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Towards zero prevalence of chronic *Pseudomonas aeruginosa* infection in children with cystic fibrosis☆

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Abstract

Background: Data from the Belgian Cystic Fibrosis Registry consistently show that in one of the seven reference centres, the prevalence of *Pseudomonas aeruginosa* is half that observed at the national level.
Objectives: To report the characteristics of non-transplanted patients in this clinic at the end of 2003, with special focus on paediatric patients. To describe and discuss our policy of inhaled antibiotic therapy.
Findings: The prevalence of *P. aeruginosa* among 116 patients is 20.7%. The chronic colonization rate is 19.8% but only 2.8% in patients aged under 18 ($n=72$). Serologic data strongly support these results. Most paediatric patients (95%) are prescribed inhaled antibiotics, at least on an intermittent basis but the mean number of days of intravenous antibiotic treatment is four times lower than in other CF children in Belgium. 70% of children have an FEV1 $\geq$ 90% predicted.
Discussion: We have reported a distinctly low rate of chronic colonization by *P. aeruginosa* in a cohort of CF children and suspect that a strategy of early, often «prophylactic» use of inhaled antibiotics, progressively implemented for over 15 years has substantially contributed to these results. Given the major impact of chronic *P. aeruginosa* colonization on prognosis in CF, it is suggested that a large prospective study of this approach is warranted.

Keywords: Cystic fibrosis; *Pseudomonas*; Inhaled antibiotics; Prophylaxis

1. Introduction

In cystic fibrosis (CF), the prevalence of the respiratory pathogens may vary considerably from one country or centre to another, probably reflecting differences in patient monitoring, cohort isolation and antibiotic treatment policies [1,2]. One of the aims of Cystic Fibrosis registries is to identify differences in meaningful parameters between centres as analysis of their determinants can result in improvements in care [3].

Data from the Belgian CF registry [4] consistently showed that in one of the seven Belgian cystic fibrosis reference centres, the prevalence of PA was particularly low, around 25%, roughly half that observed at the national level. This finding was accounted for by a very low prevalence of PA in paediatric patients. Data also suggested that a specific, often prophylactic, antibiotic treatment strategy might have contributed to this particularity.

To the best of our knowledge, such a low prevalence of PA in a CF clinic has not been reported previously. The aim of this retrospective work is to describe the characteristics of this clinic at the end of 2003 with special focus on the paediatric patients, to specify the rate of chronic coloniza-

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tion by PA in these patients and to discuss the modalities of inhaled antibiotic therapy we progressively chose to implement from 1986 onwards.

2. Methods

A retrospective analysis of data from all patients receiving full-time care at the UCL centre (Cliniques St Luc-Brussels) in 2003 was undertaken, using the unit-specific database, patients' medical files and the Microbiology Department's database. Patients who had benefited from a lung transplant were excluded. Criteria for the diagnosis of cystic fibrosis met current consensus [5].

Since the clinic opened in 1986, standard practice with these patients has been to get a respiratory culture performed at every clinic visit, with no more than 3 months between visits. Patients who do not expectorate spontaneously undergo a full session of physiotherapy, after which either expectorations are obtained or a deep pharyngeal aspiration is performed, as recommended [6]. PA is isolated from samples using standard microbiological methods [7]. As soon as the bacteriological results are available, patients always receive, along with their prescriptions, written instructions detailing recommended antibiotic treatment and reminding them to stop it if possible at least 4 days before their next visit. Lung health is ascertained using the surrogate marker of FEV1. Spirometry is routinely performed at each consultation (Jaeger Masterscope, Würzburg, Germany). From the age of 6, Knudson's reference values are used [8]. These have been criticized [9] but they permit comparisons with both North American and Belgian registers. PA prevalence was determined for each year between 1999 and 2004 and defined as the percentage of PA-positive cultures at the last visit of the year. Status of PA infection was defined using Lee's classification [10] which takes into account the results of all cultures performed over the previous 12 months. Each successive calendar month is defined as: (1) PA+ (one or more PA-positive cultures that month), (2) PA− (all cultures that month negative for PA), or (3) no culture performed that month. Patients are then categorized as: (1) "Never" (never any PA growth), (2) "Free" (no growth of PA during the previous 12 months but previously PA culture-positive, (3) "Intermittent" (50% or less months when samples had been taken that were PA culture-positive), or (4) "Chronic" (more than 50% of months when samples had been taken that were PA culture-positive).

At the end of 2004, PA serology was investigated in all patients, using an Elisa technique to determine IgG levels against a whole cell protein extract kindly provided by N. Høiby (Rigshopitalet, Copenhagen, Denmark). High IgG levels with this method are strongly associated with chronic colonization [11]. When comparing its results and Lee's criteria in 162 CF patients at another clinic, a cut-off level of 17 AU was shown to predict chronic colonization by PA with high sensitivity and specificity (88% and 96% respectively) [12].

The modalities of inhaled antibiotic therapy prescribed to patients at the end of 2003 have been summarized and related to their bacteriological status. Annual data reports from the Belgian Cystic Fibrosis Registry [4] enabled us to compare prescribing patterns of therapeutic interventions at St Luc with those at other centres. Additional data about cohorting policies and intervention in the case of first PA isolate were collected by the means of a brief questionnaire sent to pulmonologists of the other Belgian centres.

Unpaired Student's *t*-test and Chi-square or Fischer's Exact Test were used for statistical analysis. *p* values lower than 0.05 were considered significant.

3. Results

During the past 6 years, the prevalence of PA in CF patients at St Luc has been low: 24.5% in 1999, 24.4% in 2000, 28.8% in 2001, 21.6% in 2002, 20.7% in 2003, 15% in 2004 ($n = 130$).

Table 1 summarizes the main characteristics of the 116 non-transplanted patients receiving full-time care at St Luc at the end of 2003.

Table 2 summarizes bacteriological data in our clinic at the end of 2003. According to Lee et al. [10], the rate of chronic PA colonization is 19.8%. It attains 47.7% in adults, but is only 2.8% in patients aged under 18, (2/72: one 16-

Table 1
Characteristics of patients treated at the St Luc clinic at the end of 2003[a]

	All	<18 years old	≥18 years old
Number	116	72	44
Number of males (%)	58 (50)	37 (51.4)	21 (47.7)
Average age, in years (±S.D.)	16 (±10.8)	9 (±4.9)	27.5 (±7.7)
≥18 years old (%)	38		
Median age at the time of diagnosis, in months	7.4	4.3	24
Average period of time between diagnosis and first appointment at the St Luc centre, in years (±S.D.)	4.4 (±6.7)	1.5 (±3)	9.1 (±8.3)
Median period of time between diagnosis and first appointment at the St Luc centre, in years	0.4	0.1	8.4
% of patients having received full time care at St Luc <2 years after diagnosis	56.9	79.2	20.4
PS[b] (%)	19	15.3	25
Genotyped (%)	100	100	100
ΔF508/ΔF508 (%)	54.3	55.6	52.3
Meconial ileus (%)	16.4	20.8	9.1
Average FEV1 in % pr. (±S.D.)	82 (±23%)	94 (±14.2)	67 (±22.8)

[a] Patients with lung-transplant are excluded.
[b] PS: pancreatic sufficient (no need for pancreatic enzyme substitution).

Table 2
Summary of bacteriological data of 116 non-transplanted patients at the end of 2003

	<18 years	≥18 years	Whole clinic
N	72	44	116
Chronic colonisation by PA (according to Lee) (%)	2.8	47.7	19.8
Last visit			
Normal flora or sterile (%)	80.6	18.2	56.9
PA (%)	2.8	50	20.7
Mucoid strain	–	13.6	5.2
MSSA (%)	8.3	22.7	13.8
MRSA (%)	1.4	4.5	2.6
Hemophilus influenzae (%)	1.4	–	0.9
Aspergillus (%)	9.7	29.5	17.2
Stenotrophomonas maltophilia (%)	1.4	11.4	5.2
Achromobacter xylosoxidans (%)	1.4	6.8	2.6
BCC (%)	–	2.3	0.9
B cenocepacia	–	–	–

year-old patient colonized for 5 years when he first attended the clinic and another 16-year-old patient who was lost at follow-up for 15 months and was colonized on his return to the centre). Among paediatric patients, PA antibodies levels suggestive of chronic colonisation were only found in these 2 patients. Mean (±S.D.) values (AU) for "chronic", "intermittent", "free" and "never" patients were 25±8.5, 2±3.1, 2.8±3.7 and 1.3±2.5, respectively. Chronic colonization by PA in adult patients was often established when they first attended the clinic (11/21, 52.3%).

In contrast, PA prevalence at the national level was 48% in 2000. The median age of patients at St Luc (14.6 years) (2003) is comparable to that at national level (14.7) (2001), as are the proportion of adult patients (38% vs. 39.6%), the proportion of patients homozygous for the ΔF508 mutation (54.3% vs. 55.4%), the meconial ileus rate (16.4% vs. 15.6%), the average number of annual outpatient visits by a pulmonologist (5.2) and the rate of DNase prescription (41% vs. 49.4%). The proportion of PS patients is higher at St Luc than in the register as a whole (19% vs. 11.4%). Inhaled steroids (54% vs. 35.1%) and bronchodilators (92% vs. 59.4%) were more often prescribed at St Luc. More strikingly, although PA prevalence was half at St Luc, inhaled antibiotics were more often prescribed at the last visit of the year (89% vs. 43.7%).

Detailed data concerning the mean number of days of intravenous antibiotic treatment in CF children were available in the Belgian registry for 2003 and 2002. This number was significantly lower at St Luc (1.34 and 1.25, respectively) than for the children followed elsewhere (5.15 and 5.4, respectively, $p<0.001$).

At the end of 2003, the average FEV1 (±S.D.) of patients aged between 6 and under 18 is 94% predicted (±14.7). FEV1 is ≥90% predicted in 70% of these children, 40–69% predicted in 6.2%. No child has an FEV1<40% predicted.

Table 3 describes the modalities of inhaled antibiotic therapy prescribed to the 72 paediatric patients at their last visit in 2003. When continuous inhaled antibiotic therapy is prescribed, the period of time during which this treatment is taken is specified. Intermittent inhaled therapy almost always refers to a treatment to be initiated for 3 weeks (usually together with oral amoxiclav) in case of other than trivial presumed viral upper airway infection.

At the end of 2003, 94.4% of patients aged under 18 were on intermittent or continuous inhaled antibiotic therapy. Inhaled antiobiotics prescribed to paediatric patients were as follows: TOBI (2/68: 2.9%), Colimycin alone (only if *Pseudomonas aeruginosa* had been isolated previously, 11/68: 16.2%), injectable forms of tobramycin (28/68: 41.2%) and Amikacin (27/68: 39.7%). In all cases, an inhaled bronchodilator was also prescribed. Except in the case of TOBI, antibiotics and salbutamol were mixed which has been shown to be acceptable [13] and saved nebulization time. The daily dose of tobramycin (or amikacin) prescribed was low in comparison with TOBI, around 5–10 (15–30) mg/kg/day (Table 4).

Most children (68%) used an ultrasonic nebulizer (devices without direct contact between crystal and drugs – mainly Systam brand). The others used a mechanical compressor (mainly Pari Turbo boy with Pari LC+nebulizer or Porta Neb+Ventsream nebulizer). Use of a mouthpiece (rather than a facemask) was repeatedly encouraged from age 4.

Strict segregation of patients on a bacteriological basis including in the outpatient setting was applied in 5 of the 6

Table 3
Modalities of inhaled antibiotic therapy prescribed for the 72 paediatric patients at the end of 2003, based on their bacteriological status according to Lee et al.

Lee's classification		Inhaled antibiotic therapy			Continuous inhaled antibiotic therapy[a]	
		No	Intermittent	Continuous	Duration in years (mean±S.D.)	Range
	n (%)	*n* (%)	*n* (%)	*n* (%)		
Chronic	2 (2.8%)	0	0	2 (100%)	[b]	
Intermittent	5 (6.9%)	0	0	5 (100%)	2±1.9	(0.4–4.2)
Free	27 (37.5%)	2 (7.4%)	3 (11.1%)	22 (81.5%)	3.2±1.4	(1.1–6)
Never	38 (52.8%)	2 (5.3%)	10 (26.3%)	26 (68.4%)	2.4±1.3	(0.9–5.6)
Total	72 (100%)	4 (5.5%)	13 (18.1%)	55 (76.4%)		

[a] In many cases preceded by a long period of intermittent inhaled antibiotic therapy.
[b] As soon as a patient was regarded as chronically colonized, continuous inhaled antibiotic therapy was always prescribed.

Table 4
Usual dosages of prophylactic inhaled antibiotics at St Luc

Tobramycin (80 mg/2 ml)	4–8 kg	20 mg twice a day	5–10 mg/kg/day
	8–15 kg	40 mg twice a day	5.3–10 mg/kg/day
	15–30 kg	80 mg twice a day	5.3–10.6 mg/kg/day
Amikacin (500 mg/2 ml)	30–50 kg	250 mg twice a day	10–16.7 mg/kg/day
	>50	500 mg twice a day	<20 mg/kg/day
Colomycin		500,000–1,000,000 U twice a day	

other centres with 3 having implemented it for 6–10 years. In none of the 5 largest centres was intravenous antibiotic treatment prescribed as the first-line intervention in the case of first isolation of PA.

4. Discussion

The PA prevalence reported here is particularly low, half that observed at the national level which is itself in keeping with current data from other European countries and US [14–17]. More importantly, the rate of respiratory chronic colonization by this pathogen is very low in paediatric patients, almost 6 times less than that recently reported using the same definition by Lee et al. [18]. The interest of these data lies in the well-established negative impact of chronic PA colonization on prognosis in cystic fibrosis patients. Chronic PA colonization is associated with a lower FEV1 in childhood [19], an accelerated rate of decline of FEV1 [20–22] and a shorter median life expectancy [22,23].

Preventing PA chronic colonization is now considered the most important challenge for the CF clinician, as it frequently determines the patient's future quality of life and long-term survival as well as the cost of care [7,24,25]. Early treatment at the time of the first PA colonization greatly reduces the incidence of chronic colonization [18,26–31]. Unfortunately, there is no current consensus about the optimal eradication regimen and the failure rate of this approach has been estimated around 15–27% [18,28,31]. Moreover, even when it succeeds, a different strain of PA will often be isolated within 12 months [32].

It has recently been suggested that early «prophylactic» administration of inhaled antibiotics may be beneficial [33]. In a preliminary study initiated in 1986, Heinzl et al. prescribed long-term prophylactic gentamycin inhalation for a cumulative period of 132 years in young CF children at special risk of PA-acquisition. The treatment was well tolerated and not associated with any PA-acquisition. Nevertheless, a recent European consensus stated that given the lack of studies, the burden of this approach and the effectiveness of early antibiotic treatment when PA is first isolated, it could not be currently recommended [3].

Central to the discussion is the definition of chronic PA colonization which remains debated. We chose to adopt Lee's definition [10] for several reasons. It has been validated; it does not involve antibodies dosages which are not always available and whose interpretation is critically dependent on methodological options; it is based on the results of all the cultures performed over the previous 12 months, then appearing especially meaningful for relevant practical issues such as patient segregation.

Among paediatric patients, high levels of specific serum antibodies against PA were only found in the two patients classified as chronically colonized. This finding concurs with previous data [11]. Using this definition, Lee et al. recently described a fall from 24% to 18% in the rate of chronic PA colonization in their paediatric population between 1990 and 2000 [18]. Like in Denmark, close microbiological monitoring permitting early aggressive treatment of the first isolates of PA and patient segregation according to bacteriological status were regarded as key-factors contributing to such improvement [18,24,34]. Yet this rate of 18% remains well above the rate reported at the St Luc Cystic Fibrosis Reference Centre.

At their last hospital appointment in 2003, the FEV1 of 70% of paediatric patients was $\geq$90% of the predicted value. In Belgium, the corresponding rate in the national registry was 44.8% in 2001 [4]. In the USA, where the average of the best value per quarter is used, the rate attained 45.2 in 2003 [17]. Such encouraging results are to be expected when very few patients are chronically colonized by PA but many other factors could be involved.

Detailed comparison with data from other centres in Belgium using the 2000 cystic fibrosis registry proved to be difficult and has not been attempted. One reason for this is that some data are missing in the registry. For example, while bacteriological data are available for all patients treated at St Luc, this was not the case for 17.7% of other patients in the registry. In the registry, information on socio-economic status is very limited which makes it impossible to exclude a selection bias. The impact of socio-economic status on prognosis has been well documented in the USA [35] but the quality of the Belgian national healthcare system, based on solidarity, is likely to greatly reduce it. In addition, the register does not enable us to assess the implementation of cohort isolation in the Belgian centres. Such a policy has been strict from the start at St Luc. The questionnaire sent to the pulmonologists of all other Belgian centres confirmed that they implemented it later for outpatients, which may have contributed to the difference in PA prevalence [24]. Nevertheless other centres around the world have had strict policies on this point for a long time and segregation alone cannot explain the difference in PA prevalence [18].

The proportion of PS patients is higher at the St Luc (15%<18 years, 19% for the whole clinic) than in the registry (11.4%). This can be explained by the fact that some patients with intermediate sweat chloride levels were diagnosed in the context of a large study [36] and by a recruitment bias related to an expertise in nasal PD measurements [37]. Chronic PA colonization seems to

occur later in PS patients [38] but this factor cannot account for the difference observed.

The low prevalence of PA in children at St Luc might be expected to be associated with a better clinical outcome. As mentioned above, data from the 2003 registry do not yet permit a comparison between centres. Fortunately, data collected for an other ongoing belgian (multicentric) study provide this information and are consistent with the expectations. They concern all the 6–18 years old children followed in the 6 main CF centres in Belgium at the end of the year 2003 for whom at least one spirometry and one respiratory culture were available for this year. PA prevalence was 5% at St Luc and 28% for the 178 other children ($p<0.01$). The mean FEV1 and WFH were significantly higher at St Luc (FEV1: 95%±15 vs. 83%±22, $p<0.01$; WFH: 100%±11 vs. 93%±11, $p<0.01$).

A significant reduction of the mean number of days of intravenous antibiotic treatment was observed in CF children at St Luc, which is important for several reasons: (1) it demonstrates that the low prevalence of PA in these patients is not due to more frequent IV treatments; (2) as the difference is very significant in comparison with other belgian CF children and as all but one centres do not prescribe IV AB as the first line treatment of initial colonization by Ps A (see T1R1), this suggest a reduction in the number of exacerbations comparable to that repeatedly reported in controlled studies about the use of inhaled Tobramycin in colonized patients; (3) this reduction of IV AB treatment can be expected to be associated with an increased quality of life and could be a counterpart to the burden of the treatment; (4) as in 2002 and 2003, 80% and 75% of these days took place in the hospital setting, this reduction is associated with decreased hospital-bed utilization and associated costs.

Specific to our centre in Belgium at this time was a policy of early, often «prophylactic», inhaled antibiotic therapy progressively implemented for over 15 years. Gradually better structured, this policy is to some extent similar to the experience reported by Heinzl et al. [33]. We suspect it to have greatly contributed to the singularity of the bacteriological results obtained at St Luc.

The St Luc Cystic Fibrosis clinic was launched in 1986. All patients are seen by the same paediatric pulmonologist (PL). From the outset, standard practice for patients receiving care at our Centre involved having sputum or pharyngeal aspirates taken at every hospital appointment, with no more than 3 months between visits, early treatment of first PA isolate, contacts between patients actively discouraged, strict segregation of patients on a bacteriological basis both in the outpatient setting and during hospitalization, dedicated respiratory function equipment with no closed circuits, mouthpieces and connectors that are discarded or sterilized after each use, chest physiotherapy as from diagnosis of the disease.

Eradication regimens prescribed to patients after their first growth of PA evolved over time. Inhaled colomycin [26] and then oral ciprofloxacin too [27] were initially prescribed for at least 3 weeks. If the culture remained positive, the treatment was repeated or, in rare cases, intravenous antibiotic therapy prescribed. Before the benefits of continuing this initial treatment for 3 months were demonstrated [28], the inhaled antibiotic therapy was often extended to 3–6 months or more, particularly if it was not the first time PA had been isolated. It sometimes even remained continuous, especially with patients whose compliance was felt to be less reliable or when a clinical benefit seemed evident, as evidenced by a decrease in or disappearance of chronic cough. Evidence that chronic PA colonization could not be prevented in almost 20% of cases where the patient received conventional regimens of early antibiotic therapy has strengthened this attitude [18,28,31]. Recently, the effectiveness of long-term aminoglycoside nebulization to prevent chronic PA colonization has been documented [29,30].

Moreover, an increasing number of patients in whom PA had never been isolated were prescribed temporary or sometimes long-term and then continuous “prophylactic” treatment. As in Heinzl’s study [33], most of them were infants or children presenting risk factors for acquisition of PA as described in the literature [39–42]: meconium ileus surgery, repeated or long-term hospitalisation especially early in life, admission to an intensive care unit, persistence of *Staphylococcus aureus* in the respiratory secretions despite oral antibiotic therapy. Prescribing an antibiotic active against *Hemophilus influenzae* when patients have a cold is a common practice with CF [7]. When doing so, we always added intermittent use of inhaled antibiotics, given the evidence that respiratory virus infections may pave the way for PA [43]. Finally, inhaled antibiotic therapy has sometimes been proposed when a cough was observed on a daily basis, after having looked for and treated when indicated gastro-oesophageal reflux and bronchial hyperreactivity. While not entirely systematic, this approach has been increasingly adopted as data accumulated confirming the good tolerance of long-term inhaled antibiotic therapy [44] and its effectiveness was observed.

Given the lack of prospective studies, this policy might be considered as intuitive at best. Yet, a number of theoretical considerations can make early use of inhaled antibiotics attractive. It is now acknowledged that PA infection in CF occurs much earlier than previously believed and that the sensitivity of even rigorous bacteriological monitoring might not be optimal for early detection of the presence of this pathogen [42,45,46]. Early treatment is crucial to avoid irreversible chronic colonization which worsens prognosis though its failure rate is far from negligible. Aminoglycosides are also effective against other pathogens often encountered in CF (e.g. *S. aureus* and *H. influenzae*). Delivery of inhaled medications can be predicted to be better when airways damage is minimal. Airways inflammation in CF is usually believed to be secondary to infection so inhaled antibiotics could to some

extent be regarded as the safest anti-inflammatory treatment currently available for this disease. It is paradoxical that the possible benefit of prophylactic antibiotic therapy to target this pathogen has barely been studied so far, contrary to what has been the case with *S. aureus*.

The currently recommended daily dose of TOBI is the same for an adult and a 6-year-old child. In comparison, the daily dose of tobramycin (or amikacin) we prescribed was 2–3 times lower, around 5–10 (15–30) mg/kg/day. Relating dose to weight in this way does not make much sense, because penetration of inhaled medication into the lungs does not vary linearly with weight or age [47]. Caution is warranted however with infants and young children for who only limited data on systemic absorption are available. Serum creatinine was measured at least once per year and remained normal in all cases. Audiometry was not performed systematically because available data in the literature seem very reassuring in this respect. It should also be realized that these small doses were delivered in a rather inefficient way because a standard unvented nebulizer was used and young children had to use a facemask. Even when a mouthpiece is used, such nebulizers are expected to deposit only about 10% of the dose in the lungs [48] while the Pari LC Jet which is used with TOBI would deliver approximately 15% of the dose [49] and the more modern LC Star could deliver as much as 35% to the lungs [50]. In the Heinzl's study, 12 young children received continuous higher doses of inhaled gentamycin (80 mg twice daily <12 months, 120 mg twice daily >12 months) for more than 6 years (6–12 years), without evidence of hearing or renal impairment [33]. Yet, wide-scale very long term safety data are currently lacking.

Danish authors have recently reported very encouraging results using a more conservative approach where monthly bacteriological controls and regular measurements of the antibody response hopefully allowed optimal early use of oral ciprofloxacin and inhaled colistin for periods of 3 weeks or 3 months [51]. This treatment however has often to be repeated and such close follow-up has been considered unrealistic in many countries [52].

One theoretical risk of prophylactic inhalation of aminoglycosides is that it could lead to the emergence of resistant strains of PA which we have not observed. In fact, characteristics of PA isolates initially infecting the CF airway are known to be more favourable to eradication with appropriate antibiotic therapy [45,53,54]. They are usually nonmucoid, highly susceptible to antibiotics and present in lower density than in established infections, so the probability of mutations is also lower.

There is concern that prolonged intermittent treatment with inhaled tobramycin might increase isolation of emergent pathogens and especially fungal organisms [55] but this was not observed in this small sample of paediatric patients most of whom had normal spirometry.

Inhaled antibiotics are a time-consuming treatment. Compliance was not investigated but seems clearly supported by the bacteriological results. In our clinic, a single pulmonologist personally cares for all the patients while 2–6 physicians are involved in the respiratory care of CF patients in the other Belgian centres. Conceivably, this unusual continuity of care may have facilitated coherence of attitudes and perhaps favoured adherence to treatment.

There is no reason to suspect that an excess mortality of chronically colonised children at St Luc could have contributed to our results. Between 1986 and 2003, only 4 CF children treated at the clinic died. When they first attended the clinic, three of them were already chronically colonised by PA. They were 11.2, 7.2 and 7.1 years old at this time and corresponding values for FEV1 (% predicted) were 48%, 27% and 21%, respectively. The fourth child also suffered from autism. He died when he was 17 from hepatic failure, liver transplant being contraindicated. Although numbers are small, the overall mortality rate of CF patients at St Luc between 1999 and 2002 is comparable to that recorded at the national level in the registry (5 patients/467 patient years: 1.07% vs. 35/2.718 patient years: 1.28%), with a median age at death of 30 years (vs. 23 years in the registry).

We made no attempt to estimate the cost/benefit ratio of our approach. Inhaled antibiotics are obviously expensive, even at relatively low doses. On the other hand, Baumann et al. [25] recently reported that in a paediatric CF clinic, the annual costs of patients with chronic PA infection were more than three times higher than those of uninfected patients.

In this descriptive retrospective study, we have reported a particularly low rate of chronic colonization by PA in a cohort of paediatric CF patients. We have not however demonstrated that it is accounted for by our strategy of early, often «prophylactic» use of inhaled antibiotics, progressively implemented for over 15 years although this is an attractive hypothesis. In fact, current objective data are well reflected by a recent statement from a european consensus about early intervention and prevention of lung disease in cystic fibrosis: this approach has not been well studied and is not currently recommended (DIII) [3].

Nevertheless, in our experience, it seems to be very effective. Given the major impact of chronic PA colonization on CF prognosis, it is suggested that a large prospective study of this approach is warranted, not only in order to assess its efficacy and confirm long-term safety but also in order to determine its relative impact with respect to other factors and its potential cost-effectiveness.

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