Comparative efficacy of two doses of nebulized colistimethate for the eradication of *Pseudomonas aeruginosa* in children with cystic fibrosis

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BACKGROUND: Cystic fibrosis (CF) affects the respiratory and digestive systems. It evolves toward deterioration of pulmonary function through colonization with *Pseudomonas aeruginosa*. There is no consensus with respect to its eradication. Nebulized colistimethate is used for eradication treatment, but the optimal dose and duration is yet to be determined.

OBJECTIVES: To compare the efficacy of two doses of nebulized colistimethate (30 mg versus 75 mg twice daily) for the eradication of *P. aeruginosa* in children with CF and intermittent colonization.

METHODS: A cohort study with both historical (30 mg) and prospective (75 mg) arms was conducted from 1999 to 2003. Medical records were used to collect data.

RESULTS: Eighty-one patients were recruited in the retrospective group, for a total of 111 treatment courses. Twenty patients were recruited in the prospective group, for a total of 20 events. There was no statistically significant difference in the rate of eradication of *P. aeruginosa* at days 28 and 90, neither when comparing the doses of colistimethate nor duration of treatment. There was a statistically significant difference ($P=0.004$) between days 1 and 90 in all analyzed subgroups (regardless of dose or duration of treatment) for forced vital capacity only. In the group of patients in whom eradication was achieved at day 28 (after receiving a three-week treatment course of colistimethate), 50% of patients developed a new infection 5.75 months later, on average, regardless of the dose administered. In the group of patients who achieved eradication at day 90 (after receiving a 15-week treatment course of colistimethate), 50% of the 14 patients developed a new infection after an average period of 7.3 months ($P=0.28$).

CONCLUSIONS: There is no difference in the efficacy between a 30 mg dose and a 75 mg dose of colistimethate for *P. aeruginosa* eradication in children with CF and intermittent colonization.

Key Words: Colistimethate; Cystic fibrosis; *Pseudomonas aeruginosa*; Pulmonary function tests

Cystic fibrosis (CF) is the most common lethal hereditary disorder in Caucasians. It has an autosomal recessive mode of transmission, and its incidence varies according to race (incidence in Caucasians is higher than in Africans, which is higher than in Asians) (1-5). It has been estimated that one in 20 Canadians carries the CF gene (6). CF is caused by a defect

tude comparative sur l'efficacit de deux doses de colistimthate en arosol pour la suppression de *Pseudomonas aeruginosa* chez des enfants atteints de mucoviscidose

CONTEXTE : La mucoviscidose touche les appareils digestif et respiratoire. La maladie volue vers une dtrioration du fonctionnement pulmonaire en raison d'une colonisation des tissus par *Pseudomonas aeruginosa*, et le traitement suppressif ne fait pas consensus. On utilise dj le colistimthate en arosol cette fin, mais il reste encore en dterminer la dose et la dure optimales.

BUT : L'tude avait pour but de comparer l'efficacit de deux doses de colistimthate en arosol (30 mg contre 75 mg, deux fois par jour) en vue de la suppression de *P. aeruginosa* chez des enfants atteints de mucoviscidose et sujets une colonisation pisodes.

MTHODE : Une tude de cohortes, comportant la fois un volet historique (30 mg) et un volet prospectif (75 mg), a t mene de 1999 2003. La collecte de donnes s'est faite partir de l'examen de dossiers mdicaux.

RSULTATS : Quatre-vingt-onze patients ont t retenus dans le groupe rtrospectif, pour un total de 111 cures, et vingt patients ont t slectionns dans le groupe prospectif, pour un total de 20 vnements. Aucun cart statistiquement significatif n'a t relev en ce qui concerne le taux de suppression de *P. aeruginosa* au bout de 28 jours et de 90 jours, quelles que soient la dose de colistimthate ou la dure du traitement. Cependant, il est ressorti un cart statistiquement significatif ($P=0.004$) entre la 1re journe et la 90e journe dans tous les sous-groupes analyss (peu importe la dose de mdicament ou la dure du traitement) pour ce qui est de la capacit vitale force seulement. Dans le groupe de patients chez qui il y avait eu suppression de la bactrie au bout de 28 jours (aprs 3 semaines de traitement par le colistimthate), une nouvelle infection est apparue chez 50 % des patients au bout de 5,75 mois en moyenne, indpendamment de la dose administre; dans le groupe de patients chez qui il y avait eu suppression de la bactrie au bout de 90 jours (aprs 15 semaines de traitement par le colistimthate), une nouvelle infection est apparue chez 50 % des patients concerns (14) au bout de 7,3 mois en moyenne ($P=0.28$).

CONCLUSION : Il n'y a aucune diffrence d'efficacit entre la dose de 30 mg et de 75 mg de colistimthate en vue de la suppression de *P. aeruginosa* chez des enfants atteints de mucoviscidose et sujets une colonisation pisodes.

in the gene encoding for the CF transmembrane regulator, a channel regulating electrolyte transport across epithelial cell membranes (1,3). According to the most recent statistics in the Canadian CF registry, the median survival age for the period from 1996 to 2000 was 35.6 years (6). CF is diagnosed in affected patients at a median age of three to six months. It is based on

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Figure 1 Cohort profile of a study comparing the efficacy of two doses of nebulized colistimethate (Col) for the eradication of *Pseudomonas aeruginosa* in children with cystic fibrosis. BID Twice daily

the presence of symptoms, two positive sweat tests and, if available, results of molecular DNA analysis for specific gene mutations (1,6).

CF generally leads to respiratory disease, as well as exocrine pancreatic insufficiency (1). Pulmonary disease is the main cause of morbidity and mortality in CF patients (1,7). It is characterized by the acquisition and subsequent persistence of certain pathogens in the lung, along with periodic exacerbations of variable severity. Bacteria typically involved in the first months of life are *Staphylococcus aureus* and nontypable *Haemophilus influenzae*. The first positive culture with *Pseudomonas aeruginosa* usually occurs after the first year of life (3,8). The latter is omnipresent in the environment, particularly in humid conditions.

The majority of CF patients have their first bronchial colonization with *P aeruginosa* before the age of three years (2,6,8). Colonization can be defined as the persistence of organisms within the lumen of the respiratory tract, while infection is defined by evidence of tissue invasion (eg, symptomatic disease, immunological response or x-ray changes) (9). In CF, persistence of *P aeruginosa* in the bronchi has been referred to as a colonization. However, in recent years, the presence of *P aeruginosa* in the bronchi is often regarded as an infection, because tissue damage occurs after years of its presence. For simplicity, *P aeruginosa* infection is referred to as colonization throughout the present article.

Without treatment, initial colonization with *P aeruginosa* generally becomes chronic and leads, along with chronic inflammation, to progressive deterioration of pulmonary function (2,5,10). It is thought that early treatment of initial colonization with *P aeruginosa* can delay chronic colonization (2,11-14).

As of June 2003, at the CHU Sainte-Justine (CHUSJ), Montreal, Quebec, there is a cohort of approximately 250 CF patients classified by their colonization status regarding *P aeruginosa*: first colonization, intermittent colonization (alternating positive and negative cultures) or chronic colonization (presence of positive cultures for more than six consecutive months as defined by the Danish Cystic Fibrosis Center, Copenhagen, Denmark [12]).

Many different antibiotics can treat *P aeruginosa*. However, there are little data to indicate which treatment is optimal, regardless of the colonization status (2,9,11-12,15-24). The available therapeutic options include broad-spectrum penicillins, third- and fourth-generation cephalosporins, carbapenems,

aminoglycosides, quinolones and polymyxins (colistimethate) (1,2,11,12,25,26). Published studies and our clinical experience with nebulized antibiotics in CF deal mostly with tobramycin and colistimethate (2,9,11-22,25-30).

Colistimethate is an interesting agent to use by nebulization due to its relatively narrow spectrum of activity including *P aeruginosa*, the low reported toxicity with this route of administration and the small estimated rate of resistant *P aeruginosa* strains (13,16). Colistimethate is a mix of cationic polypeptides composed primarily of polymyxin E1 and E2 (13,15). It is a prodrug (colistimethate sodium) that is hydrolyzed in vivo to colistin, its active form. Colistin interacts with the lipopolysaccharides contained in bacterial cytoplasmic membrane, causing it to break down, leading to cell death. Colistimethate was introduced in the 1960s for the treatment of acute and chronic infections due to Gram-negative rods such as *P aeruginosa*, *Aerobacter aerogenes*, *Escherichia coli* and *Klebsiella pneumoniae* (13,31). Nephrotoxicity and neurotoxicity with intravenous administration halted its use in the 1970s (13,16). Although nebulized colistimethate has been used for several years, it is not officially indicated for the eradication of *P aeruginosa* in CF (1,2,11-16,25-27).

In North America, there is no consensus on the optimal dose of colistimethate to be used. In a clinical setting, eradication doses vary from 30 mg to 75 mg twice daily for a duration of three weeks to three months (2,9,11-22,25-30). (Due to small differences in the pharmaceutical products available in Europe and America, a dose of 30,000 U of colistimethate in Europe is equivalent to a dose of 1 mg in America [32].) In 1999, the outpatient CF clinic of the CHUSJ applied a treatment protocol including colistimethate for the eradication of *P aeruginosa* in patients with first or intermittent colonization. For patients with a previous negative culture, nebulized colistimethate was used at a dose of 30 mg twice daily for three weeks. If patients remained colonized after this initial treatment, three additional months of therapy were given. The European consensus on antibiotic therapy against *P aeruginosa* in CF published in 2000 recommended the use of a higher dose of nebulized colistimethate to maximize the rate of eradication, and to delay recolonization and chronic colonization (2). The goal of the present study was to compare the efficacy of two nebulized doses of colistimethate (30 mg versus 75 mg twice daily) in children with intermittent colonization CF (code 200).

METHODS

A cohort study was undertaken to compare the efficacy of two doses of nebulized colistimethate (30 mg versus 75 mg twice daily) in children aged 0 to 18 years with CF and intermittent colonization (Figure 1). The study included retrospective group controls (30 mg twice daily) and a prospective group (75 mg twice daily) for a duration of three weeks, followed by an additional three months of treatment (ie, a total duration of 15 weeks) when there was no eradication after three weeks. Patients were recruited from July 1, 1999, to December 21, 2002, for the retrospective part of the study, and from January 10 to October 6, 2003, for the prospective part. Patients having a first colonization or chronic colonization with *P aeruginosa* were excluded, as were patients who neither spoke nor wrote French nor English. Information leaflets were given to patients and parents. Colistimethate was dispensed by the patient's community pharmacist of choice on receiving the prescription

and a treatment plan by fax from the CF clinic pharmacist. The protocol was approved by the CHUSJ Ethics Committee.

The retrospective group was selected using the list of CF patients followed up at the CHUSJ who met the inclusion criteria. The prospective group was selected from patients with a new positive *P aeruginosa* culture who met the inclusion criteria. For the two study groups, medical records were used to confirm the CF diagnosis and the data for observed study variables. The rate of eradication of *P aeruginosa*, change in pulmonary function, and the delay between eradication and the next episode of colonization (time to recolonization) were measured in the retrospective and prospective groups. Adverse effects occurring during the treatment were documented systematically only in the prospective cohort of patients.

The rate of *P aeruginosa* eradication was measured using throat cultures (for patients too young or unable to expectorate sputum) or sputum samples approximately four weeks (day 28) and 12 weeks (day 90) after the beginning of the first eradication treatment (day 1), as well as during subsequent follow-up. The microbiological method used for isolation of *P aeruginosa* is described by many authors and conforms to the standardized procedures established by the American Society of Microbiology (33-38). To ensure reliability of culture results, patients were instructed not to eat nor drink for at least 1 h before sampling, although this was not written systematically in the medical record. Despite the fact that assessment of bacterial growth was completed using a semiquantitative method, a culture was considered positive with any presence of *P aeruginosa*. Susceptibility testing was performed with the antibiotics currently used to treat *P aeruginosa*. Results were interpreted using values established by the National Committee for Clinical Laboratory Standards (39), except for colistimethate, for which another value was used in the absence of a National Committee for Clinical Laboratory Standards value (40).

Change in pulmonary function was determined using specific spirometry assessments, such as forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁) and forced expiratory flow during 25% to 75% of FVC. Spirometry assessments at the CHUSJ were completed using the MasterScreen system (Erich JAEGER GmbH, Germany). This system and the accompanying spirometry technique follow the criteria established by the American Thoracic Society/European Respiratory Society Task Force (41-45). Pulmonary function test results obtained closest to the period before the beginning of treatment (day 1) and those obtained approximately three months after beginning treatment (day 90) were collated.

The period of recolonization was determined using results obtained from control cultures. The start of this period was measured from the date at which a culture confirming eradication (day 28 or day 90) was obtained and ended on the occurrence of new colonization. If no episode of recolonization was observed before the end of the study, the dates chosen for ending observation were December 23, 2002, at the latest, for the retrospective cohort, and March 17, 2004, for the prospective cohort. Every colonization episode was considered to be an independent occurrence. Thus, more than one episode could have occurred in the same patient. In cases in which eradication was not obtained at day 28 or day 90, the patient was excluded from the survival analysis. Frequency tables and frequency distributions were set up for the different study variables. For rate of eradication, Fisher's exact test or the χ^2 test was used. Change in pulmonary function was evaluated using

TABLE 1
Demographic data in a study comparing the efficacy of two doses of nebulized colistimethate for the eradication of *Pseudomonas aeruginosa* in children with cystic fibrosis

Baseline characteristics	Retrospective study group, n=81	Prospective study group, n=20	P
Treatment episodes, n (%)			
Total	111 (100)	20 (100)	
1	59 (72.5)	20 (100)	
2	14 (17.5)		
3	7 (8.8)		
4	1 (1.3)		
Male sex, %	61	50	NS
Age, years			
Mean $\pm$ SD	6.3 $\pm$ 4.2	8.8 $\pm$ 4.2	NS
Median (interval)	5.9 (0.3–15.7)	9.3 (2.0–16.7)	
Weight, kg			
Mean $\pm$ SD	22.2 $\pm$ 13.2	27.9 $\pm$ 13.0	NS
Median (interval)	19.2 (4.8–64.4)	24.1 (11.5–58.4)	
Height, cm			
Mean $\pm$ SD	110.2 $\pm$ 27.4	123.9 $\pm$ 13.0	NS
Median (interval)	107.8 (55.7–169.5)	124.5 (81.90–163.4)	

NS Not significant

the ANOVA test. The Kaplan-Meier and log-rank tests were used to analyze time to recolonization (survival analysis). A questionnaire was developed to document the occurrence of adverse effects in the prospective study group during the first eradication treatment (three weeks).

RESULTS

Eighty-one patients were recruited for the retrospective study group, for a total of 111 events (eradication treatments), while 20 patients were recruited in the prospective study group, for a total of 20 events. All recruited patients were Caucasian, and all had a CF diagnosis confirmed by two positive sweat tests and symptoms suggestive of CF. Baseline characteristics per treatment event are shown in Table 1. Events in the prospective group occurred in older patients than those in the retrospective group. This can be explained by the fact that CF patients at the CHUSJ are followed up on a long-term basis, and patients became older between the two phases.

Pulmonary parameters and eradication rates for both doses of colistimethate at day 28 and day 90 are shown in Table 2. Study analyses were completed on an event basis as opposed to a patient basis. With respect to pulmonary parameters, a significant improvement in both study groups for FVC was observed (time effect; $P=0.004$). No temporal change (time effect) was observed for FEV₁ and forced expiratory flow parameters. There was no statistically significant difference in any pulmonary parameter with respect to dose, or to the presence or absence of eradication at day 90. No statistically significant difference in the rate of *P aeruginosa* eradication at day 28 and day 90 was observed, regardless of the colistimethate dose used. A post-hoc power analysis was performed, given the study sample and difference in proportions between the two groups. Initially, a 20% difference was expected to be clinically significant. Given the current sample size and a power of 80%, the present study would have been able to detect a difference of 33% or more between the two groups.

TABLE 2
Pulmonary parameters and eradication rates for two doses of colistimethate used for the eradication of *Pseudomonas aeruginosa* in children with cystic fibrosis

	Retrospective study group* (n=60)	Prospective study group† (n=16)	P‡
FVC (% of predicted value)			
Day 1 (n=76)	99.1±12.7	99.3±11.5	0.967
Day 90 (n=76)	101.4±12.7	104.8±10.2	0.325
Day 90 – day 1 (n=76)	2.3±9.5	5.6±8.8	0.220
Forced expiratory volume in 1 s (% of predicted value)			
Day 1 (n=76)	94.0±14.7	90.4±13.0	0.372
Day 90 (n=76)	94.7±14.3	94.4±12.4	0.957
Day 90 – day 1 (n=76)	0.7±11.9	4.1±8.2	0.284
Forced expiratory flow during 25% to 75% of FVC (% of predicted value)			
Day 1 (n=76)	88.2±37.7	68.1±29.4	0.052
Day 90 (n=76)	86.8±38.3	75.2±24.0	0.252
Day 90 – day 1 (n=76)	–1.32±26.1	7.11±22.5	0.242
Eradication rate			
Day 28 (n=127)	55.1%	55%	NS
Day 90 (n=129)	50%	52.6%	NS

*Colistimethate 30 mg twice daily for three or 15 weeks; †Colistimethate 75 mg twice daily for three or 15 weeks; ‡Not significant (NS). Day 1 implies before the beginning of treatment; Day 90 – day 1 indicates the difference between day 90 and day 1; FVC Forced vital capacity

The Kaplan-Meier method (Figure 2) was used to conduct a survival analysis to compare the time (in months) from eradication to the occurrence of a new colonization in both groups for patients who had had eradication at day 28 (n=59) and day 90 (n=14). Further survival analyses were performed with the log-rank comparison test, as well as with the Breslow and Tarone-Ware tests. Similar results were obtained with all three tests. Of the patients who received a three-week treatment of colistimethate and in whom eradication had been achieved at day 28, 50% had a new colonization 5.75 months later, on average, regardless of the administered dose. Of patients who received a 15-week treatment of colistimethate and in whom eradication had been achieved at day 90, 50% of the 14 patients had a new infection after 7.3 months, on average (P=0.28). Thus, the results of these comparisons do not show a significant difference in the delay to recolonization between treatment periods of three and 15 weeks. The prospective study group (n=14), however, had a limited number of subjects for this type of analysis. The occurrence of adverse effects was documented in the prospective study group.

A questionnaire was used to collect adverse effect information from parents and children in the prospective group. The most frequently reported adverse effects were increased cough (n=8), chest pain (n=3), throat pain (n=2), voice changes (n=2) and dizziness occurring during the 30 min nebulization with fading thereafter. Twelve of the 17 patients reported one or more adverse effects. Three patients did not return the questionnaire to investigators.

DISCUSSION

Ninety per cent of deaths in CF patients are related to respiratory disease. The latter is mostly due to chronic colonization with *P. aeruginosa*, which eventually leads to repeated

Figure 2) Survival curve depending on duration of colistimethate treatment for the eradication of *Pseudomonas aeruginosa* in children with cystic fibrosis

exacerbations and pulmonary damage. Thus, it is important to treat this bacteria quickly to prevent, if possible, or at least delay chronic colonization (1,2,11-14). Previous studies on *P. aeruginosa* eradication are hard to compare, because they included few patients; there were important patient differences compared with our patients; and they used different designs, doses and antibiotic regimens (some used only one antibiotic, while others used more than one antibiotic in combination) (9,11-15,17-22,25-27,29,30,46). The effect of colistimethate on patients having intermittent colonization with *P. aeruginosa* has not been clearly evaluated in published studies. Studies have dealt mainly with initial colonization (9,17-18,20) or chronic colonization (19,21-22).

We did not show any differences between the two doses of colistimethate (30 mg or 75 mg twice daily) with respect to rates of eradication at day 28 and day 90. Only Littlewood et al (9) have studied the efficacy of nebulized colistimethate in monotherapy for first colonization. A dose of 15 mg twice daily, used for an unspecified duration, resulted in a reduction in the frequency of positive *P. aeruginosa* cultures, from 42% to 6% in seven patients aged 21 months to 14 years. These measurements were done prospectively over three to 14 months, and no statistical analyses were reported. In a cohort study, Vazquez et al (20) also demonstrated the effect of colistimethate in combination with other antipseudomonal agents for first colonizations. Using a prospective study design, eight patients (mean age 8.1 years) received oral ciprofloxacin at a dose of 35 mg/kg/day for two weeks, followed by 30 mg of nebulized colistimethate administered twice daily along with nebulized tobramycin 100 mg administered twice daily. They were compared with a historical control group of eight patients (mean age 4.8 years) who had received a systematic antibiotic treatment due to a pulmonary exacerbation that had occurred five to 52 months after initial *P. aeruginosa* colonization. At the end of the study, 4.6% of the cultures (four of 87) in the prospective group were positive, compared with 86% of the cultures (109 of 120) in the control group (P<0.001).

No other study has compared durations of treatment for nebulized colistimethate monotherapy. However, Frederiksen et al (18) performed a retrospective study comparing placebo with a treatment algorithm comprised of nebulized colistimethate, 30 mg twice daily, and oral ciprofloxacin, 25 mg/kg/day to 50 mg/kg/day divided twice daily for three weeks (part 1); nebulized colistimethate, 75 mg twice daily, and ciprofloxacin at the same dose for three weeks (part 2); and nebulized colistimethate, 75 mg twice daily, and ciprofloxacin at the same dose for three months (part 3). Analysis of the three parts of the study showed that treatment for three months with colistimethate combined with ciprofloxacin was more effective at preventing colonization than a three-week treatment ($P < 0.05$). This treatment algorithm for a group of patients with a mean age of 7.4 years is similar to the one used at the CHUSJ and is comparable to the one used in our study. However, Frederiksen et al did not hypothesize as to whether dose (75 mg) or duration of treatment (three months) explained this difference.

The rates of eradication observed in our study are not as high as those obtained by other authors (9,17,18,20). This can be explained, among other reasons, by the different anti-pseudomonal treatments used, which can be more or less aggressive according to practice in different clinics (antibiotic monotherapy versus combination therapy, different treatment durations). The doses of colistimethate recommended in the last European guidelines (47) ranged from 67 mg to 100 mg via nebulization twice daily, doses that are much higher than those used in published studies and those normally used at the CHUSJ (47). Differences between our results and those of other studies can also be explained by patient differences, an important one being the exclusion of first colonization patients in our study. In the most recent European consensus on early eradication (47), early treatment at the first colonization was recommended to maximize chances of success.

We did not show any differences with respect to respiratory parameters between the two doses of colistimethate (30 mg or 75 mg) or between the treatment durations (three weeks or 15 weeks). In our study, the lack of effect on pulmonary function tests may be attributed to the absence of those measurements in many medical records, because it is nearly impossible for children under five years old to perform reliable tests. It is also possible that colonization has little impact on pulmonary function tests in the early stages, or that pulmonary function testing is not a measure sensitive enough to detect deleterious effects of a recent bacterial colonization in the lungs (48). Frederiksen et al (18) observed median improvements in FVC of 12% and 16% during the first and second years of follow-up, respectively, in the group treated with colistimethate, compared with median deteriorations of 3% and 8% in the group treated otherwise for the same follow-up periods ($P < 0.005$ and $P < 0.05$) (18). Furthermore, the median FEV₁ values were improved by 5% and 3% in the group administered colistimethate, as opposed to median decreases of 5% and 6% in the control group for the same follow-up periods ($P < 0.01$ and $P < 0.05$). Knowing that the normal course of the disease is marked by considerable deterioration in pulmonary function, Jensen and colleagues (19) conducted a randomized, controlled study evaluating the effect of nebulized colistimethate, 30 mg twice daily for three months, on pulmonary parameters versus placebo. Forty patients aged seven to 35 years and chronically colonized with *P aeruginosa* were involved in the

study. The authors found mean ($\pm$ SD) deteriorations in FVC values of $7\% \pm 8\%$ for the group given colistimethate and $18\% \pm 14\%$ for the control group between day 0 and day 90. Mean ($\pm$ SD) decreases in FEV₁ of $11\% \pm 6\%$ and $17\% \pm 11\%$ for the treatment and placebo groups, respectively, were also observed. The smaller deterioration in FVC observed in the treatment group was significant and allowed the authors to conclude that treatment with colistimethate slowed the deterioration of pulmonary function. In addition, because the effect on pulmonary function was superior to that observed in our study, this implies that older age and greater severity of pulmonary disease positively influences improvement of FVC secondary to treatment with colistimethate – the study population used by Jensen et al (19) was older and chronically colonized. In our study, the pulmonary function values observed at day 1 show that the patients did not have severe disease, thus limiting their potential for improvement.

We did not show any difference in time to reinfection as a function of a three- or 15-week treatment period. It should be mentioned that survival analyses usually require greater sample sizes to allow applicability of the results. To our knowledge, these are the first data published pertaining to delay in reinfection as a function of two treatment durations. Munck et al (49) conducted a cohort study in which 19 patients received 18 to 21 days of ceftazidime (300 mg/kg/day) ($n=18$) or imipenem (75 mg/kg/day) ($n=1$) with intravenous tobramycin (7.5 mg/kg/day), followed by colistimethate at doses of 30 mg to 110 mg for two months, doses that varied according to age (49). The authors reported a median ($\pm$ SD) time to recolonization that is superior to our study, 8.0 ± 5.7 months. This difference can be explained by the use of a more aggressive treatment regimen.

Of the 20 patients in the prospective group, 17 patients returned their survey on adverse effects. Twelve of these 17 patients reported having experienced adverse effects; we have not systematically recorded data for the historical cohort. Published studies dealing with adverse reactions of nebulized colistimethate and a small number of clinical experiences with colistimethate have shown an acceptable toxicity profile (9,14,17-21). This can be explained by the expected low systemic absorption. Based on its low oral bioavailability and the large size of the molecule, very small amounts of the drug are expected to pass into the pulmonary capillaries (32).

We did not show that either age, sex or duration of treatment contributed to altering time to recolonization. Other variables that could also have been evaluated were frequency of physiotherapy during treatment, density of bacterial cultures at treatment initiation, presence of other pulmonary colonizations (for example, *S aureus*) and concomitant administration of other medications, such as recombinant dornase-alpha and antistaphylococcal antibiotics. As it is, dornase-alpha can theoretically allow better penetration of the nebulized antibiotic from improvement on mucociliary clearance, whereas long-term use of antistaphylococcal antibiotics can increase the risk of colonization with *P aeruginosa* (22,50).

This study had several limitations. The use of an open-label study protocol was an important limit. A randomized, controlled, clinical study is, without a doubt, the most appropriate study design for comparing two doses of a drug. However, such a design would have required a larger sample size, which we were not able to acquire due to our limited number of patients and the time restraints of the study. To limit bias, our study

targeted only CF patients with intermittent colonization; carrying out the study shows that including only a subgroup of the cohort of treated patients seriously limits recruitment. The use of throat cultures instead of sputum or bronchial alveolar lavage cultures was also a limit of the present study. However, these cultures could not have been performed differently in many patients because of their young age and because we considered bronchial alveolar lavage to be too invasive for patients who did not have pulmonary exacerbations. These results can be applied to a population of CF patients who have experienced more than one episode of colonization with *P aeruginosa*, considering that the course of their disease almost always leads to intermittent and, eventually, chronic colonization with this bacteria.

CONCLUSIONS

No differences in efficacy were shown between doses of 30 mg and 75 mg of nebulized colistimethate as monotherapy for the eradication of *P aeruginosa* in children with CF and intermittent colonization. The optimal antibiotic regimen for early *P aeruginosa* eradication has yet to be determined. Increasing the dose of a single antibiotic, namely, colistimethate, appears to be insufficient to obtain durable eradication. The present study suggests that earlier and more aggressive eradication regimens need to be developed.

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REFERENCES

- Bosso JA. Cystic fibrosis. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*, 4th edn. Connecticut: Appleton & Lange, 1999:508-20.
- Döring G, Conway SP, Heijerman HG, et al. Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: A European consensus. *Eur Respir J* 2000;16:749-67.
- Hart CA, Beeching NJ, Duerden BI. Respiratory infections. *J Med Microbiol* 2002;51:903-14.
- Wagener JS, Headley AA. Cystic fibrosis: Current trends in respiratory care. *Respir Care* 2003;48:23-7.
- Williams CN. Cystic fibrosis: Genotype phenotype correlations and future genetic therapy. *Can J Gastroenterol* 1998;12:474-5.
- Canadian Cystic Fibrosis Foundation. Report of the Canadian Patient Data Registry, 2000. Toronto: Canadian Cystic Fibrosis Foundation, 2001.
- LiPuma JJ. Expanding microbiology of pulmonary infection in cystic fibrosis. *Pediatr Infect Dis J* 2000;19:471-4.
- Burns JL, Gibson RL, McNamara S. Longitudinal assesment of *Pseudomonas aeruginosa* in young children with cystic fibrosis. *J Infect Dis* 2001;183:444-52.
- Littlewood JM, Miller MG, Ghoneim AT, Ramsden CH. Nebulised colomycin for early *Pseudomonas* colonization in cystic fibrosis. *Lancet* 1985;1:865.
- Heijerman H. Infection and inflammation in cystic fibrosis: A short review. *J Cyst Fibros* 2005;4(Suppl 2):3-5.
- Banerjee D, Stableforth. The treatment of respiratory pseudomonas infection in cystic fibrosis. *Drugs* 2000;60:1053-64.
- Højby N. Prospects for the prevention and control of pseudomonal infection in children with cystic fibrosis. *Paediatr Drugs* 2000;2:451-63.
- Beringer P. The clinical use of colistin in patients with cystic fibrosis. *Curr Opin Pulm Med* 2001;7:434-40.
- Hoiby N, Frederiksen B, Pressler T. Eradication of early *Pseudomonas aeruginosa* infection. *J Cyst Fibros* 2005;4(Suppl 2):49-54.
- Management of respiratory *Pseudomonas* infections in cystic fibrosis: Many strategies to consider. *Drug Ther Perspect* 2001;17:5-9.
- Littlewood JM, Koch C, Lambert PA, et al. A ten year review of colomycin. *Respir Med* 2000;94:632-40.
- Valerius NH, Koch C, Hoiby N. Prevention of chronic *Pseudomonas aeruginosa* colonisation in cystic fibrosis by early treatment. *Lancet* 1991;338:725-6.
- Frederiksen B, Koch C, Højby N. Antibiotic treatment of initial colonization with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. *Pediatr Pulmonol* 1997;23:330-5.
- Jensen T, Pedersen SS, Garne S, Heilmann C, Hoiby N, Koch C. Colistin inhalation therapy in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection. *J Antimicrob Chemother* 1987;19:831-8.
- Vazquez C, Municio M, Corera M, Gaztelurrutia L, Sojo A, Vitoria JC. Early treatment of *Pseudomonas aeruginosa* colonization in cystic fibrosis. *Acta Paediatr* 1993;82:308-9.
- ME Hodson, CG Gallagher, JR Govan. Randomised UK/Eire clinical trial of the efficacy and safety of tobramycin 300 mg/5 mL nebulizer solution or nebulised colistin in CF patients. 24th European Cystic Fibrosis Conference. Stockholm, June 4 to 8, 2000.
- Hodson ME, Gallagher CG, Govan JRW. A randomized clinical trial of nebulized tobramycin or colistin in cystic fibrosis. *Eur Respir J* 2002;20:658-64.
- Salcedo A, Giron RM, Beltran B, Martinez A, Maiz L, Suarez L; Fundacion Sira Carrasco. [Consensus conference: Home intravenous antibiotic treatment for cystic fibrosis. The Sira Carrasco Foundation. 26 April 2002.] *Arch Bronconeumol* 2003;39:469-75.
- Elphick HE, Tan A. Single versus combination intravenous antibiotic therapy for people with cystic fibrosis. *Cochrane Database Syst Rev* 2005;(2):CD002007.
- Sermet-Gaudelus I, Le Cocquic Y, Ferroni A, et al. Nebulized antibiotics in cystic fibrosis. *Pediatr Drugs* 2002;4:455-67.
- Toso C, Williams DM, Noone PG. Inhaled antibiotics in cystic fibrosis: A review. *Ann Pharmacother* 1996;30:840-50.
- Campbell PW III, Saiman L. Use of aerosolized antibiotics in patients with cystic fibrosis. *Chest* 1999;116:775-88.
- Ryan G, Mukhopadhyay S, Singh M. Nebulised anti-pseudomonal antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* 2003;(3):CD001021.
- Webb AK, Dodd ME. Nebulised antibiotics for adults with cystic fibrosis. *Thorax* 1997;52(Suppl 2):S69-71.
- Moss RB. Administration of aerolized antibiotics in cystic fibrosis patients. *Chest* 2001;120:S107-13.
- Coly-Mycin M Product Monograph. Kirkland: Pfizer Canada Inc, 2001.
- Thomson Micromedex. "Colistin" DRUGDEX System. <<http://www.micromedex.com/products/drugdex/>> (Version current at October 18, 2007).
- Isenberg HD, Baron EJ, D'Amato RE. Recommendations for isolations of bacteria from clinical specimens. In: *Manual of Clinical Microbiology*, 5th edn. Washington, DC: American Society for Microbiology, 1991:216-21.
- Gilligan PH. Report on the consensus document for microbiology and infectious diseases in cystic fibrosis. *Clin Microbiol Newsl* 1996;18:83-7.
- Gilligan PH. Microbiology of airway disease in patients with cystic fibrosis. *Clin Microbiol Rev* 1991;4:35-51.
- Aronoff SC, Beall RJ, Burns JL, et al. Microbiology and infectious disease in cystic fibrosis. Consensus Conference on Microbiology and Infectious Disease in Cystic Fibrosis. Bethesda: Cystic Fibrosis Foundation, 1994;5:2-26.
- Sahm DE, Washington JA. Antibacterial susceptibility tests: Dilution methods. In: *Manual of Clinical Microbiology*, 5th edn. Washington, DC: American Society for Microbiology, 1991:1105-16.
- Isenberg HD. *Clinical Microbiology Procedures Handbook*. Washington DC: American Society for Microbiology, 1994.
- National Committee for Clinical Laboratory Standards. Method for dilution antimicrobial susceptibility tests for bacteria that grow

- aerobically. Approved standards M7-A2. Villanova: National Committee for Clinical Laboratory Standards, 1990.
40. Catchpole CR, Andrews JM, Brenwald N, Wise R. A reassessment of the in-vitro activity of colistin sulphomethate sodium. *J Antimicrob Chemother* 1997;39:255-60.
 41. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J* 2005;26:153-61.
 42. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
 43. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005;26:511-22.
 44. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon dioxide uptake in the lung. *Eur Respir J* 2005;26:720-35.
 45. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948-68.
 46. Hamer DH. Treatment of nosocomial pneumonia and tracheobronchitis caused by multidrug-resistant *Pseudomonas aeruginosa* with aerolized colistin. *Am J Respir Crit Care Med* 2000;162:328-30.
 47. Döring G, Hoiby N; Consensus Study Group. Early intervention and prevention of lung disease in cystic fibrosis: A European consensus. *J Cyst Fibros* 2004;3:67-91.
 48. Nixon GM, Armstrong DS, Carzino R, et al. Clinical outcome after early *Pseudomonas aeruginosa* infection in cystic fibrosis. *J Pediatr* 2001;138:699-704.
 49. Munck A, Bonacorsi S, Mariani-Kurkdjian P, et al. Genotypic characterization of *Pseudomonas aeruginosa* strains recovered from patients with cystic fibrosis after initial and subsequent colonization. *Pediatr Pulmonol* 2001;32:288-92.
 50. Stutman HR, Lieberman JM, Nussbaum E, Marks MI. Antibiotic prophylaxis in infants and young children with cystic fibrosis: Randomized controlled trial. *J Pediatr* 2002;140:299-305.
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