Real life evaluation of intravenous antibiotic treatment in a paediatric cystic fibrosis centre: Outcome of home therapy is not inferior

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SUMMARY
Background: Limited data exist on the efficacy and safety of home intravenous antibiotic (IV-AB) therapy for pulmonary infection specifically in children with cystic fibrosis (CF).
Methods: We report on the outcome of IV-AB in the home vs hospital setting based on retrospective single centre patient data from 1999 to 2004 (age >5 and <18 years). Treatment location was chosen based on estimation of competence, adherence, social background and patient preference. Primary outcome parameter was change in FEV1. Secondary outcome parameters were weight and IgG as well as occurrence of complications.
Results: One hundred and thirty-one treatment observations (TOs) were analysed for 47 patients. Mean age was 13.32 (±2.9) years and mean FEV1 65 (±19) % predicted. Fifty-four (41%) TO’s were home and 77 (59%) were hospital treatments. Percent change in FEV1 and weight gain was comparable in the 2 settings. Complications were rare in both groups.
Conclusion: The outcome of IV-AB therapy for lung infection in children with CF was not inferior in the home compared to the hospital setting. In our centre, home IV-AB treatment is a valuable treatment option for children with CF.

INTRODUCTION
Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the CFTR gene, a gene coding for a transmembrane epithelial chloride channel. For most patients the cardinal disease feature is chronic bacterial lung infection with organisms like Staphylococcus aureus, Haemophilus...
influenzae and – with increasing age – non-fermenting Gram negatives like Pseudomonas aeruginosa. This relentless bacterial infection leads to chronic neutrophilic inflammation and progressive lung damage ultimately leading to respiratory failure.1,2

Frequent and long duration antibiotic (AB) treatment via different routes is the cornerstone in slowing down progression of lung disease. While oral and inhaled antibiotics provide sufficient treatment for many CF lung infections, intravenous AB (IV-AB) is often needed especially in the treatment of P. aeruginosa (Pa) infection. Courses of at least 2 weeks are given to treat exacerbation of respiratory infection. For some patients elective 3 monthly IV-AB treatment may have advantages over treating exacerbations only.3,4 Both regimens may involve 4 treatments a year of 14 days duration each. Therefore home IV-AB therapy is being used in many centres: it is less disruptive for the patient’s social life and has economic advantages.5 Insufficient medication compliance and low adherence with physiotherapy as well as lack of rest are possible pitfalls and may reduce the efficacy of home therapy. In several countries the experience with and outcome of home IV-AB therapy are being reported since the 1980s, most publications concerning adults.6–10 Over the last 15 years several studies compared the efficacy and safety of home vs hospital therapy with very different study designs11–19 and only few studies selectively showing paediatric data.

Since home therapy for IV-AB has an important place in our paediatric CF centre, we wanted to evaluate if the outcome of IV-AB therapy in the home setting was equivalent to hospital treatment for paediatric and adolescent CF patients.

Material and methods

Study population

Charts of CF patients followed in our centre and treated with IV-AB for 14 days for pulmonary infection between January 1st 1999 and December 31st 2004 were included in this retrospective analysis provided their age was between 5 and 18 years at the time of treatment. A ‘pulmonary exacerbation’ was defined as: worsening of respiratory infection warranting the institution of IV antibiotic therapy. The diagnosis of CF was made by sweat testing and genotype in patients with typical clinical signs and symptoms.

Exclusion criteria were: IV-AB therapy longer than 14 days and/or for reason other than pulmonary infection (e.g. infection of indwelling catheter), cognitive impairment (leading to inability to perform lung function) or other medical conditions possibly interfering with treatment outcome.

Patients were selected using the computerized database of the CF reference of the University Hospital Data of Leuven, Belgium. Data were collected from the medical records and the database. The study was approved by the local ethical committee.

Home vs hospital based therapy

Every patient started ‘in-hospital’ treatment during 3 days, after which ‘home therapy’ was continued at home. For ‘hospital treatment’ the full treatment was received in our hospital. Since these data refer to a retrospective analysis and not a prospective study, patients were not ‘selected’ nor ‘randomized’ to either treatment location. In our clinic if a patient needs IV therapy, the request for home therapy usually comes from the patient or parent. The team will then consider this question and evaluate the following items: (1) age of the patients (never home IV below age 5 and usually not before age 12), (2) does the medical condition of the patient allow safe home therapy (disease severity, other factors like antibiotic allergies or co-morbidities), (3) has the patient previous experience with IV in hospital (we never perform the first IV treatment at home), (4) how are the social background and support (since burden of therapy is high for home therapy), (5) are the parents and patient skilled enough to perform the medical acts needed, and (6) how do we estimate adherence with therapy in this family (medication, physiotherapy).

Final decision about treatment location is based primarily on estimation of competence and treatment adherence (as was carefully judged by the treating multidisciplinary team). Previous IV therapy and request for home therapy by patient or parents are important factors in this decision. Allocation to home therapy was therefore not based on strict criteria. It reflects our previous and current clinical practice.

For both groups antibiotics combination was chosen based on recent sputum culture and antibiotic sensitivity. Most patients were treated with piperacillin–tazobactam, ceftazidim or meropenem in combination with tobramycin.

During hospitalisation the multidisciplinary CF team was involved in the care. Chest physiotherapy was provided twice daily by the CF physiotherapist. In the home group, the parents (or for older children the patient) were instructed to prepare and administer IV medication. Physiotherapy was continued as routine (independently or with the home physiotherapist with a frequency of at twice daily chest physiotherapy during IV treatment). At the end of therapy, home IV patients were evaluated in clinic with lung function and blood biochemistry.

During the years of the study no home care support was provided by the CF nurse specialist. Patients had, however, the possibility of contacting the medical team for questions and practical issues throughout the therapy.

Baseline parameters

The following parameters were noted:

1. age, gender, and experience with IV therapy (4 categories: 1st, 2nd, 3rd, 4th or more therapy),
2. Lung function expressed in absolute values and % predicted according to Knudson20 (measured with Master screen spirometry Jaeger Paed according to ATS guidelines).21 If available lung function after a bronchodilator was taken (as a rule lung function is performed before and after salbutamol. Exceptionally, only prebronchodilator lung function is performed if reversibility is absent repeatedly).
3. weight, BMI and BMI z-score,22
4. IgG in mg/dl as measure of lung infection,
(5) infecting organism (chronic or intermittent infection with *P. aeruginosa* defined according to the European consensus definition,23 infection with *Burkholderia cepacia*, infection with other microorganisms (*S. aureus, Alcaligenes xylosoxidans, Stenotrophomonas maltophilia*)),

(6) indwelling catheter yes/no.

**Outcome parameters**

Primary outcome parameter was improvement in FEV₁ (expressed as the absolute difference in l/s), FEV₁ % predicted after — before and 'FEV₁', percent change calculated as absolute change in FEV₁/(FEV₁ at start) × 100'. Secondary outcome parameters were weight gain (weight at end of therapy — weight begin therapy and change in BMI and BMI z-score), change in IgG (absolute change and % change) and complications during IV therapy (catheter infection, allergic reaction, hemoptysis, pneumothorax).

**Data selection and statistical analysis**

For variables with a normal distribution, an independent sample Student’s t-test was used for continuously scaled variables. A Chi-square was selected for comparison of nominal variables. All statistical procedures were conducted using SPSSwin version 11.

Since data represented treatment episodes and not patients, patients with 4 IV therapies yearly represent a large number of treatment episodes possibly distorting the data. Therefore, only the first treatment of every year was included in the analysis. To exclude the variable ‘experience with IV therapy’ only treatments of patients with at least 4 previous IV treatments (home or hospital) were selected.

**Results**

From 96 patients in follow-up aged 5–18 years, 131 TO (representing 47 patients) were included in the analysis (13 patients were included once, 10 twice, 9 three times, 7 four times, 5 five times and 3 six times). Fifty-four TO’s (41%) were performed at home and 77 (59%) in hospital; 53 (40%) episodes occurred in male and 78 (60%) episodes in female patients. For 79 (60%) treatments an indwelling catheter was in place.

Ninety-four TO’s were in-patients with chronic *Pa* infection (72%), 5 (4%) in-patients with intermittent *Pa*, 9 (7%) in-patients with *Bc* infection and 23 (17%) in-patients with other infecting organisms (*S. aureus, S. maltophilia, A. xylosoxidans*, etc.). The comparison of the baseline characteristics and the infecting organism for the home and hospital setting. This was the case for FEV₁ in absolute values (0.21 l/s ± 0.25 in home and 0.23 l/s ± 0.4 in hospital; *p* = 0.71), improvement of FEV₁ percent predicted (7.4% ± 9.8 and 8.0% ± 13.3; *p* = 0.80) and for percent change in FEV₁ (17 ± 27 and 17 ± 24; *p* = 0.94).

**Secondary outcome parameters**

Mean weight gain was 0.7 kg ± 1.0 in the home setting and 0.4 kg ± 1.4 for the hospital setting (*p* = 0.14). Change in BMI (0.33 ± 0.46 vs 0.17 ± 0.59; *p* = 0.08), change in BMI z-score (0.20 ± 0.28 vs 0.12 ± 0.46; *p* = 0.30) and relative weight change (2.1 ± 3.0 vs 1.14 ± 3.80; *p* = 0.12) were also comparable in the 2 settings.

IgG decrease was larger in the hospital setting (−69 ± 173 mg/dl vs −21 ± 167 mg/dl, respectively), however, this was not statistically significant (*p* = 0.15). Percent change in IgG did neither differ significantly (−0.1 ± 0.09 home vs −0.03 ± 0.12 hospital; *p* = 0.30).

The number of complications was low and did not differ between the 2 settings (*p* = 0.66): 2 allergic reactions to antibiotics in each setting, 1 pneumothorax after home IV-AB therapy and 1 case of hemoptysis in the hospital setting.

**Discussion**

IV-AB therapy has an important place in the treatment of CF lung infection especially in patients chronically colonized with *Pa*. Our data reported here are encouraging and do not show inferior outcome of IV therapy administered by parents at home compared to hospital treatment in our centre, even though little support is currently given in the home setting. We are, however, aware, that these results reflect our centre practice and may not be generalised.

A recent US retrospective chart study by Nazer et al.19 (see Table 2 for literature overview) reported better outcome after hospital compared to home therapy in CF patients (upper age 20 years) treated for acute pulmonary exacerbation. Percent change in FEV₁ was 23% in the home and 39% in the hospital group (compared to 17% in each of

**Table 1 Baseline characteristics of the home and hospital treatment observations.**

<table>
<thead>
<tr>
<th></th>
<th>Home (n = 54)</th>
<th>Hospital (n = 77)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean (SD)</td>
<td>13.54 (2.6)</td>
<td>13.17 (3.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Weight (kg) mean (SD)</td>
<td>42.7 (14.6)</td>
<td>40.7 (12.9)</td>
<td>0.98</td>
</tr>
<tr>
<td>BMI z-score mean (SD)</td>
<td>–1.1 (1.2)</td>
<td>–1.2 (1.4)</td>
<td>0.76</td>
</tr>
<tr>
<td>FEV₁ (l/s) mean (SD)</td>
<td>1.62 (0.64)</td>
<td>1.69 (0.73)</td>
<td>0.14</td>
</tr>
<tr>
<td>FEV₁ % predicted mean (SD)</td>
<td>63 (19)</td>
<td>66 (20)</td>
<td>0.82</td>
</tr>
<tr>
<td>IgG (mg%) mean (SD)</td>
<td>1688 (549)</td>
<td>1430 (473)</td>
<td>0.25</td>
</tr>
<tr>
<td>Male/female mean (SD)</td>
<td>9/45</td>
<td>44/33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Indwelling catheter yes/no</td>
<td>32/22</td>
<td>47/30</td>
<td>0.84</td>
</tr>
<tr>
<td>R/indication: Chronic Pa</td>
<td>37</td>
<td>57</td>
<td>0.49</td>
</tr>
<tr>
<td>R/indication: Int. Pa</td>
<td>1</td>
<td>4</td>
<td>0.33</td>
</tr>
<tr>
<td>R/indication: other</td>
<td>12</td>
<td>11</td>
<td>0.24</td>
</tr>
<tr>
<td>R/indication: B. cepacia</td>
<td>4</td>
<td>5</td>
<td>0.84</td>
</tr>
<tr>
<td>First author</td>
<td>Year of publication</td>
<td>Country</td>
<td>Study design</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Strandvik 1992</td>
<td>Sweden</td>
<td>Retrospective</td>
<td>Distance from hospital Patient’s choice</td>
</tr>
<tr>
<td>Pond 1993</td>
<td>UK</td>
<td>Retrospective</td>
<td>Compliance, Competence</td>
</tr>
<tr>
<td>Bosworth 1997</td>
<td>US, Utah</td>
<td>Retrospective</td>
<td>Financial, competence, social support</td>
</tr>
<tr>
<td>Wolter 1997</td>
<td>Australia</td>
<td>Prospective, randomized (2 factor mixed)</td>
<td>Randomized (second treatment allocation in the other group)</td>
</tr>
<tr>
<td>Riethmueller 2002</td>
<td>Germany</td>
<td>Prospective open</td>
<td>Range? 16 in home and 15 in hospital group</td>
</tr>
<tr>
<td>Thornton 2004 2005</td>
<td>UK</td>
<td>Retrospective</td>
<td>Ultimately patients choice; competence, clinic picture</td>
</tr>
</tbody>
</table>

(continued on next page)
our groups). Decision on treatment location was based on patient and caregiver preferences as well as available resources. Differences in FEV₁ increase were more pronounced for patients with severe lung disease. The mean patient age in the above US study was comparable to our data, however, the mean FEV₁ at start of therapy was more than 10% lower.

Another retrospective US study by Bosworth and Nelson¹⁵ also reported superiority of hospital based therapy with 28% improvement in FEV₁ after hospital but only 11% at home. Data only concerned patients chronically infected with Pa with a mean age of 18 years and a mean FEV₁ % predicted around 45%. Of the 149 hospital and 95 home treatments only 32 and 27 were analysed to have comparable groups for age and LF. In the retrospective 1 year study of Thornton¹³ success of IV-AB therapy in adult CF patients is analysed with a very different study design: effect of therapy is evaluated after a period of 1 year and home therapy is defined as receiving at least 60% of therapy in the home setting. Treatment proved to be effective (defined as decline in FEV₁ of less than 2% over 1 year) in 59% of patients in the hospital vs only in 43% of patients in the home therapy group. Mean number of IV courses per year was 4 (range 1–9) and overall 88% of patients were Pa colonized. As in our study, more females were represented in the home group in this study.¹³ Outcome of home therapy was better for females compared to males (no gender difference in our study: data not shown). The larger proportion of females in the home treatment observation group most likely reflects their gender disadvantage in CF and therefore an increased need for IV therapy.²⁴ Another factor may be that girls are believed to be more compliant and are more keen to take on their therapy at home.

Three other European studies¹⁰–¹² support the use of home IV-AB therapy, 2 of them including mainly adults.¹²,¹⁰ In the recent open prospective German study¹¹ on elective IV-AB therapy in paediatric and adolescent CF patients (mean age 15–16 years) the 2 settings proved to be similarly effective for lung function, weight and inflammatory markers.

A disadvantage of a retrospective study is that certain parameters cannot be retrieved (for example, factors that guide the decision for home therapy, patient satisfaction, etc); moreover since patients are allocated and not randomized (and patient preference plays a role in choice of treatment location), groups are not always comparable at baseline. Although we did not register number of IV therapies needed per year, we may expect this value will be higher in the home therapy group. Especially patient with high therapy burden will prefer the home over the hospital setting mainly for QOL reasons. We are aware of the limitation of our study in this regard (no strict allocation to home or hospital therapy, no compliance monitoring, no standardisation of home physiotherapy, no QOL data), however, these data reflect the real life situation. Some patients are unable/unwilling to perform home therapy; others are advised against home therapy if the prescribed treatment is not followed (for example, chest physiotherapy). Data specifically on physiotherapy (frequency, type, with physiotherapist or self-managed) were not registered and the impact of these variables could unfortunately not be analysed. In one adult study patients were prospectively randomized for home or hospital treatment.²⁵ Although this design has

<table>
<thead>
<tr>
<th>First author</th>
<th>Year of publication</th>
<th>Country</th>
<th>Study design</th>
<th>Age range</th>
<th>Allocation of groups</th>
<th>Baseline FEV₁ (mean)</th>
<th>Number</th>
<th>Course at home</th>
<th>FEV₁ % change</th>
<th>Need for IV antibiotics</th>
<th>Additional information</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nazer</td>
<td>2006</td>
<td>USA, Michigan</td>
<td>Retrospective</td>
<td>6–21</td>
<td>52% preference, resources, experience, physicians</td>
<td>52%</td>
<td>79</td>
<td>64 at home, 66 in hospital</td>
<td>79% at home, 64 in hospital</td>
<td>23% vs 39% in hospital</td>
<td>Home: longer courses</td>
<td>FEV₁, weight, IgG, complications, complications, hospital group, patient preference</td>
</tr>
<tr>
<td>Proesmans</td>
<td>2008</td>
<td>Belgium</td>
<td>Retrospective</td>
<td>6–17</td>
<td>63% for home, 66% for hospital group</td>
<td>54%</td>
<td>54</td>
<td>77 at home, 64 in hospital</td>
<td>54% at home, 77 in hospital</td>
<td>39% vs 39% in hospital</td>
<td>FEV₁, weight, IgG, complications</td>
<td>FEV₁, weight, IgG, complications, patient preference, hospital group, patient preference</td>
</tr>
</tbody>
</table>
theoretical advantages, only 31 of the 114 treatments episodes were included in the study because of patients refusal to be randomized. As a consequence, patients included in the study may not be representative for daily centre practice. The above mentioned study of Riethmueller et al. was also planned as a prospective randomized study but was made open since adolescent patients refused to be randomized suggesting this design may neither be realistic nor ideal for comparing home and hospital treatment.11

The different results between some European and US studies may not only be explained by differences in study design and disease severity. The aspect of selecting and preparing patients for home therapy may be underestimated as an important factor. In our centre, the decision is not only guided by the patient’s preference but also by the team’s evaluation of the compliance with therapy, social support as well as parental technical skills. Factors like distance from hospital and available resources are hardly involved. Many patients have access to their usual physiotherapist for support of airway clearance.

We did not use the parameter ‘time to next pulmonary’ exacerbation in this analysis. Although an important measure in CF studies, we feel that in this retrospective study set-up where patients are not randomized, need for IV therapy is most likely higher in the home group. Therefore, time to next exacerbation would rather reflect disease severity than success of therapy.

Our study did not address the issue of cost neither the aspect of QOL but other studies have reported on these aspects.26 It is no surprise that home therapy has lower health-related cost.5

Home therapy for CF lung disease is a reality in many CF centres. It may be better to adopt a ‘non-inferiority’ trial design (provided the patient’s competence and preference are taken into consideration) rather than to test the hypothesis that hospital IV therapy is necessarily better. The aim of our study was therefore ‘a real life evaluation’ of our daily practice as a test of quality control and not a prospective comparative study. The outcome of home IV-AB therapy in the treatment of lung infection in children and adolescents with cystic fibrosis was not inferior to hospital therapy when looking at lung function, weight and total IgG as outcome parameters. Selecting and preparing patients for home therapy may be an important factor for success.

Conflict of interest statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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