-second and high–spatial-frequency reconstruction algorithm) was scored independently by an experienced scientist at Erasmus Medical Centre, Rotterdam, the Netherlands, blinded to subject allocation using the cystic fibrosis CT (CF-CT) score, a validated upgraded version of the Brody-II score. Scans were performed with patients awake when possible and with use of general anesthesia when patients were unable to cooperate. On inspiratory images, each lobe was scored for bronchiectasis, airway wall thickening, mucus plugging, and parenchymal disease. Air trapping was scored on the expiratory images taken at 3 equally spaced levels from the top of the aortic arch to 1 cm above the diaphragm. Ranges for these 5 component scores were 0 through 72, 0 through 54, 0 through 36, 0 through 54, and 0 through 18 points, respectively. The results were reported as percentages of the maximum possible score for each component and of the maximum total score of 234. To enable descriptive comparison of structural change severity, the component scores were categorized into groups based on their distribution (inspiratory images: 0, >0%-5%, and >5%; expiratory images: 0, >0%-20%, and >20% for air trapping).

**Lung Function**

Lung function was measured post bronchodilatation using a standard spirometer. Each center used American Thoracic Society criteria with standard deviation (z scores) calculated from British reference values (http://www.lungfunction.org/growinglungs).

**Adverse Events**

Adverse events associated with BAL and *P aeruginosa* eradication therapy were recorded prospectively.

**Outcome Measures**

The primary outcome measures at age 5 years were the presence of *P aeruginosa* infection, diagnosed as 10³ CFU/mL or greater on BAL culture; and evidence of structural lung disease, measured by the total CF-CT score (reported as percentage of the maximum possible total score). Secondary outcome measures at age 5 years included z scores for weight, height, and body mass index (calculated as weight in kilograms divided by height in meters squared); lung function parameters; CF-CT score components; respiratory exacerbation rate; number and duration of hospitalizations for respiratory exacerbations not associated with *P aeruginosa* infection; number of episodes of *P aeruginosa* infection per child-year; and final BAL microbiology and inflammatory indices.

**Sample Size and Statistical Analysis**

We aimed originally to recruit 240 children, based on anticipated *P aeruginosa* prevalence in BAL cultures at age 5 years of 30% in the control (standard therapy) group and a target of 15% reduction in the intervention group, with 80% power and a 2-sided 5% significance level. A priori, we also planned to reevaluate the sample size estimates once data became available for variability in CF-CT scores, the second primary outcome measure for this study.

Recruitment was slower than anticipated, attributable mainly to lower-than-expected birth prevalence of cystic fibrosis, and the sample-size target was revisited in 2004 after approximately 130 infants were recruited. At this time, data on variability in Bhalla CF-CT scores from a Dutch study of 48 children with cystic fibrosis (mean age, 11 years) were published, and we determined that a feasible target sample size of 160 children would provide 80% power for a mean difference of 1.5% (% maximum score) (0.45 SDs). The revised target also appeared to provide adequate power for the *P aeruginosa* prevalence end point, when the control-group prevalence at 5 years was predicted to be as high as 40%, based on the observed rates of infection at 2 years of follow-up in 2004. (At study end, however, the control prevalence of *P aeruginosa* was much lower, in retrospect rendering this component of the power calculation essentially irrelevant.)

Standard methods were used for statistical analysis using Stata version 11.0 (StataCorp, College Station, Texas). The study was designed to be analyzed as intention-to-treat because of concerns about differential dropout. Primary analysis was based on all patients who provided final outcome data, analyzed according to randomized group. Outcomes were missing for fewer than 10% of randomized participants, so results are insensitive to assumptions about these missing values. In a sensitivity analysis we explored the effect of as-
sons. The Cox regression method was formal adjustment for multiple comparison sandwich method. There was no calculated using the robust "informers allowing for clustering effects were from the same patient, standard errors log-transformed data). When comparisons involved repeated measures from the same patient, standard errors allowing for clustering effects were calculated using the robust “information sandwich” method. There was no formal adjustment for multiple comparisons.22 The Cox regression method was used to compare time to first diagnosis of 

P. aeruginosa infection between study groups. Incidence rate ratios (IRRs) were estimated using Poisson regression analysis, with allowance for overdispersion attributable to variation between patients.

Weight, height, and body mass index z scores were calculated from the 2000 CDC Growth Reference Charts (http://www.cdc.gov/growthcharts). Group comparisons are presented with 95% CIs and 2-sided P values; P < .05 was used to define statistical significance.

**RESULTS**

Of 267 eligible infants, 97 (36%) were either ineligible or declined participation (Figure 1), leaving 170 for enrollment at a mean age of 3.6 (SD, 1.6) months. Eighty-four were randomized to receive BAL-directed therapy and 86 to receive standard therapy. Two infants randomized to the standard therapy group were withdrawn because they did not have classic cystic fibrosis (Figure 1). Thus, the 2 treatment groups each had 84 infants with similar demographic and clinical features (Table 1). The sex and cystic fibrosis genotype distributions of infants not enrolled (53% male and 55% ΔF508 homozygotes) were similar to those of study participants. Infants in the BAL-directed therapy group underwent baseline BAL at a mean age of 4.9 (SD, 1.5) months.

Overall, 157 of 168 children (93%) completed the study. At 5 years, BAL was performed in 79 of 84 children (94%) in the BAL-directed therapy group and in 77 of 84 (92%) in the standard therapy group; high-resolution chest CT scans were performed in 78 of 84 children (93%) in the BAL-directed therapy group and 77 of 84 (92%) in the standard therapy group (Figure 1). No between-group difference for the primary outcome of 
P. aeruginosa infection diagnosed by BAL culture (Table 2) was detected (8/79 [10%] in the BAL-directed therapy group vs 9/76 [12%] in the standard therapy group; risk difference, −1.7% [95% CI, −11.6% to 8.1%]; P = .73).

For the primary outcome of total CF-CT score, data were obtained in 76 children (90%) in both study groups. The mean total CF-CT scores for the BAL-directed therapy and standard therapy groups were 3.0% and 2.8%, respectively (mean difference, 0.19% [95% CI, −0.94% to 1.33%]; P = .74) (Figure 2). Bronchiectasis was detected in 45 of 77 scans (58%) in the BAL-directed therapy group and 42 of 76 scans (55%) in the standard therapy group (risk difference, 3.2% [95% CI, −13% to 19%]; P = .69). Air trapping was detected in 35 of 77 children (45%) in both the BAL-directed therapy and the standard therapy groups (risk difference, 0% [95% CI, −16% to 16%]; P > .99). No between-group differences were observed for components of the CF-CT scores (Figure 2 and eTable 1).

Similarly, no between-group differences were found for weight, height, and body mass index z scores; postbronchodilator lung function values (Table 3); or BAL-fluid inflammatory indices (eTable 2). During the study, 1047 (range, 0-29) exacerbations (incidence rate, 3.68/person-year) were recorded for the BAL-directed therapy group, compared with 1033 (range, 0-25; incidence rate, 3.65/person-year) for the standard therapy group (IRR, 1.01 [95% CI, 0.85 to 1.19]; P = .94). Children in the BAL-directed therapy and standard therapy groups had 218 (0.37/person-year) and 140 (0.37/person-year) infections, respectively.
year) hospitalizations, respectively, for non–P aeruginosa respiratory exacerbations (IRR, 1.52 [95% CI, 0.98 to 2.35]; \( P = .06 \)). Duration of these hospital admissions was shorter for the BAL-directed therapy group, with mean 8.0 (SD, 6.3) days compared with 11.5 (SD, 7.5) days in the standard therapy group (mean difference, −3.4 [95% CI, −5.4 to −1.5]; \( P = .001 \)).

There were 1226 (incidence rate, 3.13/person-year) oropharyngeal cultures collected in the BAL-directed therapy group and 1164 (3.04/person-year) in the standard therapy group during the study (IRR, 1.03; \( P = .76 \)). For children who acquired infection with P aeruginosa during the trial, the mean age at first diagnosis of infection was 2.4 (SD, 1.5) and 2.2 (SD, 1.3) years in the BAL-directed therapy and standard therapy groups, respectively. There was no difference between the groups in age at first acquisition of P aeruginosa (hazard ratio, 0.81 [95% CI, 0.53 to 1.23]; \( P = .33 \)) (eFigure).

For children who completed final outcomes, the overall number of separate P aeruginosa infections diagnosed per child ranged from 0 to 5 throughout the study period, and these were distributed evenly between study groups (eTable 3). Similarly, for all randomized children, when using only BAL culture to diagnose P aeruginosa infection in the BAL-directed therapy group and

### Table 1. Initial Demographic and Clinical Characteristics of Study Participants (N = 168)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BAL-Directed Therapy (n = 84)</th>
<th>Standard Therapy (n = 84)</th>
<th>( \text{Risk Difference, } % ) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), mo</td>
<td>3.76 (1.62)</td>
<td>3.73 (1.69)</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>44 (52)</td>
<td>44 (52)</td>
<td></td>
</tr>
<tr>
<td>Homozygous ( \Delta F508 ) mutation</td>
<td>57 (68)</td>
<td>54 (64)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>73 (87)</td>
<td>71 (85)</td>
<td></td>
</tr>
<tr>
<td>Meconium ileus</td>
<td>17 (20)</td>
<td>16 (19)</td>
<td></td>
</tr>
<tr>
<td>Weight at enrollment Mean (SD), kg</td>
<td>5.69 (1.41)</td>
<td>5.63 (1.50)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD), ( z ) score</td>
<td>−0.74 (1.12)</td>
<td>−0.78 (1.17)</td>
<td></td>
</tr>
<tr>
<td>Sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand</td>
<td>11 (13)</td>
<td>15 (18)</td>
<td></td>
</tr>
<tr>
<td>Australian states</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Queensland (2 centers)</td>
<td>31 (37)</td>
<td>29 (35)</td>
<td></td>
</tr>
<tr>
<td>Victoria (2 centers)</td>
<td>21 (25)</td>
<td>19 (23)</td>
<td></td>
</tr>
<tr>
<td>New South Wales (2 centers)</td>
<td>19 (23)</td>
<td>18 (21)</td>
<td></td>
</tr>
<tr>
<td>South Australia</td>
<td>2 (2)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>Highest parental education level for both parents(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed year 10</td>
<td>15 (19)</td>
<td>9 (12)</td>
<td></td>
</tr>
<tr>
<td>Completed secondary education</td>
<td>13 (17)</td>
<td>20 (27)</td>
<td></td>
</tr>
<tr>
<td>Trade</td>
<td>41 (53)</td>
<td>35 (48)</td>
<td></td>
</tr>
<tr>
<td>Completed tertiary education</td>
<td>8 (10)</td>
<td>9 (12)</td>
<td></td>
</tr>
<tr>
<td>Exposure to environmental tobacco smoke During pregnancy</td>
<td>22 (26)</td>
<td>13 (15)</td>
<td></td>
</tr>
<tr>
<td>Concurrent smoking in the household(^b)</td>
<td>30 (36)</td>
<td>23 (28)</td>
<td></td>
</tr>
<tr>
<td>Preterm delivery &lt;37 wk(^c)</td>
<td>8 (10)</td>
<td>9 (11)</td>
<td></td>
</tr>
<tr>
<td>Presence of respiratory symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>36 (43)</td>
<td>37 (44)</td>
<td></td>
</tr>
<tr>
<td>Wheeze(^d)</td>
<td>11 (13)</td>
<td>6 (7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: BAL, bronchoalveolar lavage.
\(^a\)Lower respiratory tract infection defined by 10^3 colony-forming units/mL or greater of bacterial pathogens in BAL fluid culture.
\(^b\)While 60 children in the BAL-directed therapy group completed the study, only 79 had a final outcome BAL. Denominators vary because quantitative bacterial counts were not recorded for every final outcome BAL culture.
\(^c\)By \( \chi^2 \) test, unless expected counts were less than 5, in which case Fisher exact test was used.
\(^d\)Achromobacter xylosoxidans.
\(^e\)One each of Enterobacter cloacae and Klebsiella pneumoniae.

### Table 2. Prevalence of Lower Respiratory Tract Infection Diagnosed by Bronchoalveolar Lavage Fluid Culture at Age 5 Years, by Treatment Group\(^a\)

<table>
<thead>
<tr>
<th>Organism</th>
<th>No./Total (%)</th>
<th>BAL-Directed Therapy (n = 79)</th>
<th>Standard Therapy (n = 77)</th>
<th>( \text{Risk Difference, } % ) (95% CI)</th>
<th>( P ) Value(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilus influenzae</td>
<td>32/79 (41)</td>
<td>23/76 (30)</td>
<td></td>
<td>10.2 (−4.7 to 25.2)</td>
<td>.18</td>
</tr>
<tr>
<td>Staphylococcus aureus, including MRSA</td>
<td>22/78 (28)</td>
<td>28/76 (37)</td>
<td></td>
<td>−8.6 (−23.4 to 6.1)</td>
<td>.25</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>8/79 (10)</td>
<td>9/76 (12)</td>
<td></td>
<td>−1.7 (−11.6 to 8.1)</td>
<td>.73</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>7/79 (9)</td>
<td>2/77 (3)</td>
<td></td>
<td>6.3 (−0.9 to 13.5)</td>
<td>.17</td>
</tr>
<tr>
<td>Aspergillus species</td>
<td>6/78 (8)</td>
<td>7/75 (9)</td>
<td></td>
<td>−1.6 (−10.5 to 7.2)</td>
<td>.72</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>2/79 (3)</td>
<td>3/76 (4)</td>
<td></td>
<td>−1.4 (−7.0 to 4.2)</td>
<td>.68</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>3/79 (4)</td>
<td>1/77 (1)</td>
<td></td>
<td>2.5 (−2.4 to 7.4)</td>
<td>.62</td>
</tr>
<tr>
<td>Other gram-negative bacilli</td>
<td>1/79 (1)(^d)</td>
<td>2/76 (3)(^e)</td>
<td></td>
<td>−1.4 (−5.7 to 3.0)</td>
<td>.62</td>
</tr>
<tr>
<td>No BAL evidence of infection</td>
<td>11/77 (14)</td>
<td>15/75 (20)</td>
<td></td>
<td>−5.7 (−17.7 to 6.2)</td>
<td>.35</td>
</tr>
</tbody>
</table>

Abbreviations: BAL, bronchoalveolar lavage; CI, confidence interval; MRSA, methicillin-resistant Staphylococcus aureus.
\(^a\)Lower respiratory tract infection defined by 10^3 colony-forming units/mL or greater of bacterial pathogens in BAL fluid culture.
\(^b\)While 60 children in the BAL-directed therapy group completed the study, only 79 had a final outcome BAL. Denominators vary because quantitative bacterial counts were not recorded for every final outcome BAL culture.
\(^c\)By \( \chi^2 \) test, unless expected counts were less than 5, in which case Fisher exact test was used.
\(^d\)Achromobacter xylosoxidans.
\(^e\)One each of Enterobacter cloacae and Klebsiella pneumoniae.

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only oropharyngeal culture in the standard therapy group, there were 65 episodes (0.17/person-year) of *P aeruginosa* infection diagnosed by BAL culture in the BAL-directed therapy group and 78 (0.22/person-year) by oropharyngeal culture in the standard therapy group (IRR, 0.78; *P* = .21). When only oropharyngeal culture results were compared between the 2 groups, there were 86 episodes (0.24/person-year) in the BAL-directed therapy group vs 78 episodes (0.22/person-year) in the standard therapy group (IRR, 1.08; *P* = .69).

Seventeen children had *P aeruginosa* infection diagnosed at the final outcome BAL. Of these, 13 had received a diagnosis of *P aeruginosa* infection previously (eTable 4). Overall, 39 of 84 children (46%) in the BAL-directed therapy group and 43 of 84 (51%) in the standard therapy group had *P aeruginosa* infection diagnosed during the study and received at least 1 course of antibiotic therapy for eradication. In 38 of 39 children (97%) and 39 of 43 (91%) in the BAL-directed therapy and standard therapy groups, respectively, the organism was cleared following 1 or 2 courses of eradication treatment. At the time of the final outcome BAL, 1 child in the BAL-directed therapy group and 4 receiving standard therapy had already met the definition for chronic *P aeruginosa* infection. However, of these 5 children, only the 1 child from the BAL-directed therapy group had *P aeruginosa* infection detected at final BAL.

Analyses for cultures of *P aeruginosa* at concentrations less than 10^3 CFU/mL and sensitivity analyses including patients who refused eradication treatment, excluding those with protocol violations, and adjusting for maternal and household smoking are presented in the eSupplement. Results were not substantially different.

Overall, few children used concomitant medications such as inhaled hypertonic saline, dornase alfa, and azithromycin, although inhaled corticosteroids were used frequently in both study groups (eTable 5).

**Table 3.** Secondary Outcome Measures (z Scores) at Age 5 Years

<table>
<thead>
<tr>
<th>Measure</th>
<th>BAL-Directed Therapy (n = 80)^a</th>
<th>Standard Therapy (n = 77)^b</th>
<th>Mean Difference (95% CI)</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>−0.66 (1.25)</td>
<td>−0.41 (1.23)</td>
<td>−0.15 (−0.58 to 0.28)</td>
<td>.49</td>
</tr>
<tr>
<td>FVC</td>
<td>−0.04 (1.31)</td>
<td>0.01 (1.20)</td>
<td>−0.06 (−0.49 to 0.38)</td>
<td>.80</td>
</tr>
<tr>
<td>FEF 25%−75%</td>
<td>−1.10 (1.27)</td>
<td>−0.71 (1.28)</td>
<td>−0.39 (−0.84 to 0.07)</td>
<td>.09</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>−0.86 (1.54)</td>
<td>−0.74 (1.29)</td>
<td>−0.11 (−0.61 to 0.38)</td>
<td>.66</td>
</tr>
<tr>
<td>Weight</td>
<td>−0.15 (0.88)</td>
<td>−0.21 (0.82)</td>
<td>0.06 (−0.21 to 0.32)</td>
<td>.68</td>
</tr>
<tr>
<td>Height</td>
<td>−0.13 (0.83)</td>
<td>−0.19 (0.98)</td>
<td>0.06 (−0.23 to 0.35)</td>
<td>.69</td>
</tr>
<tr>
<td>BMI^c</td>
<td>0.03 (0.93)</td>
<td>0.01 (0.83)</td>
<td>0.02 (−0.25 to 0.30)</td>
<td>.87</td>
</tr>
</tbody>
</table>

Abbreviations: BAL, bronchoalveolar lavage; BMI, body mass index; FEF 25%−75%, forced expiratory flow at 25% to 75% of FVC; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second.

^a n=63 for FEF and 66 for remaining lung function measures.

^b n=62 for FEF and 63 for remaining lung function measures.

^c Calculated as weight in kilograms divided by height in meters squared.

**Figure 2.** Raw Cystic Fibrosis–Computed Tomography Scores, by Treatment Group, Calculated as Percentage of Total Possible Score on Each Scale

Y-axis intervals shown in blue indicate range from 0% to 25%. For total score, n=76 (90%) for both groups. For bronchiectasis score, n=77 (92%) for the bronchoalveolar lavage (BAL)–directed therapy group and n=76 (90%) for the standard therapy group. For air trapping, n=77 (92%) for both groups.
The most commonly reported adverse effect was transient worsening of cough in 96 children following 151 BAL procedures (29%). Overall, the rate and nature of adverse events were similar to those reported previously in a subset of participants from the current study.7 Similarly, children receiving P aeruginosa eradication therapy experienced few adverse events during the course of treatment (e-supplement).

COMMENT

In this randomized controlled trial, BAL-directed therapy did not reduce structural lung abnormalities seen on high-resolution chest CT scans or prevalence of P aeruginosa infection at age 5 years when compared with standard treatment. The trial found an unexpectedly low prevalence of P aeruginosa infection, which limited its statistical power for this particular primary outcome. If we had anticipated a prevalence of P aeruginosa infection as low as 12%, we would not have specified this measure as one of our primary outcomes, because it would have been impractical to design a sufficiently large study to detect plausible reductions in prevalence. Based on our data, 59 children would need to undergo BAL-directed therapy to prevent a single P aeruginosa infection at age 5 years. Even the most optimistic interpretation of the 95% CI for the effect of intervention suggests that the number needed to treat would be 9. In addition, although the 95% CI for the comparison of rates of P aeruginosa infection was wide, there was no indication of more subtle benefits by way of improved nutrition or lung function parameters.

Despite adherence to standard infection control procedures15,17 at all participating centers, more than half of the children had at least 1 episode of P aeruginosa infection diagnosed during the 5 years of the study. Nevertheless, both BAL-directed and standard therapy resulted in a much lower than expected prevalence of P aeruginosa infection at age 5 years in children with cystic fibrosis diagnosed through newborn screening and managed with an aggressive P aeruginosa eradication program.8,14 Indeed, at age 5 years, only 1 child met our criteria for chronic P aeruginosa infection.

Comparing eradication rates between studies is complicated by different patient characteristics (eg, initial cystic fibrosis diagnosis following newborn screening or symptoms) and varying definitions of infection or eradication13, however, eradication rates for this study are similar to those reported elsewhere and in particular to rates for the ELITE (Early Inhaled Tobramycin for Eradication) study, with around 90% of patients having negative cultures for P aeruginosa after completing treatment.11 This observation is also consistent with recent reports of a marked decline in prevalence of chronic P aeruginosa infection in children with cystic fibrosis following early and aggressive antipseudomonal treatment strategies and increased attention to infection control policies.24-26

While this study did not provide full eradication treatment for children with concentrations of P aeruginosa less than 10³ CFU/mL in their BAL fluid, given the low prevalence of P aeruginosa infection at age 5 years in those with small numbers of this pathogen in their lower airways, it is unlikely that even more aggressive therapy of children with a low bacterial load would have had any effect on final outcomes. The optimal treatment for eradicating P aeruginosa is yet to be determined.

Compared with children receiving standard therapy, BAL-directed therapy was associated with reduced length of stay for non-P aeruginosa respiratory-related hospital admissions, which may partially offset the increased health care costs associated with the procedure. Physician behavior may have changed the pattern of admissions if BAL was being used to further characterize suspected lower respiratory tract infections, leading to hospitalizations of shorter duration.

Despite children in this study having excellent nutritional and clinical status, relatively normal lung function, and having received aggressive treatment of infection, many had mild structural changes on high-resolution chest CT scans, with 57% showing signs of bronchiectasis and 45% demonstrating air trapping. Air trapping had a greater range of severity across the cohort, and its role as a sensitive marker of early lung disease warrants further study.27,28 The long-term clinical implications and potential for resolution of these structural changes is currently uncertain, because reversible bronchiectasis is described in young children.29,30 It is likely, however, that given the progressive nature of cystic fibrosis lung disease, at least some of these changes represent permanent damage.

This is the first large, multicenter, randomized controlled trial in young children with cystic fibrosis to use CF-CT scores as a primary outcome measure. High-resolution chest CT scans have not yet been validated as a clinical outcome measure.
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measure for clinical trials in young children with cystic fibrosis. However, cystic fibrosis–related parameters such as trapped air have been used successfully in small pilot studies. 33 High-resolution chest CT scans provide a sensitive direct measure of structural lung damage caused by cystic fibrosis, especially bronchiectasis, which is the most important component of cystic fibrosis lung disease associated with increased morbidity and early mortality. 35–36 While lung function remains the major surrogate measure for cystic fibrosis lung disease, spirometry is unable to detect early bronchiectasis. Nonetheless, the use and benefit of high-resolution chest CT scans, especially in young children, needs to be balanced by the potential risks of increased radiation exposure. 36,37

This study highlights some difficulties associated with a multicenter trial. Various centers had different CT scanners, which changed during the study, and the research protocol was not always followed. In addition, there were treatment differences between sites, with 3 using antistaphylococcal prophylaxis routinely in the first year of life. However, randomization and stratification by site ensured that comparisons between treatment groups remained valid, and the consistent absence of between-group differences across a wide range of outcome measures provides reassurance that an intervention-related benefit was not missed.

Further limitations of this study include that chest CT and BAL were not performed in all patients at baseline to assess initial lung disease, although it is unlikely that there were differences given the young age of the patients. In addition, only 64% of eligible children were enrolled, although those not participating were similar in sex and phenotype. A recent Australian longitudinal, observational study of annual BAL and CT scanning in newborn-screened infants with cystic fibrosis reported a prevalence of bronchiectasis of 40% to 60% by age 4 to 6 years, 27 similar to our study, which suggests that study participants were likely overall to be representative of other Australian children diagnosed with cystic fibrosis through newborn screening. Last, the BAL-directed therapy group in the current study had greater exposure to environmental tobacco smoke compared with the standard therapy group, with 26% vs 15%, respectively, being exposed during pregnancy and 36% vs 28% having concurrent household exposure at baseline, which may have been associated with more severe baseline lung disease. Nevertheless, adjusting for exposure to tobacco smoke made no difference to the evidence for an intervention effect.

This study highlights the importance of examining diagnostic and management interventions using appropriately designed randomized controlled trials in a clinical practice setting. BAL-directed therapy provided no clinical, microbiologic, or radiographic advantage and led to an increased risk of predominantly mild adverse events as a direct result of bronchoscopy as well as disadvantages such as the need to fast prior to the procedure, exposure to anesthesia, and potential perioperative anxiety. 38 BAL remains a useful research tool in young, nonexpectorating children with cystic fibrosis. In clinical practice, however, BAL is perhaps best reserved for young children whose conditions are deteriorating despite parenteral antibiotic therapy; when unusual or antibiotic-resistant pathogens, including clonal P aeruginosa strains, are suspected, 39,40, and to diagnose patients with chronic P aeruginosa infection.

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