Cost of care and clinical condition in paediatric cystic fibrosis patients

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Abstract

Background: The clinical course of cystic fibrosis (CF) shows considerable variation resulting in differences in health care utilisation. We investigated important clinical parameters and their relation to costs. Methods: We collected clinical parameters together with health care utilisation of a representative paediatric CF population (n = 138 patients) attending Hanover Medical School over a period of 1 year. 49% of the patients were chronically infected with Pseudomonas aeruginosa. Costs were calculated on the basis of the annual individual health care utilisation from the perspective of health insurance. Results: Total annual expenditure per patient amounted to €23,989 (S.D. 18,026), with home drug treatment representing the most important single cost factor (47% of total costs). While costs rose with age and doubled in the first 18 years, they correlated foremost with P. aeruginosa airway colonisation status and lung function expressed as FEV1. Costs of patients with chronic P. aeruginosa infection were more than three times higher than of uninfected patients. Conclusions: Health care expenditures for patients with CF vary with the clinical course. The variation can be explained to a large extend by clinical parameters.

Keywords: Cystic fibrosis; Pseudomonas aeruginosa; Costs; Health economics; Prevention

1. Introduction

Life expectancy of patients with cystic fibrosis (CF) has improved considerably during the past decades following the introduction of a number of therapeutic measures including pancreatic enzyme supplementation, antibiotic therapy and mucolytic drugs [1]. Consequently, the increased prevalence of CF together with newly introduced therapies have augmented health care utilisation and expenditure.

The clinical course of CF is known to vary considerably even under similar standards of care [2]. Although in Germany almost half of the CF patients (47%) now reach adulthood with a lung function value within the normal range (forced expiratory volume in 1 s, FEV1, >80% predicted), a third still die below the age of 18 years [3]. Patients with moderate or advanced lung disease appear to have more frequent health care utilisation including more frequent clinic visits and hospital stays [4].

In the assessment of new health care interventions such as new therapies or screening programmes, data on medical consumption and their related costs are required to estimate their economic impact. Health care interventions lead to direct costs, but they may also have a positive or negative impact on costs of conventional therapy. Since outcome measures of clinical trials frequently consist of clinical parameters, such as FEV1, infection status, or nutritional status, it is important to evaluate the relationship between clinical parameters and costs of care. We hypothesised that health care expenditures for patients with CF vary with the clinical course and investigated the relevance of clinical parameters in predicting annual treatment costs. We demonstrate in a paediatric CF population that a selection of parameters can explain over 60% of the variation of costs.

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2. Materials and methods

2.1. Subjects

The study was located at the cystic fibrosis clinic of the Paediatric Department of Hanover Medical School. This is one of the three largest units in Germany, serving a population of approximately 10 million in a model of shared care. All patients who regularly attended the unit were included in this study. Exclusion criteria were additional diseases unrelated to CF that may incur significant costs or a shared care with other CF-centres in order not to miss health care consumption documented elsewhere. The patients were seen in the CF clinic four times per year on a regular basis. At each visit, lung function tests, anthropometrical measures and sputum or throat swab cultures were performed. Lung function values were corrected for height, weight and gender and calculated as percent of predicted values [5]. Nutritional status was determined as percentage of ideal weight corrected for height, age and gender [6]. Chest radiographs were evaluated according to the scoring system of Crispin and Norman by a single experienced radiologist [7]. Patients were considered chronically infected with P. aeruginosa if more than 50% of cultures were positive in the preceding 12 months. Patients with positive cultures of less than 50% were rated intermittently colonised [8]. Chronically infected patients were treated with either inhaled tobramycin (80 mg b.d.) or colistin (10^6 U b.d.). Patients with chronic P. aeruginosa infection and clinical exacerbation defined as deterioration of lung function were treated with intravenous antibiotics for 2 weeks, which was repeated in 3-month intervals.

Out of the n=196 patients seen in the unit in 1996, all patients who received care only by this unit (n=138, n=74 (54%) male) were included in the study. The excluded patients were either seen in a model of shared care also by other units (n=55), or suffered also from a second disorder (leukaemia, cerebral palsy and psychosis, respectively, n=3). Mean age was 10.1 years (S.D. 5.6, range 0–18), with a mean FEV1 of 84.5% (S.D. 23.8, range 23–125, n=101). Weight index ranged from 70 to 143%, with a mean of 94.7% (S.D. 12.3). 67 (48.6%) patients were chronically infected with P. aeruginosa, another 15 (10.9%) intermittently. As expected, FEV1 declined with age, while rate of chronic infection with P. aeruginosa rose (Table 1).

Comparisons between the study population and the German CF registry of the same year (n=2358) showed no consistent differences for age and the rate of chronic P. aeruginosa infection [9]. However, there were slight differences in mean FEV1 and nutritional status (Table 1).

<table>
<thead>
<tr>
<th>Age [years]</th>
<th>FEV1 [% pred.]</th>
<th>Weight index</th>
<th>Chronic P. aeruginosa infection [%]</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>–</td>
<td>95.0 (9.1)</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>3–6</td>
<td>–</td>
<td>95.8 (8.8)</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>6–9</td>
<td>97.1 (22.5)</td>
<td>95.5 (9.4)</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>9–12</td>
<td>93.6 (16.1)</td>
<td>94.4 (12.9)</td>
<td>52</td>
<td>27</td>
</tr>
<tr>
<td>12–15</td>
<td>82.5 (19.4)</td>
<td>94.5 (11.0)</td>
<td>65</td>
<td>17</td>
</tr>
<tr>
<td>&gt;15</td>
<td>72.7 (26.4)</td>
<td>94.0 (16.7)</td>
<td>78</td>
<td>37</td>
</tr>
<tr>
<td>Mean (S.D.)</td>
<td>84.5 (23.8)</td>
<td>94.7 (12.3)</td>
<td>48.6</td>
<td>138</td>
</tr>
<tr>
<td>German CF</td>
<td>79.7 (23.5)</td>
<td>97.0 (11.6)</td>
<td>48.3</td>
<td>2358</td>
</tr>
</tbody>
</table>

For definition of chronic P. aeruginosa infection refer to Section 2.2.

2.2. Assessment of health care consumption

Data on diagnostic and other health care services were retrieved from databases of the hospital administration, seven diagnostic departments, the clinical database of the CF unit and the patients’ records. Data on external services were obtained from the patients’ records. In addition, the families were asked to document the visits to their local general practitioner, physiotherapist and the utilisation of health care aids.

This retrieval resulted in over 21,000 documented diagnostic procedures of 181 categories and approximately 3800 documented prescriptions of 61 different drugs.

2.3. Calculation of costs

Costs were calculated from the perspective of health care insurances. Although the German health care market is largely regulated, there is some variation in prices depending on the health insurance. Public insurances reimburse out-patient services on a fee-for-service basis with largely fixed prices [10], and inpatient services by an overall fee for each hospital day (€536 in this study). Fees for privately insured patients allow for some variation in both the out- and inpatient sector [11].

Medical consumption was therefore stratified to the in- and outpatient sector and the health care expenses calculated separately for patients with public and private health care insurance, respectively. The proportion of patients in our study covered by public insurances was 98% (n=135), which was slightly higher than the proportion in the general German population (94%). Due to the fixed prices for reimbursement by public health insurances, expenses could be calculated with high accuracy. Expenses for the three study patients with private health insurance were directly obtained from the bills invoiced to the patients.
Costs were aggregated to annual costs on the basis of a 1-year observation period in 1996–1997, together with the related prices and converted into Euro (€ = 1.95583 DM). Mean values of clinical data were used if several measures were obtained in that year. Long-term costs and life years gained were calculated with an annual discount rate of 5% [13].

2.4. Statistics

Data were compiled in a relational database. Normal distribution of data was analysed by the Shapiro–Wilk test. Groups were compared by the two-sided unpaired Student’s T-test following Levene’s test of equality of variances. Ordinal and least square linear regression analysis was used for analysis of dependence of cost data from clinical variables. For stepwise multiple regression analysis, ordinal variables were transformed into a set of variables indicating the presence or absence of a single value of the original ordinal variable. Bivariate correlations were calculated with the Pearson’s coefficient. Calculations were performed with the Statistical Package for Social Sciences (SPSS, V. 11).

3. Results

3.1. Medical consumption

Patients attended the CF outpatient-clinic on average 3.3 times per year (S.D. 1.3, range 0–7). Hospital care amounted to 14.4 days (S.D. 18.4, range 0–96), commonly in combination with intravenous antibiotic treatment. Patients performed on average 4.7 lung function tests [patients >6 years: 6.2 (3.6), n = 97]. In addition, 1.2 radiographs, 1.1 ultrasound scans, 10.5 microbiatorial cultures and 111.1 blood tests per patient were performed. Medical services used by the patients in CF clinic, hospital care and at home are summarised in Table 2.

3.2. Total annual costs

Total annual expenditure per patient amounted to €23,989 (S.D. 18,026), with outpatient care accounting for 59% (€14,222, S.D. 9368), and €9767 (S.D. 11,811) for hospital care. 47% of total expenditure was spent on outpatient drugs, with costs for inhaled antibiotics and pancreatic enzymes being the most expensive single drugs (38 and 22% of drug expenditure, respectively). Dornase alpha contributed 4.7% to the total drug expenditure. Other costs for outpatient services were comparatively small, with charges of the CF clinic accounting for 2% of total expenses of the health insurance (Fig. 1). As shown in Fig. 2, total costs rose with age and almost doubled within the first 18 years. This was mainly due to the tripling costs of home drug therapy, and to more frequent and prolonged hospital stays. Outpatient costs other than drug expenditure, however, remained largely unchanged. Children <3 years had higher costs for hospital care than children from 3 to 9 years, mostly due to hospital stays in relation to establishing the diagnosis.

3.3. Analysis of clinical determinants of cost levels

Male and female patients did not differ with regard to total costs. There was a moderate correlation between age and total costs (r = 0.42, P < 0.001). We speculated that the rise in costs was due to both increased drug dosages along with weight increase and to progress of disease. However, anthropometric measures failed to correlate with total costs (weight: r = 0.052; length: r = 0.022; body surface: r = 0.007; P = n.s.). In contrast, costs were highly related to progression of lung disease, as demonstrated by a negative correlation to FEV1 (r = −0.71, P < 0.001, Fig. 3a), or a score for radiological signs of lung pathology (Crispin–Norman score, r = 0.633, P < 0.001), together explaining 49% of variance of cost. Nutritional status, however, was only marginally related to the cost of therapy (r = 0.24, P = 0.005, Fig. 3b).

Since P. aeruginosa airway infection may lead to both a progress of lung disease and intensified therapy, we determined the treatment costs in relation to the P. aeruginosa colonisation status. Annual costs of patients who were not colonised (n = 56) were relatively low (€10,861 (S.D. 7105) and showed no age-related
increase (Fig. 4). In contrast, annual costs of chronically colonised patients were three times as high (€36,421, S.D. 17,449, n=67), while costs of intermittently infected patients (n=15) were only slightly above the level of uninfected patients (€17,476, S.D. 8447). In regression analysis, status of colonisation with *P. aeruginosa* explained 44% of differences in total costs, being a much stronger predictor than age (Table 3). Thus, the
age-dependent rise of costs of the study population was largely due to the increasing proportion of patients with chronic *P. aeruginosa* infection (Fig. 4).

### 3.4. Lifetime cost of cystic fibrosis from the perspective of health insurance

On the basis of age-specific annual costs (Fig. 2), the aggregated and annually discounted costs of treatment from age 0 to 18 years are €252,023. To extrapolate the data into adulthood, we hypothesised that medical consumption largely depends on the stage of disease and that the therapy of adolescents is not fundamentally different to adult treatment. Compared to the German adult CF patients, the adolescent patients with a pathological lung function (age above 15 years, FEV$_1$ < 80%, *n* = 22) had comparable mean (S.D.) FEV$_1$ [54% (23.7) vs. 56% (17.7)] and a higher *P. aeruginosa* colonisation rate (75 vs. 86%) [9]. Annual costs of this cohort were €39,439 (S.D. 21,748). When annual costs of this cohort were extrapolated to the median predicted survival age of 32 years [3], lifetime expenditures amount to approximately €396,000.

### 3.5. Annual cost of CF in Germany

In the annual national registry 2,358 patients aged below 18 years are documented [9]. Based on the costs determined in this study, annual expenditure for these patients amount to €56.6 million, which was approximately 0.038% of the German health insurance budget of that year (€150 billion) [14]. Extrapolation of annual costs of CF patients including adults (*n* = 3582) leads to total annual costs for CF of €105 million or 0.07% of the budget.

### 3.6. Cost effectiveness analysis: cost per year of life gained

Prior to the introduction of enzyme substitution and antibiotic therapy, the natural course of cystic fibrosis frequently resulted in death in early childhood. Today, due to a number of therapeutic measures, which have been calculated in this study, the median predicted survival age has risen to over 30 years in industrialised nations [3,4,15]. If life expectancy of an untreated patient is estimated as 3 years, the sum of (discounted) years gained by a life long therapy amounts to 14.3 years. Thus the cost of each gained year is approximately €31,000.

### 3.7. Sensitivity analysis

Although the calculations of costs in this study are based on the actual utilisation of health care resources

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**Table 3**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$R^2$</th>
<th><em>P</em></th>
<th>Sum of $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonisation status</td>
<td>0.54</td>
<td>&lt;0.001</td>
<td>0.62</td>
</tr>
<tr>
<td>FEV1</td>
<td>0.50</td>
<td>&lt;0.001</td>
<td>0.62</td>
</tr>
<tr>
<td>Crispin Norman score</td>
<td>0.38</td>
<td>&lt;0.001</td>
<td>0.63</td>
</tr>
<tr>
<td>Age</td>
<td>0.15</td>
<td>&lt;0.001</td>
<td>0.64</td>
</tr>
<tr>
<td>Nutritional index</td>
<td>0.05</td>
<td>0.006</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Parameters are listed according to the amount of variance explained in single regression analysis ($R^2$). The sum of $R^2$ was calculated by multiple stepwise regression analysis.

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**Fig. 4.** Mean (S.D.) total annual cost from perspective of health insurance depending on age and status of colonisation with *P. aeruginosa*. Costs of chronically infected patients were significantly different to costs of intermittently infected and to costs of uninfected patients for all age groups (*P* < 0.05, * and †, respectively). Mean costs of intermittently infected patients were significantly different to uninfected in age group 6–12 years (*). Comparison of different age groups with the same status of infection revealed significant differences only for intermittently and chronically infected patients (age < 6 vs. both older groups, *P* < 0.05), and intermittently infected patients (age < 6 vs. age 6–12, *P* < 0.05, not indicated).
and therefore relatively accurate, extrapolation to a national level bears more uncertainties that have to be addressed in sensitivity analyses. Important aspects of therapy such as the use of oral antibiotics and pancreatic enzymes were comparable between the study population and the data of the national survey. Differences, however, were found in the frequency of treatment with inhaled antibiotics (study group 47%, national report 24%), and dornase alpha (8% vs. 20%). Calculation of annual costs according to the average utilisation of these two therapies in the national survey would increase the total annual costs per patient by €500, or less than 2%. Hospital treatment occurred predominantly in the Pediatric Department of Hanover Medical School, accounting for 87% of all expenditures for hospital treatment and approximately a third of total costs. As a tertiary centre, fees for care in this institution are relatively high. If hospital care had occurred elsewhere at a 20% lower fee, total annual costs per patient would have decreased by 6.5% or €1700. Krauth et al. estimated the costs of 14 days of hospital treatment as €9564 for a German adult population, which is virtually identical to the costs in our study [16]. According to these sensitivity analyses, our data appear to be representative within a range of 10%.

4. Discussion

We investigated the costs of cystic fibrosis paediatric patients from the perspective of health care insurance and determined the differences between various stages of disease. Costs rose considerably with age, but the increase depended largely on the rising morbidity as reflected by \( \text{P. aeruginosa} \) colonisation status and lung function.

The finding that costs increase with disease severity or age has also been described by others. A recent American study classified patients according to their \( \text{FEV}_1 \) into three groups, reporting considerably increased costs in patients with severe lung disease (\( \text{FEV}_1 < 40\% \)) [17]. A Dutch cross-sectional study analysed the relation of costs to age and showed a marked increase after the age of 15 years [18]. From the perspective of a health care provider, a UK study reported high costs for adult patients with a high level of care [19].

A strength of this study is that it combines economic and several clinical aspects of cystic fibrosis therapy. \( \text{FEV}_1 \) is the primary outcome parameter in numerous clinical studies, and it also appears to be an acceptable determinant of treatment costs. Costs hard change with age in patients who preserve a good lung function. Patients who become colonised with \( \text{P. aeruginosa} \), however, are frequently commenced on expensive antibiotic drug therapy. From the clinician’s point of view, it may be surprising that nutritional status was largely unrelated to treatment costs although a relationship between nutritional status and lung function has been repeatedly described [20]. Extensive (and expensive) treatment such as intravenous and inhaled antibiotic therapy, however, is commenced prior to a clinical condition, where weight deteriorates.

With differences between health care systems, this study may not be representative outside the German borders. Studies performed in other countries, however, report surprisingly similar structures of CF-related costs with comparable proportions of hospital care, drugs and total expenses [17–19]. A Dutch study reported 13.4 days of hospital treatment for CF patients aged below 20 years [18], which is in the same range as our data (14.4 days). While the Dutch data lead to a similar estimation of CF treatment costs in relation to the total health care budget, as in our study [18], average costs in an English and American study were lower. The British National Health Service, or an American health maintenance organisation may operate at relatively low costs compared to the German health care system, with a high priced drug market and a fee-for-service reimbursement in outpatient care.

The current mortality is a result of therapeutic efforts that have been undertaken over the past 30 years, but our cost effectiveness analysis employs the costs of current therapy. With a potential further rise in life expectancy the cost per gained year of life may evolve differently in the future. Since every gained year induces another year of treatment, lifetime costs are likely to increase with further advances of therapy, for instance the more widespread use of lung transplantation. Costs per year gained, however, may decrease, particularly if preventive strategies succeed in delaying onset of chronic \( \text{P. aeruginosa} \) infection [21,22]. Delaying onset of \( \text{P. aeruginosa} \) infection by 1 year would save more than €25,000 per patient, equivalent to the difference of average annual costs for an chronically vs. uninfected patient. If a prevention programme for the German CF population <18 years succeeded in delaying the onset of infection by 1 year, the marginal costs could be up to €30 million to break even with the achieved savings in this age group.

In summary, the data from this study argue for the enhancement of strategies aimed at preventing either decline of \( \text{FEV}_1 \) or onset of \( \text{P. aeruginosa} \) infection. If, for instance, an effective vaccine was developed, it may be more cost effective than limiting lung disease once chronic infection has been established.

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References