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Journal of Cystic Fibrosis 10 (2011) 175 – 180

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Original article

Economic effects of an eradication protocol for first appearance of *Pseudomonas aeruginosa* in cystic fibrosis patients: 1995 vs. 2009

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Received 10 July 2010; received in revised form 8 January 2011; accepted 10 January 2011

Abstract

Background: Acquisition of Pseudomonas aeruginosa (Psa) and infection with mucoid strains is associated with repeated pulmonary exacerbations which often require intravenous and long-term nebulised antibiotic treatments, repeated hospitalizations and leads to a more precipitous decline in lung function. Anti-Psa antibiotic therapy early in the course of Psa infection in patients with cystic fibrosis (CF) may result in eradication of Psa and prevention or delay of colonization with the organism. From January 1995 to December 2009 our paediatric CF clinic has followed an early eradication protocol for the first appearance of Psa. In this paper we report on the economic effects after 15 years as reflected in hospitalization and antibiotic usage and cost.

Methods: The Psa-eradication protocol includes 2 weeks of IV piperacillin and tobramycin, followed by oral ciprofloxacin for 3 weeks, and nebulised colistimethate for 6 months. The same protocol is used for newly diagnosed CF patients who grow Psa on their first visit or who grow a mucoid strain, multiresistant strain of Psa or whose Psa co-cultured with Burkholderia cepacia complex, and for patients in whom Psa recurs after initial clearance.

Results: 195 Psa eradication courses were completed from 1995 to 2009 with an overall Psa clearance rate of 90%. Patients that only cultured a Psa classic (non-mucoid) strain had a clearance rate was 96.5%. The percentage of children chronically infected with Psa has declined from 44% in 1994 to 15% in 2009.Total days spent in hospital for all reasons declined by 43%; chronic Psa hospital days declined by 75%; IV and nebulised anti-Psa antibiotic costs reduced by 44%.

Conclusions: Results indicate that application of a Pseudomonas eradication protocol as described in this report has economic and resource utilization benefits in addition to clinical benefits.

Keywords: Pseudomonas aeruginosa; Eradication; Economic; Cost; Hospitalization; Antibiotics

1. Introduction

Pseudomonas aeruginosa (*Psa*) is the predominant pathogen affecting patients with cystic fibrosis (CF) [1]. Cystic fibrosis patients infected with *Psa* have increased pulmonary disease and experience more rapid decline in pulmonary function than patients who are *Psa* culture and antibody negative [2–6]. Acquisition of *Psa* and subsequent chronic infection with mucoid strains result in repeated pulmonary exacerbations, which often require intensive intravenous (IV) and long term nebulised antibiotic treatments, repeated hospitalizations and despite these interventions, are likely to have a more precipitous decline in lung function over time.

Since the initial report by Littlewood et al. [7] evidence suggests that anti-*Pseudomonas* antibiotic therapy early in the course of *Psa* infection may prevent or delay chronic infection. Several early eradication protocols and randomized clinical trials report a delay in chronic infection with *Psa* and in some cases achieved eradication [7–13].

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doi:10.1016/j.jcf.2011.01.002

Since 1995 our paediatric CF Clinic has followed an early eradication protocol for initial appearance of *Psa*. Successful implementation of this protocol has required a paradigm shift from symptom-triggered treatment to microbial culture-based pre-symptomatic therapy, and "buy-in" from patients and clinic staff alike; having a significant impact on our clinic. In this paper we report the economic effects of this protocol after 15 years of implementation, as reflected by hospitalization and antibiotic usage and cost.

2. Patients and methods

CF patients ages newborn to 18 years (demographics for patient cohorts in 1994, 2000, 2005, 2008 and 2009 shown in Table 1) attend the CF outpatient clinic every 3–4 months, or more frequently if clinically indicated. Sputum, or throat culture if sputum is not produced, is taken at every clinic visit in conjunction with airway clearance, performed under the supervision of a CF physiotherapist. Growth and nutritional parameters are recorded and reviewed by the CF clinic dietician. Pulmonary function testing is performed at each visit in all children $\geq$6 years of age.

The protocol includes:

- 2 weeks of IV piperacillin (600 mg/kg/day divided q6h) and tobramycin (12 mg/kg/day divided q8h)
- followed by oral ciprofloxacin (30 mg/kg/day) for 3 weeks
- and nebulised colistimethate (100 mg of colistin base bid) for 6 months.

IV access over the 2-week course is secured by the insertion of a midline or PICC line. Tobramycin peak and trough serum levels are checked after the third dose, and then weekly to ensure that optimal therapeutic and non-toxic drug levels are achieved. Aminoglycoside ototoxicity and nephrotoxicity are monitored through audiology and renal function testing (serum creatinine and nuclear GFR). Sputum, or a throat culture if the patient is non-productive, is obtained at the start of treatment, weekly while receiving IV antibiotics, one month after completion of the IV course, and thereafter at regular 3-monthly CF clinic visits. Physiotherapy technique is reviewed and treatments are maintained three times daily. Nutritional support is optimized and daily IV lipids administered while the patient is on IV antibiotics, in addition to a high calorie, high protein diet plus pancreatic enzymes. Although it is technically possible to carry out this regimen at home, the cost and limited access to home IV services, coupled with difficulties in monitoring patients at home given the large geographic area served by the clinic (approximately 364,800 sq. miles), limited family time available when both parents work outside the home, and perceived benefits of intensive review and physiotherapy supervision by clinic staff in hospital has meant that 189 of the 195 (97%) IV courses were given in hospital followed by administration of oral and nebulised antibiotics at home.

Table 1
Clinic patient demographic data by age cohort.

Age cohort	1994	2000	2005	2008	2009
0–6 yr	45	37	47	29	34
7–12 yr	44	45	39	41	45
13–18 yr	41	48	61	54	44
Total # of clinic patients M/F	130	130	147	124	123
	68/62	70/60	72/75	69/55	68/55
# of *Psa* eradication treatments/year	None	10	12	23	10

Newly diagnosed CF patients who grew *Psa* on their first clinic visit (n=11) were also treated with this eradication protocol, in addition to 6 patients who grew a mucoid strain at their first appearance of *Psa*, and 9 patients whose initial cultures either grew a multi-resistant strain of *Psa*, or whose *Psa* co-cultured with *Burkholderia cepacia complex.* The same protocol is repeated for patients in whom *Psa* recurred at a later time after their initial clearance of *Psa* (n=75). Overall results include all of these patients. Clearance of *Psa* is defined as 3 negative consecutive cultures for *Psa* over a 6 month period with a minimum interval of 3 months between cultures. Chronic infection is defined as more than 50% of cultures being *Psa* positive in the preceding year (Leeds criteria) [15,16].

Inpatient and outpatient antibiotic costs of anti-*Pseudomonas* IV and nebulised medications were obtained annually through analysis of pharmacy records. Hospital patient days for pulmonary exacerbations with *Pseudomonas* infection and *Pseudomonas* eradication protocols were obtained from retrospective review of hospital records. Hospital per diem cost was calculated using 1994 rates and for comparison purposes was not adjusted for inflation.

3. Results

3.1. Efficacy

A total of 195 *Psa* eradication courses have been completed during the period from January 1995 to December 2009, with an overall *Psa* clearance success rate of 90%. When only *Psa* classic (non-mucoid strain) was cultured (n=87), the clearance rate was 96.5%. As a result of this intervention the percentage of all clinic patients chronically infected with *Psa* has declined from 44% in 1994 to 29% in 2000, 18% in 2005, 14% in 2008 and 15% in 2009 (Fig. 1). The mean age at first culture of *Psa* was 7 years (range 6 months to 16 years of age). The number of *Psa* eradication courses per year is shown in Table 1.

Of the 195 *Psa* eradication treatment courses, 176 were *Psa* culture negative after completion of the antibiotic course. Cultures were monitored a minimum of every 3 months for up to 150 months (12.5 years). When expressed as median time to recurrence (Kaplan–Meier plot), the T ½ was 30 months (T ½=the time at which half of the treated patients showed a re-growth of *Psa*) (Fig. 2) [18]. 30% re-cultured *Psa* after a median interval of 18 months (range 11 to 72 months). Some patients remain *Psa* negative on follow up for up to 150 months. After intensive *Psa* treatment protocol, surveillance for the presence of other

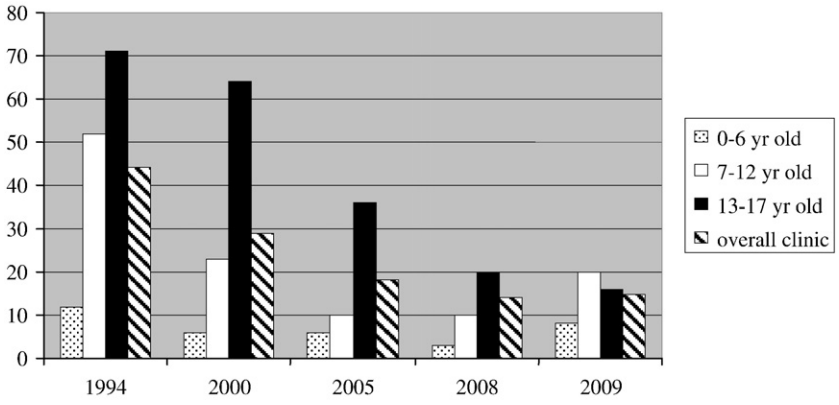

Fig. 1. Percent chronic *Pseudomonas aeruginosa* infection rate by age cohort.

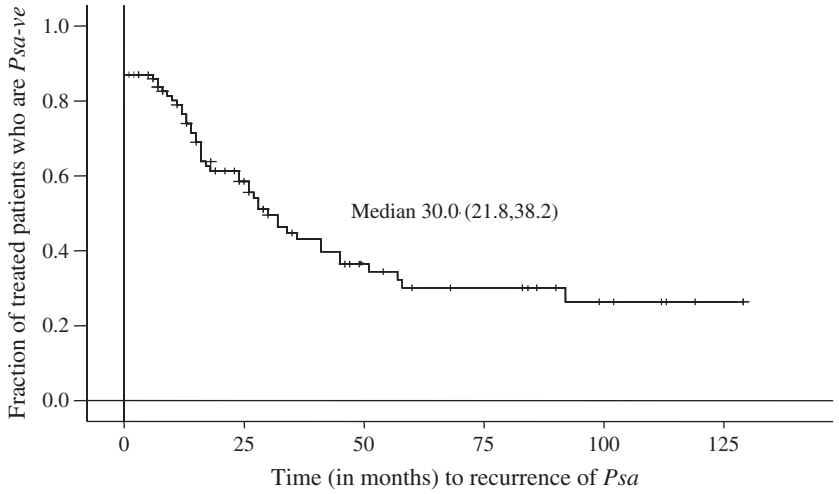

Fig. 2. Kaplan–Meier plot of time to recurrence of *Pseudomonas aeruginosa* [18].

respiratory organisms is the same as 1 year prior to the emergence of *Psa* (Fig. 3) when reviewed retrospectively for up to 7 years [19]. Pulmonary function (FEV_1 % predicted) decline per year is less precipitous in patients who are *Psa* negative (−0.63% predicted/yr) compared to those chronically infected with *Psa* (−1.31% predicted/yr) (Fig. 4) [18].

3.2. Safety

No serious adverse events occurred as a result of this treatment protocol. Four patients developed skin sensitivity reactions which subsided upon substitution of meropenem for piperacillin. No significant renal function abnormalities were

Organism	1 yr pre-treatment n=31 patients	1 yr pre-treatment (160 cultures)	Isolate at time of *Psa* appearance (49 cultures)	Post-treatment (531 cultures)
*			*Psa* only 29%	
Staphylococcus aureus	38% of patients	58% of all cultures	57% of all cultures	62% of all cultures
Candida	13	10	14	18
Haemophilus influenzae	18	20	8	6
S. maltophilia	7	5	6	4
Aspergillus fumigatus	4	1	6	3
Acinetobacter	2	1	0	1
Alcaligenes xylosoxidans	<1	<1	0	1
B. cepacia complex	2	1	1	1
MRSA	0	0	0	<1
Atypical mycobacterium	0	0	0	<1

Fig. 3. Surveillance of other organisms 1 yr pre-*Psa* treatment and post treatment [19].

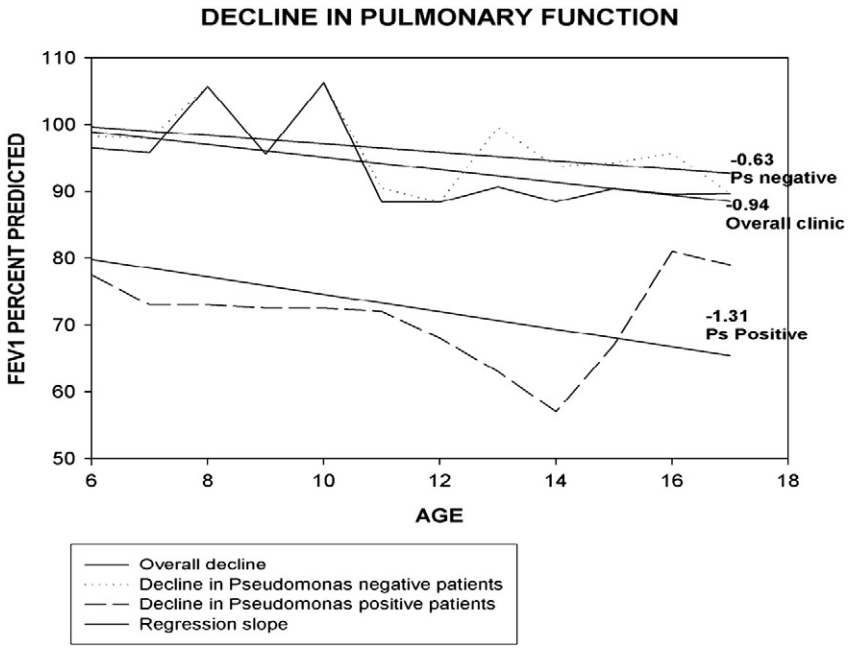

Fig. 4. Effect of *Psa* on annual decline in pulmonary function (FEV_1 % predicted) for 2007.

encountered after protocol treatment courses of intravenous aminoglycoside exposure. These results have recently been analysed and reported for the period January 2006 to May 2009 using ^{99m}Tc-DPTA nuclear GFR, annual urinalysis, and serum creatinine and urea measurements [14]. No resistant strains of *Psa* emerged as a result of treatment.

3.3. Cost benefit

Since instituting this early eradication protocol, the decreasing number of CF patients chronically infected with *Psa* has had an impact on hospital admissions, days in hospital (Table 2) and use of anti-pseudomonal antibiotics (Table 3). Although criteria for admission have not changed, total days spent in hospital for all reasons have declined from 1753 in 1994, to 1855 in 2000, 1285 in 2005, 1130 in 2008 and 991 days in 2009. Patients with chronic *Psa* accounted for 990 hospital days in 1994, 980 days in 2000, 550 days in 2005, 290 days in 2008 and 241 days in 2009. In 2008 the majority of the chronic *Pseudomonas* patient hospital days (225 days) were due to 4 patients, 2 of whom were being assessed for lung transplant and required several hospital admissions during the year. In 2009 *Psa* eradication protocol admissions accounted for 134 hospital days (13% of total hospital days) in 10 patients.

The cost from total hospital days for all CF related admissions (Table 4) declined from $3.85 million CAD in

Table 2
1994 vs. 2009 Comparison of patients chronically infected with *Pseudomonas* and hospital day utilization.

Year	% of clinic patients chronically infected with *Pseudomonas aeruginosa*	Hospital days for patients with chronic *Pseudomonas* (% of total hospital days)	Hospital days for *Pseudomonas* eradication protocols (% of total hospital days)	Total *Psa*-related hospital days	Total hospital days
1994	44	990 (56%)	None	990	1753
2000	29	980 (53%)	130 (7%)	1110	1855
2005	18	550 (43%)	168 (13%)	718	1285
2008	14	290 (26%)	330 (29%)	620	1130
2009	15	241 (24%)	134 (13%)	375	991

Table 3
Cost of intravenous and nebulised anti-*Pseudomonas* antibiotics.

Year	$ IV anti-*Psa* antibiotics for chronic *Psa* and eradication treatment protocols	$ Nebulised antibiotics for chronic *Psa*		$ Nebulised antibiotics for eradication 6 month treatment protocol (at home)	$ Total nebulised antibiotic cost	$Total IV and nebulised antibiotic cost
		In hospital	At home			
1994	$94,000	$39,000	$600,000	–	$639,000	$733,000
2009	$40,000	$11,700	$260,000	$100,000	$371,700	$411,700
% decrease 1994–2009	57%	70%	56%	–	42%	44%

Table 4
Hospital utilization costs based on an estimated average cost of $2200 CAD[a]/day.

Year	Cost for all CF admissions (average cost of $2200 CAD[a]/day)	Cost for pulmonary exacerbations related to chronic *Pseudomonas* infection (average cost of $2200 CAD[a]/day)
1994	$3.85 million (1753 days)	$2.17 million (990 days)
2000	$4.08 million (1855 days)	$2.15 million (980 days)
2005	$2.83 million (1285 days)	$1.21 million (550 days)
2008	$2.48 million (1130 days)	$638,000 (290 days)
2009	$2.18 million (991 days)	$530,200 (241 days)
% decrease 1994–2009	43%	75%

[a] Based on 1994 daily hospital bed cost.

1994 to $2.18 million in 2009 (based on 1994 costs), a 43% decrease. Those hospital bed costs for pulmonary exacerbations in patients with chronic *Pseudomonas* infection reduced from $2.17 million in 1994 to $530,200 in 2009.

Similarly, the in-hospital IV anti-pseudomonal antibiotic use declined from approximately $94,000 a year in 1994 to $40,000 a year in 2009 (this includes both the cost of IV eradication protocol treatments and treatments for pulmonary exacerbations due to chronic *Psa* infection). In-hospital use of nebulised colistimethate for patients with chronic *Psa* also decreased from approximately $39,000 per year in 1994 to $11,700 per year in 2009.

Costs for home nebulised antibiotics also decreased, with 19 patients receiving either nebulised colistimethate or TOBI® for chronic *Psa* in 2009 at a cost of approximately $260,000 per year. Home use of nebulised colistimethate for 6 months as per our eradication protocol came to a cost of $100,000 in 2009. The total cost for home nebulised antibiotics for both chronic *Psa* and *Psa* eradication protocols was $360,000 in 2009. This compares to a home antibiotic aerosol cost of $600,000 in 1994 for chronic *Psa* alone (Table 3). (28 day cost of TOBI® = $2835 CAD, 28 day cost of colistimethate = $1156 CAD).

4. Discussion

Over a 15 year period of close surveillance for the appearance of *P. aeruginosa,* this protocol for the first appearance of *Psa* and repeat treatments upon the reappearance of *Psa* has decreased the prevalence and delayed the establishment of chronic *Psa* infection in our paediatric clinic. Eradication treatment courses were well tolerated, and provided an opportunity to optimize nutritional support, provide physiotherapy review and supervision, and reinforce adherence. This was a retrospective review and therefore patient questionnaires or QOL data was not available.

During this reporting period, the clinic population's acceptance of this treatment protocol was noteworthy in an era when early eradication of *Psa* was not yet considered standard of care for CF. Patients and families were given a full explanation of the rationale of the protocol, and notified that success could not be guaranteed. Over time, however, the success of the protocol became an accepted norm for the clinic.

In addition to its putative effects on improved life expectancy, quality of life, and maintenance of pulmonary function, this *Psa* eradication protocol has had an impact on hospital bed utilization and use of IV and nebulised anti-*Psa* antibiotics. Intravenous and aerosol antibiotic costs during hospital admission are borne by Canada's universal health care system. However, the cost of home use for these medications must be borne by families with varying degrees of support from "pharmacare" or other insurance plans. Overall, therefore, the decrease in costs observed is of benefit to both public funding agencies and to families, and is one of the factors contributing to the continued acceptance of this protocol by clinic families.

The long term effect on the prevalence of chronic *Psa* infection among CF patients depends on the overall efficacy of the eradication regime employed. The clearance rate of 90% for all patients, and 96% for patients only infected with a classic (non-mucoid) strain of *Psa* is reflected in the decrease in the overall prevalence of *Psa* infection in the entire clinic from 44% in 1994 to 15% in 2009. In the 2008 Canadian Cystic Fibrosis Patient Data Registry (CPDR) [17] the prevalence of *P. aeruginosa* in 11–17 years old patients is 40%, compared to 18.7% in that same cohort of patients in our CF clinic. Similarly, pulmonary function is maintained when there is less chronic *Psa* infection as shown in the cohort of 18 year old patients graduating to our colleagues at the Adult CF Clinic (Table 5).

Other protocols not requiring IV antibiotics for the initial stage have been described but insufficient data have yet to be reported with which to compare long-term results. Different regimens may be better suited for specific population groups; for example outpatient nebulised antibiotic regimens for adults not able to take time away from work; or newborns identified by Newborn Screening Programs with close surveillance of cultures for the first appearance of *Psa. Psa* antibody and/or *Psa* RAPD type guided eradication protocols may assist in optimizing efficacy and long term outcome. The ELITE trial has reported a 92% clearance rate for *Psa* in 88 of 123 CF anti-*Psa* antibody negative patients 1 month after treatment with inhaled TOBI [13]. This trial represents a far less intensive initial treatment regimen and reduced burden to patients and families. However, if the ELITE results had been analysed on an intent-to-treat basis for all 123 patients enrolled, presumably the results would be less satisfactory.

In this report, we have presented the long term results of a review of costs associated with *Psa* acquisition in CF. Results indicate that application of our eradication protocol over a 15 year period has had economic and resource utilization benefits in addition to clinical results. This was a retrospective study with no control or comparator group and therefore

Table 5
Pulmonary function and chronic *Psa* infection for 18 yr old patients at time of Graduation to the Adult CF Clinic 2005–2009.

Outcome	2005	2006	2007	2008	2009
Number of graduates	6	12	13	13	8
Mean FEV_1 % predicted	77	76.2	78.8	89.3	94.1
Psa culture positive (%)	50	66	46.6	39.5	12.5

FEV_1, forced expiratory volume in 1 s.

interpretation of the data is site specific. Future development of more effective protocols is desirable as it impacts the long term prevalence of *P. aeruginosa* and the subsequent cost of drug and hospital bed utilization as well as the clinical status of CF patients.

Acknowledgements

The authors wish to acknowledge the valuable help and advice of members of the CF Clinic at BC Children's Hospital, especially Shelagh Jenkins, Anna Gravelle, Maggie McIlwaine and Dr. Mark Chilvers. We are also grateful to Dr. Ruth Milner for statistical support.

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