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Trends in the Use of Routine Therapies in Cystic Fibrosis: 1995–2005

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Summary

Many therapies are used to treat manifestations of cystic fibrosis (CF). Trends in routine therapy use in Epidemiologic Study of Cystic Fibrosis patients were studied from 1995 through 2005. 15,087 patients were assessed in 1995; 12,778 in 2005. Observed differences in therapy use of 2% were statistically significant at $P < 0.001$. Comparing the 1995 and 2005 populations, mean age was 13.9 vs. 15.5 years; weight-for-age percentile was 30.3 vs. 36.9; and mean forced expiratory volume in 1 s (FEV₁) was 73.7 (n = 7065) vs. 78.7 (n = 7867) percent predicted. Use of several therapies increased, including airway clearance (69.9 to 89.6%), inhaled bronchodilators (72.0 to 84.0%), dornase alfa (44.8 to 67.2%), inhaled corticosteroids (16.0 to 49.3%), inhaled antibiotics (6.5 to 43.1%), oral nutritional supplements (18.3 to 24.5%), and insulin/oral hypoglycemic agents (4.9 to 10.2%). Use of mast cell stabilizers (from 22.0 to 5.3%) and oral bronchodilators (from 10.4 to 1.5%) decreased. Less dramatic changes occurred for pancreatic enzymes (92.6 to 91.0%), oral nonquinolone antibiotics (44.7 to 39.8%), oral corticosteroids (7.8 to 5.2%), mucolytics (4.4 to 2.5%), NSAIDs/high-dose ibuprofen (3.6 to 3.3%), enteral nutrition (5.2 vs. 8.2%), and oxygen (4.7 to 4.5%). Therapies not tracked in 1995 were evident in 2005, including oral macrolide antibiotics (33.8%), leukotriene inhibitors/antagonists (10.8%), and inhaled hypertonic saline (2.6%). Routine therapies were generally used more often by older

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Disclosure of Conflict of Interest

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patients and those with lower FEV₁. Notable increases in use of therapies, particularly of inhaled therapies, suggest that overall patient treatment burden must have risen correspondingly.

Keywords

cystic fibrosis; epidemiology; therapy

INTRODUCTION

Many therapies are used to treat the pulmonary and gastrointestinal manifestations of cystic fibrosis (CF).^{1,2} Some have been available for more than 50 years (*e.g.*, airway clearance and pancreatic enzymes), while others have been introduced much more recently (*e.g.*, dornase alfa, high-dose ibuprofen, tobramycin inhalation solution, oral macrolide antibiotics, and inhaled hypertonic saline). Introduction into clinical practice of new therapies, combined with an increased appreciation of the pathophysiology of CF lung disease, have led to substantial changes in treatment patterns over past decades. This report characterizes changes in use of routine CF therapies from 1995 to 2005, extending a cross-sectional report of the use of CF therapies in 1995 from the Epidemiologic Study of Cystic Fibrosis (ESCF).³

METHODS

Data were obtained from ESCF, an encounter-based, longitudinal, multicenter study designed to understand the natural history of patients with CF in North America from 1994 to 2005.⁴ Informed consent was obtained according to local human subjects review boards. Data were collected from 1994 to 2005. Spirometry results, ongoing routine therapies, and any newly prescribed therapies were recorded at the time of each clinical encounter. Beginning in 2003, ESCF data were collected electronically instead of on paper and associated modifications of the ESCF case report form were made. The 2003 case report form changes included the capture of three routine therapies that had become more prominent after 1995: oral macrolide antibiotics, leukotriene inhibitors/antagonists, and inhaled hypertonic saline. In addition, beginning in 2003 nonsteroidal anti-inflammatory drugs (NSAIDs) other than high dose ibuprofen were not reported.

For this analysis, routine therapies (not associated with treatment of pulmonary exacerbations) included airway clearance (excluding exercise), oral and inhaled antibiotics (the former divided into quinolones and nonquinolones), oral and inhaled bronchodilators, oral and inhaled corticosteroids, dornase alfa, insulin and oral hypoglycemic agents, mast cell stabilizers (cromolyn and nedocromil), leukotriene inhibitors/antagonists, mucolytics (*e.g.*, N-acetyl cysteine), inhaled hypertonic saline, NSAIDs/high-dose ibuprofen, oxygen, pancreatic enzymes, and oral, enteral, and parenteral nutritional supplements. To assess therapy use for each year from 1995 to 2005, the routine therapy section of case report forms from the encounter closest to a patient's birthday (and within ± 90 days) were analyzed for each year. Use of a single encounter for each patient was intended to reduce potential ascertainment bias resulting from unequal numbers of clinic visits among patients. No attempt was made to determine adherence with therapy or to determine the percentage of

time the patient actually received the therapy during the year. In addition, demographic characteristics of the 1995 and 2005 populations were compiled. The percentage of patients using each therapy was assessed overall, as well as by age (<6, 6–12, 13–17, 18–24, 25+ years) and by disease stage (forced expiratory volume in 1 s [FEV₁] <40, 40<70, 70<100, 100 percent predicted). The FEV₁ results were reported by the sites as absolute values and converted to percent of predicted using reference equations from Wang et al⁵ for females through age 15 and males through age 17 years and Hankinson et al⁶ at older ages. A descriptive analytical approach was used for these data. Hypothesis testing was not performed. Results were interpreted based on clinical relevance and effect size, and not statistical significance, following the approach used by our prior descriptive work with ESCF.^{3,4}

RESULTS

Over the 11 years covered in this analysis, the mean age of patients studied increased from 13.9 ± 10.2 yrs (mean $\pm$ SD) in 1995 (n = 15,087) to 15.5 ± 11.1 yrs in 2005 (n = 12,778). Mean FEV₁ percent predicted, height-for-age percentile, and weight-for-age percentile also increased from 1995 to 2005 (Table 1).

A variety of shifts in the use of routine pulmonary therapies by the CF population was observed over the study period (Figure 1). Observed differences in use of therapies of 2% were statistically significant at $P < 0.001$. Reported use of airway clearance increased steadily from 69.9% in 1995 to 89.6% in 2005 (Figure 1A). Although the overall use of bronchodilators was relatively constant over the period, there was a shift towards more use of inhaled bronchodilators (from 72.0% in 1995 to 84.0% in 2005) and less use of oral bronchodilators (from 10.4% to 1.5%) over the same period (Figure 1A). The reported use of inhaled corticosteroids increased threefold from 16.0% to 49.3% (Figure 1B), while use of oral corticosteroids declined from 7.8% to 5.2% (Figure 1C). In contrast, use of mast cell stabilizers dropped precipitously from 22.0% to 5.3% (Figure 1B). Use of leukotriene inhibitors/antagonists was not captured in the 1995 ESCF case report form, but use rose steadily from the year they were first captured (2003) from 5.8% to 10.8% by 2005 (Figure 1D). There was little change in the use of NSAIDs/high-dose ibuprofen from 1995 (3.6%) to 2005 (3.3%; Figure 1C). Use of dornase alfa increased from 44.8% to 67.2% during the period (Figure 1B). There was a drop in the (already low) use of mucolytics (from 4.4% to 2.5%, data not shown). Inhaled hypertonic saline use was not captured in the 1995 ESCF case report form, but 2.6% of patients were reported to use hypertonic saline in 2005 (Figure 1D). Since the period covered by this analysis, use of inhaled hypertonic saline has risen dramatically in the US.⁷

Overall routine use of antibiotics not associated with the management of pulmonary exacerbations increased between 1995 and 2005. The largest increase was observed for the routine use of inhaled antibiotics from 6.5% to 43.1% (Figure 1B). Oral macrolide antibiotics were not specifically captured in the ESCF case report form prior to 2003, but reported oral macrolide antibiotic use rose from 24.1% to 33.8% from 2003 to 2005 (Figure 1D).

Use of oral nutritional supplements increased from 18.3% in 1995 to 24.5% in 2005 and use of insulin/oral hypoglycemic agents increased from 4.9% to 10.2% in the same period. Oral hypoglycemic agents and insulin were collected as separate variables beginning in 2003; we found the use of oral hypoglycemic agents was less than one-tenth the use of insulin. Less dramatic changes were observed for use of pancreatic enzymes (from 92.6% to 91.0%) and enteral nutrition (from 5.2% to 8.2%), and there was no change in parenteral nutrition (from 0.3% to 0.3%).

Overall, more routine therapies showed increases than decreases during the period (Figure 2), with seven therapies increasing more than 5% in use and only two therapies decreasing in use to the same extent. The greatest overall changes in use were observed for inhaled therapies, which represented five of the six largest changes in use (the other being airway clearance). Increases in the use of four inhaled therapies (bronchodilators, dornase alfa, corticosteroids, and antibiotics) ranged from 12.0 to 36.6 percentage points, while use of mast cell stabilizers dropped by 16.7 percentage points over the period (Figure 2).

In general, therapies were more frequently used by older patients and those with lower pulmonary function. Exceptions to this pattern included use of pancreatic enzymes, and oral and enteral nutritional supplements, which were lower in patients 25 years and older, whereas leukotriene inhibitors/antagonists were more frequently used by younger patients with higher lung function (age 6–12 years with FEV₁ 100% predicted). NSAIDs/high-dose ibuprofen therapy was more frequently used in patients 6–17 years old with FEV₁ 100% predicted than in other subgroups. When stratified by pulmonary function, increases in the use of dornase alfa between 1995 and 2005 resulted from more use in patients with better lung function and in those too young to have had consistently reported spirometries (Figure 3A). In contrast, increases in inhaled antibiotics and inhaled corticosteroids resulted from increased use in all patients, regardless of lung function (Figures 3B and 3C). Reported use of airway clearance increased to approximately 90% in all subgroups (Figure 3D).

DISCUSSION

The most substantial increases in use of routine therapies tracked from 1995 to 2005 were observed for inhaled medications (inhaled antibiotics, dornase alfa, inhaled corticosteroids, and inhaled bronchodilators) and for airway clearance. In 2003, ESCF case report forms first began to specifically track oral macrolide antibiotics, leukotriene inhibitors/antagonists, and inhaled hypertonic saline. For this reason, data collected prior to 2003 underestimated the use of these therapies (Figure 1D). Transition of ESCF to electronic data capture and a new case report form between 2002 and 2003 (gray zones of Figure 1) appear to have affected the reporting of some routine therapies more than others. For example, changes in the reported use of inhaled antibiotics (Figure 1B), oral corticosteroids (Figure 1C), and oral quinolones (Figure 1C) between 2002 and 2003 were noticeably different than in surrounding years, whereas changes in the use of other therapies such as inhaled corticosteroids, dornase alfa, and mast cell stabilizers during the same period were not (Figure 1B). These observations underscore the challenges associated with maintaining useful patient registries for diseases in which treatment paradigms and therapies change rapidly. One caveat in reviewing the aggregate trends in use data (Figure 1) is that the

demographics of sites (and thus of patients) participating in ESCF shifted slightly between 1995 and 2005 (Table 1), with a higher proportion of children <13 yrs of age participating in 1995 compared to 2005 (53.0% versus 45.9%). Although trends of increased or decreased use of therapies were for the most part consistent across age groups, use of therapies tended to be higher in older patients with more advanced disease (Figure 3).

Examination of the four therapies that underwent the greatest expansion of use between 1995 and 2005—dornase alfa, inhaled antibiotics, inhaled corticosteroids, and airway clearance—illustrate how use and change in use was affected by disease stage. In 1995, use of dornase alfa and inhaled antibiotics was greater in patients with more advanced lung disease, whereas use of airway clearance and inhaled corticosteroids was relatively consistent across disease stages (Figure 3). Although the use of all four therapies increased substantially by 2005, for dornase alfa there was a trend of increasing use in patients with earlier stages of lung disease (higher FEV₁) and in children too young to have had consistently reported spirometries (Figure 3A). In contrast, changes in the use of inhaled antibiotics, inhaled corticosteroids, and airway clearance were relatively insensitive to disease stage (Figures 3B–D). A strong trend for greater use of inhaled antibiotics in patients with more advanced disease in both 1995 and 2005 is perhaps due in some part to a higher incidence of chronic *Pseudomonas aeruginosa* infection in patients with advanced lung disease. However, the overall proportion of patients with *P. aeruginosa* infection dropped about 1% per year, from 65% in 1995 to 55% in 2005.

In some instances, the driving forces behind changes in use of routine therapies appear obvious. For example, some therapies were approved or introduced as a therapy for CF between 1995 and 2005, for example tobramycin inhalation solution, leukotriene inhibitors/antagonists, oral macrolide antibiotics, and inhaled hypertonic saline. Other changes may have been driven by less obvious forces. For example, increased use of dornase alfa may have been partly due to being newly approved just before 1995 and partly due to increased clinical experience as well as a clinical trial in CF children 6 to 10 years old reported in 2001.⁸ The decreased use of mast cell stabilizers during this period may represent competition from increased use of inhaled corticosteroids or the introduction of unit dose albuterol solutions.

Between 1995 and 2005, predicted median survival for CF patients in the US increased from <30 years to >36 years of age.⁷ Over this same period, average lung function progressively improved in patients with CF, and clinical symptoms progressively decreased.⁹ Our results indicate that an overall increase in the use of routine therapies, and particularly in inhaled therapies, also occurred during this period. It may be tempting to conclude that the association between increased use of routine therapies and improved health outcomes is causal. However, increases in the overall health of the CF population as a result of both increased newborn screening and diagnosis of older patients with less severe CF phenotypes likely also contributed to improved health outcomes during this period.

The substantial increase in use of inhaled therapies from 1995 to 2005 suggests that overall patient treatment burdens must have risen correspondingly, since many of these therapies can require from 10 to 30 minutes of effort multiple times per day. There are several

promising inhaled CF therapies in clinical development that may soon be available for patients, but it is difficult to envision a pattern of increase in the use of inhaled therapies continuing forward given the associated treatment burden of inhalation. However, new delivery devices with decreased administration time will likely reduce associated treatment burdens. Regardless, at some point, it is likely that clinicians will be forced to choose which of several available inhaled therapies are appropriate for individual patients. Controlled comparative studies addressing these questions are unlikely to be conducted. Encounter-based CF patient registries may offer an opportunity to evaluate the effectiveness of these therapies in selected CF subpopulations, allowing clinicians to better tailor treatment to individual patients.

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Figure 1. Annual (cross-sectional) usage of routine therapies

Panel A, use of bronchodilators and airway clearance from 1995 to 2005. Panel B, use of other inhaled therapies from 1995 to 2005. Panel C, use of other oral therapies from 1995 to 2005. Panel D, use of therapies not originally tracked in ESCF. Note that the vertical scales in Panels C and D are different from those of Panels A and B. Gray vertical boxes identify the transition period during which ESCF data collection methods were modified.

Figure 2. Use of routine therapies in 1995 and 2005 by route of administration

Gray squares represent inhaled therapies, white squares represent oral therapies, and black squares represent (lower left to upper right) enteral and parenteral nutrition and airway clearance. Therapies above the dotted line showed a net increase in use between 1995 and 2005, while therapies below the line had a net decrease in use during the period. Therapies that were used by greater than 10% of patients in either 1995 or 2005 are identified. OHG = oral hypoglycemic agents.

Figure 3. Use of routine therapies in 1995 and 2005 as a function of lung disease stage for the four therapies with the greatest increase in use
 Percentages of patients using therapies in 1995 (gray bars) and 2005 (black bars) are shown. Patients were divided into those under 6 years of age (who could not uniformly and reliably perform spirometry) and those 6 years and older as a function of their forced expiratory volume in 1 s (FEV₁) percent predicted value. Panel A, use of dornase alfa. Panel B, use of inhaled antibiotics. Panel C, use of inhaled corticosteroids. Panel D, use of airway clearance.

Table 1

Demographics of 1995 and 2005 Study Populations

	1995	2005
Sample size, n	15,087	12,778
Years of age, mean $\pm$ SD	13.9 $\pm$ 10.2	15.5 $\pm$ 11.1
FEV ₁ % predicted, ^a mean $\pm$ SD (n)	73.7 $\pm$ 26.9 (7065)	78.7 $\pm$ 25.5 (7867)
Height for age percentile, mean $\pm$ SD	31.9 $\pm$ 26.8	34.8 $\pm$ 27.7
Weight for age percentile, mean $\pm$ SD	30.3 $\pm$ 27.1	36.9 $\pm$ 28.5

^aPatients 6 years of age and older.

SD = standard deviation; FEV₁ = forced expiratory volume in 1 s.