

CYSTIC FIBROSIS

Long term clinical outcome of home and hospital intravenous antibiotic treatment in adults with cystic fibrosis

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Background: Several studies have suggested that clinical outcomes in adults with cystic fibrosis (CF) are equivalent after home and hospital treatment with intravenous antibiotics, but these studies were small and selective and only considered one course of treatment.

Methods: A retrospective longitudinal study was performed to compare the clinical outcome over a period of 1 year of all patients attending the Manchester Adult CF Unit who received intravenous antibiotics at home or in hospital. The primary outcome measure was percentage change in forced expiratory volume in 1 second (FEV₁) at the end of the 1 year period. Baseline "best" and "average" FEV₁ values were established for each patient for the year before the study. The secondary outcome measures were percentage changes in forced vital capacity (FVC) and body weight.

Results: A total of 116 patients received 454 courses of intravenous antibiotics. At the end of 1 year there had been a mean percentage decline in FEV₁ compared with the baseline "average" for patients treated mostly at home but an improvement in patients treated mostly in hospital (Tukey's HSD mean difference 10.1%, 95% CI 2.9 to 17.2, $p=0.003$). For all patients there was a mean percentage decline in FEV₁ from the baseline "best" value. For each course of treatment the mean percentage improvements in FEV₁ at the end of the course from the start of the course were significantly higher for patients treated in hospital than for those treated at home.

Conclusions: Clinical outcome, as defined by spirometric parameters and body weight, was better after a course of treatment in hospital than after home treatment, and this benefit was maintained over 1 year of treatment. The results suggest that patients treated at home need closer supervision.

Patients with cystic fibrosis (CF) experience repeated infective respiratory exacerbations leading to a continued decline in lung function.¹ The exacerbations are treated with courses of intravenous antibiotics which may be administered in hospital or at home. Home treatment for CF is well established in the UK,² often driven by the lack of inpatient beds and the preference of patients. The cited advantages of home treatment are a reduced risk of cross infection, less time off work or school for patients, and improved quality of life.³ Twelve studies have compared home and hospital treatment in adults or children,^{2 4–14} but generally included only small numbers of patients and examined single courses of treatment with a limited range of antibiotic regimens, suggesting that the studies may not be representative of usual practice. A recent Cochrane Collaboration review of home and hospital treatment³ included only one randomised controlled trial⁶ and concluded that current evidence was too limited to draw conclusions for practice. A study to examine clinical outcome in patients after home and hospital treatment with intravenous antibiotics was therefore initiated. As patients receive repeated courses of treatment, the primary aim of the study was to compare outcome after 1 year.

METHODS

Study population

This retrospective, observational, 1 year pragmatic study was conducted in the Manchester Adult CF Centre, Wythenshawe Hospital, Manchester. Here the decision whether to treat at home or in hospital is made by the physician with the patient's agreement and the multidisciplinary team assesses patients for competency and likely adherence. All patients receiving intravenous antibiotics for a respiratory exacerbation were identified from the records of patients attending

the centre between September 2000 and September 2001. The study recruited adults (≥ 16 years) with a confirmed diagnosis of CF. Patients had to experience at least one respiratory exacerbation (defined as an increase in lower respiratory tract symptoms requiring treatment with intravenous antibiotics) during the 1 year study period. Patients were excluded if they received intravenous antibiotics for conditions other than respiratory exacerbations or if they received treatment at other hospitals (shared care). The data collected were patient demographics, microbiology, concomitant treatment, presence of diabetes, pregnancy, smoking, spirometric parameters, and body weight.

Assessment of outcome

The site of home or hospital treatment for each individual course of intravenous antibiotics was decided prospectively by the treating physician (AKW) with the agreement of the patient. Courses of intravenous antibiotics were categorised retrospectively by an independent investigator (JT) according to where the treatment started and regardless of any changes part way through the course. Thus, courses where treatment was started at home were categorised as home courses, and those where treatment started in hospital as hospital courses. Patients were then allocated retrospectively to treatment groups by the independent investigator according to where they received most treatment over the 1 year study period. Only a few patients received all of their treatment at home or in hospital over the 1 year study period, so "home" patients were those in whom the intention to treat had been home in $>60\%$ of courses, "hospital" patients were those in whom the

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity

intention to treat had been hospital in >60% of courses, and “both” patients were those in whom the intention to treat had been hospital or home in 40–60% of courses.

The primary clinical outcome variable was forced expiratory volume in 1 second (FEV₁). For home treatment, spirometric tests were performed at the start and end of each course of intravenous antibiotics. In hospital, spirometric testing was performed at admission, twice weekly, and at discharge. Two baseline FEV₁ values were established in each patient for the baseline year before the 1 year study period. The “best” FEV₁ was the highest FEV₁ during the baseline year and the “average” FEV₁ was the mean of all FEV₁ values recorded during this period. The percentage predicted FEV₁ was calculated for both values.¹⁵ Baseline forced vital capacity (FVC) and body weight values were also established and the percentage predicted FVC and body mass index (BMI, body weight in kg/height in m²) were calculated.

For each patient the final FEV₁, FVC, and body weight value were recorded as the last value of the last course at the end of the 1 year study period. The percentage changes in FEV₁, FVC, and body weight from baseline “best” to final and from baseline “average” to final were calculated. FEV₁, FVC, and body weight were determined for the start and end of each course of intravenous antibiotics. For each course the percentage changes from start to end were calculated.

Approval for the study was given by South Manchester local research ethics committee and patients were informed of the study by letter.

Statistical analysis

As the desired clinical outcome after treatment with intravenous antibiotics has not been quantified, it was not possible to perform power calculations to determine sample size. However, it was planned to recruit a cohort of 100 patients to the study and statistical advice confirmed that this number was sufficient when taking into account the aims of the study.

The differences between treatment groups at baseline were compared using independent sample *t* tests for continuous variables and χ^2 tests for nominal variables (SPSS version 11.5). Outcome was evaluated using analysis of variance (ANOVA) with interaction terms for potential confounding variables where appropriate. Multiple regression analysis was conducted to determine which patient characteristics might explain the decline in lung function (percentage decline in FEV₁ from baseline “average” to the end of the 1 year study period). The following variables were entered into the model: site of treatment (expressed as percentage of courses of intravenous antibiotics administered in hospital), sex and age of patient, infection with *Burkholderia cepacia*, presence of diabetes, concomitant treatment with rhDNase, nebulised antibiotics or oral corticosteroids, baseline “average” percentage predicted FEV₁, and baseline “average” BMI. The differences in outcome after one course of treatment were compared using independent samples *t* tests.

RESULTS

Patients and treatment

Of a total clinic population of 220, 120 patients received treatment with intravenous antibiotics during the study period and 116 of these (97%) were eligible for the study. Four patients were excluded for the following reasons: refused access to medical records, shared care, final FEV₁ value missing, or clinical records missing (one patient each).

The 116 patients underwent treatment with 454 courses of intravenous antibiotics during the 1 year study period. The mean number of courses per patient was 4 (range 1–9). The

mean and median course lengths were 15 and 14 days, respectively. A wide range of course lengths (3–172 days) was explained by some patients receiving almost continuous intravenous antibiotics. A total of 213 courses (46.9%) were classified as home courses and 241 courses (53.1%) as hospital courses. Forty seven patients (40.5%) were allocated to “home”, 51 (44.0%) to “hospital”, and 18 (15.5%) to “both”. Each group received similar amounts of intravenous antibiotic treatment during the study period (mean of 4, 3.6, and 4.5 courses in “home”, “hospital” and “both” groups, respectively).

At baseline there were no statistically significant differences between the three treatment groups (tables 1 and 2) other than more female patients in the “home” treatment group than in the “hospital” treatment group (*p* = 0.025).

Outcome after 1 year

All 116 patients were included in the analysis of outcome after 1 year. There was a mean percentage decline in FEV₁ at the final value compared with the baseline “average” value. There was a mean percentage decline in the “home” group but a mean percentage improvement in the “both” and “hospital” groups (*F* = 11.105, *p* = 0.001; table 3). The mean percentage improvement was significantly higher in the “hospital” group than in the “home” group (*p* = 0.003). FEV₁ declined at the final measurement compared with baseline “best” for all patients and for the “home”, “hospital”, and “both” groups (*F* = 4.479, *p* = 0.037; table 3), and there was a trend towards a significant difference between the “home” and “hospital” groups (*p* = 0.091).

Mean FVC improved compared with baseline “average” in “hospital” and “both” groups but declined in “home” patients (*F* = 13.843, *p* < 0.001; table 3). The mean difference between “home” and “hospital” patients was statistically significant (*p* = 0.001). The mean percentage decline from baseline “best” FVC was greatest in “home” patients and least in “hospital” patients (*F* = 5.182, *p* = 0.025), and there was a trend towards a significant difference between “home” and “hospital” treatment groups (*p* = 0.063).

Body weight improved compared with baseline “average” in all treatment groups except in the “home” group (*F* = 9.689, *p* = 0.002; table 3) and was significantly higher in the “hospital” patients than in the “home” patients. There was a mean percentage decline in body weight for all patients compared with the “best” values (*F* = 8.475, *p* = 0.004; table 3); this was significantly less in the “hospital” treatment group than in the “home” treatment group.

At baseline the only difference between the patient groups was the distribution of male and female patients with significantly more women in the “home” treatment group than in the “hospital” treatment group. The results of the interaction analysis showed a significant interaction effect between the site of treatment and the sex of the patient on the percentage change in FEV₁ from baseline “average” to final (*p* = 0.002). There was a mean percentage improvement in FEV₁ in hospital treated men (8.2%, 95% CI 3.0 to 13.5) but a mean decline in hospital treated women (−1.4%, 95% CI −7.7 to 4.9). The mean decline in home treated women (−3.4%, 95% CI −8.7 to 1.9) was less than for home treated men (−10.0%, 95% CI −17.0 to −3.0). There was no significant interaction effect on the percentage change in FEV₁ from baseline “best” to the final value. Similar results were noted for FVC. For both body weight outcome measures there was a significant interaction effect between the site of treatment and the sex of the patients on outcome. For percentage change in body weight from baseline “average” to final in women there was a mean loss of weight at home (−2.7%, 95% CI −5.5 to 0.1) but a mean gain in hospital (3.2%, 95% CI −0.2 to 6.6). For men the mean changes in

Table 1 Summary of patient characteristics

	All (N = 116)	"Home" (N = 47)	"Hospital" (N = 51)	"Both" (N = 18)
Mean (range) age (years)	26 (16–47)	26 (17–43)	26 (16–47)	25 (19–42)
Male/female (%)	50.0/50.0	36.2/63.8	58.8/41.2	61.1/38.9
Infecting micro-organism (N (%))				
<i>Pseudomonas aeruginosa</i>	103 (88.9)	43 (91.5)	42 (82.4)	18 (100.0)
<i>Burkholderia cepacia</i>	18 (15.5)	6 (12.8)	9 (17.6)	3 (16.7)
Other <i>Pseudomonas</i> spp	2 (1.7)	0	2 (3.9)	0
<i>Staphylococcus aureus</i> *	17 (14.7)	8 (17.0)	7 (13.7)	2 (11.1)
Other	51 (44.0)	19 (40.4)	24 (47.1)	8 (44.4)
Concomitant treatment (N (%))				
Nebulised rhDNase	75 (64.7)	30 (63.8)	32 (62.7)	13 (72.2)
Nebulised colistin	58 (50)	26 (55.3)	21 (41.2)	11 (61.1)
Nebulised gentamicin	9 (7.8)	6 (12.8)	2 (3.9)	1 (5.6)
Nebulised tobramycin	2 (1.7)	2 (4.3)	0	0
Oral antibiotics	104 (89.7)	43 (91.5)	45 (88.2)	16 (88.9)
Inhaled/nebulised corticosteroids	109 (94.0)	45 (95.7)	48 (94.1)	16 (88.9)
Regular oral corticosteroids	12 (10.3)	5 (10.6)	5 (9.8)	2 (11.1)
Inhaled/nebulised bronchodilators	113 (97.4)	44 (93.6)	51 (100.0)	18 (100.0)
Aminophylline, theophylline, salbutamol	73 (62.9)	26 (55.3)	36 (70.6)	11 (61.1)
Diabetes (N (%))				
Yes	31 (26.7)	14 (29.8)	15 (29.4)	2 (11.1)
Smoking (N (%))	N = 101	N = 39	N = 47	N = 15
Yes	13 (12.9)	6 (15.4)	6 (12.8)	1 (6.7)
Pregnancy (N (%))	N = 56	N = 29	N = 21	N = 6
Yes	4 (7.1)	1 (3.4)	2 (9.5)	1 (16.7)

*Including two patients with methicillin resistant *Staphylococcus aureus*.

body weight were -1.9% (95% CI -5.7 to 1.8) at home and 2.5% (95% CI -0.8 to 4.9) in hospital.

Outcome after one course

Out of 454 courses, start values were missing from 15 courses (3%) where the patient was too ill to perform spirometric tests and end values were missing from 20 courses (4%) where the patient did not return to the clinic after finishing a course of home treatment. The mean improvement in FEV₁ from start to end of a course was significantly greater for hospital courses than for home courses ($p < 0.001$; table 4). Secondary outcome variables reflected the results for FEV₁ (table 4).

Characteristics influencing outcome

Regression analysis confirmed that only the site of treatment had an effect on the percentage change in FEV₁ from baseline "average" to the end of the 1 year study period (coefficient = 0.09, 95% CI 0.020 to 0.160, $p = 0.012$). Other baseline characteristics had no effect on outcome.

DISCUSSION

This study shows that clinical outcome was better after a course of intravenous antibiotics administered in hospital than after a course administered at home. The benefit of hospital treatment was maintained over 1 year.

The Cochrane Collaboration review of home and hospital treatment recommended initiation of randomised controlled trials to compare the two approaches,³ but randomised controlled trials may not be appropriate to evaluate all situations.¹⁶ Because of the variation in severity of disease and the number of antibiotic regimens used for treating respiratory infective exacerbations in CF, a randomised controlled trial of home and hospital treatment may not reflect routine practice. Anecdotal evidence suggests that patients have strong preferences regarding site of treatment and refuse to be randomised, although it may be possible to build patient preferences into the trials.¹⁷ Furthermore, a randomised controlled trial may not be the best study design for patients with chronic or lifelong diseases such as CF as they rarely evaluate long term outcomes,¹⁸ and alternative study designs such as well conducted observational studies should be considered.

Lung function, particularly FEV₁, is the most important objective clinical outcome measure in CF and it is expected that FEV₁ will improve during a course of intravenous antibiotics. In practice, the main aim of treatment with intravenous antibiotics is to achieve and maintain the patient's best lung function. In this study both the highest and mean FEV₁ values were recorded for the baseline year. The mean value possibly represented the patient's everyday condition more accurately than the highest value as the mean baseline "best" value was approximately 20% higher than the

Table 2 Mean (SD) "best" and "average" values for lung function, body weight, and body mass index (BMI) for the three treatment groups during the 1 year baseline period

	"Home" (N = 47)		"Hospital" (N = 51)		"Both" (N = 18)	
	"Best"	"Average"	"Best"	"Average"	"Best"	"Average"
FEV ₁ (l)	2.2 (0.8)	1.9 (0.7)	2.1 (0.9)	1.8 (0.8)	2.4 (0.9)	2.0 (0.7)
% predicted FEV ₁	64.7 (22.4)	54.8 (19.0)	59.3 (22.1)	49.3 (18.6)	60.6 (19.1)	50.4 (16.0)
FVC (l)	3.3 (1.1)	2.9 (1.0)	3.6 (1.2)	3.0 (1.1)	3.6 (1.1)	3.1 (1.1)
% predicted FVC	82.6 (21.4)	72.4 (19.8)	84.2 (20.1)	71.5 (19.7)	78.7 (18.3)	67.5 (16.3)
Body weight (kg)	59.0 (9.6)	56.7 (9.1)	60.0 (12.5)	57.7 (12.0)	65.1 (14.9)	62.5 (14.6)
BMI (kg/m ²)	21.6 (2.8)	20.7 (2.6)	21.5 (3.4)	20.6 (3.2)	22.0 (2.6)	21.1 (2.6)

Table 3 Mean (SD) percentage change from "best" and "average" values for lung function and body weight to end of 1 year study period

	All (N=116)		"Home" (N=47)		"Hospital" (N=51)		"Both" (N=18)	
	"Best"	"Average"	"Best"	"Average"	"Best"	"Average"	"Best"	"Average"
% change to final FEV ₁	-16.1 (15.3)	-0.3 (15.5)	-19.5 (16.0)	-5.8 (15.0)*	-13.0 (15.7)	4.3 (16.4)*	-15.6 (9.9)	1.3 (9.1)
% change to final FVC	-11.8 (14.6)	2.2 (13.5)	-15.4 (16.8)	-3.0 (15.1)†	-8.7 (13.9)	6.7 (11.5)†	-10.9 (6.6)	3.1 (9.1)
% change to final body weight	-3.5 (8.4)	0.4 (8.1)	-6.2 (8.9)‡	-2.4 (8.5)§	-1.4 (7.2)‡	2.5 (7.0)§	-2.4 (8.4)	1.8 (8.3)

*Tukey's HSD mean difference 10.1% (95% CI 2.9 to 17.2), $p=0.003$.

†Tukey's HSD mean difference 9.6% (95% CI 3.5 to 15.8), $p=0.001$.

‡Tukey's HSD mean difference 5.0% (95% CI 1.2 to 8.7), $p=0.007$.

§Tukey's HSD mean difference 4.8% (95% CI 0.9 to 8.6), $p=0.012$.

mean "average" value. Thus, the most useful clinical outcome after 1 year was the comparison with baseline "average" FEV₁. During our study the mean lung function improved between the start and end of one course of treatment. However, over 1 year there was a mean decline in lung function compared with baseline "average".

In CF, inadequate caloric intake and/or malabsorption, increased energy loss, and increased energy expenditure are associated with pulmonary morbidity and mortality.¹⁹ There is a strong correlation between FEV₁ and BMI and lung function may impinge on weight gain because of increasing energy expenditure for the work of breathing.^{20–21} Lung infection and inflammation and treatment with antibiotics also increase energy expenditure.²² Patients with CF often lose weight when ill with a respiratory infection. In our study the changes in body weight reflected the changes in lung function.

An interesting finding in our study was the difference in outcome between male and female patients. It is interesting to speculate why outcome at home was better for women than for men; it is possible that women adhere better to home treatment. It is also noteworthy that there was a mean decline in FEV₁ both at home and in hospital for women. It is recognised that survival for women with CF is less than that for men.²³ One explanation which may be worth investigating further is that women respond less well than men to intravenous antibiotic therapy.

Although our study assessed only clinical outcome, it would have been interesting to record health related quality of life (HRQoL). However, HRQoL cannot be assessed retrospectively. A validated instrument sensitive to home and hospital treatment was not available at the start of the study.

A criticism often directed at comparisons of home and hospital treatment is that hospital treated patients have more severe disease than home treated patients. In this study there was no difference in baseline patient characteristics, lung

function, or body weight between the treatment groups and the regression analysis confirmed that the site of treatment was the only predictor of outcome. Some patients refused to be admitted to hospital for treatment even when very sick, and other patients who were less ill preferred hospital treatment for domestic reasons. Any possible bias in this study will be a result of the social and domestic circumstances of the patients.

Although most previous studies concluded that clinical outcome was at least equivalent after home and hospital treatment, three recent studies reported a significantly better improvement in lung function in hospital treated patients compared with home treated patients.^{7–14} Hospital patients would be expected to fare better than home patients for a number of reasons. Patients in hospital receive closer management of their condition from the multidisciplinary team with intensive physiotherapy, greater dietetic input, and close supervision and monitoring of spirometry and body weight (table 5).

The usual antibiotic combination is a β -lactam with an aminoglycoside. Although patients receive the same intravenous antibiotics at the same total daily dose at home as in hospital, some regimens for home administration are adapted to make administration more convenient for patients at home or work, but this may reduce effectiveness of treatment. For example, β -lactam antibiotics are administered three or four times daily in hospital but only twice daily at home (although the total dose is adjusted to be the same as in hospital). Most home treated patients have totally implantable intravenous access systems fitted and, although some antibiotics are known to be more effective when administered by continuous infusion, home treated patients usually prefer to use bolus injections.

Considerable commitment is expected from patients, but they choose home treatment in order to maintain family, work and/or education commitments. Adherence by CF patients with treatment in general is recognised as being

Table 4 Mean (SD) percentage change in lung function and body weight from start to end of one course of treatment

	All courses	Home	Hospital
% change in FEV ₁	N=423	N=192	N=231
Mean (SD)	22.6 (26.2)	16.3 (19.4)*	27.8 (29.7)*
% change in FVC	N=415	N=191	N=224
Mean (SD)	22.2 (29.0)	15.5 (19.3)†	27.9 (34.3)†
% change in body weight	N=385	N=172	N=213
Mean (SD)	1.5 (4.3)	0.5 (3.1)‡	2.4 (4.9)‡

*Mean difference 11.5% (95% CI 6.7 to 16.2), $p<0.001$.

†Mean difference 12.4% (95% CI 7.1 to 17.7), $p<0.001$.

‡Mean difference 1.9% (95% CI 1.1 to 2.7), $p<0.001$.

Table 5 Comparison of home and hospital management of respiratory exacerbations

	Hospital	Home
Lung function	Admission, twice weekly, and discharge	Start and end of course
Body weight	Admission, twice weekly, and discharge	Start and end of course
Physiotherapy	Twice daily	Self-performed Assessment and advice at beginning
Nutritional input	Yes	No
Multidisciplinary assessment	Admission, twice weekly and discharge	Start and end of course

poor and may potentially result in increased infective exacerbations leading to faster disease progression.²⁴ Adherence may be worse in some patients undertaking home treatment. For example, although the competency of home treated patients to perform airway clearance is assessed, the level of adherence is not known. In several of the published studies which showed equivalent outcomes after home and hospital treatment, patients were carefully selected for home treatment^{6-9,11} suggesting that these patients were better motivated and more likely to adhere to treatment than routine practice. Furthermore, home treatment may be counterproductive; patients prefer it because they can continue with work and a normal life but this means that they are not resting and may not be receiving optimal treatment. The Manchester CF Centre does not recommend rest for patients at home because generally the patients are trying to fit home treatment around their lifestyle.

Finally, all patients managed by the Manchester CF Centre prepare and administer their intravenous antibiotics themselves and usually rely on family or friends for help in the first instance. The specialist CF nurses provide patient led support and patients receive home visits from the CF specialist nurses on request, but do not receive any other nursing support from the hospital or community. In fact, patients have declined physiotherapy support at home, stating that they do not know until the actual day whether they need help or not. Failing patency of venflons is a frequent problem at home resulting in missed doses; patients are instructed to visit the nearest outpatient department for replacement.

There are a number of possible explanations as to why most previous studies have identified no difference in outcome. Our study included many more patients and courses of treatment than previous studies. The pragmatic design meant that patients were eligible who would have been excluded from previous studies. In addition, the study included all currently used drugs and doses and was not limited to certain antibiotic regimens.

Treating all patients in hospital is not possible because of insufficient numbers of beds and the preference of patients. Closer supervision of home treatment and physiotherapy may be needed to identify problems and increase adherence to treatment. Commercial homecare companies can supply a package of care including delivery of ready prepared infusion solutions, general and nursing support, and may offer an answer. However, these approaches to improve support for home treated patients have resource implications for hospitals and the health service.

In conclusion, the present study shows that, after treatment with intravenous antibiotics for infective respiratory exacerbations in patients with CF, the long term clinical

outcome is better in patients treated in hospital than in those treated at home. As it is impossible to treat all patients in hospital, these findings suggest that more intensive supervision at home may be needed.

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