Comparative efficacy of two doses of nebulized colistimethate for the eradication of \textit{Pseudomonas aeruginosa} in children with cystic fibrosis

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

\textbf{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.

\textbf{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 \textit{P} \textit{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).

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

\textbf{Key Words:} Colistimethate; Cystic fibrosis; \textit{Pseudomonas aeruginosa}; Pulmonary function tests

\textbf{Étude comparative sur l’efficacité de deux doses de colistiméthate en aérosol pour la suppression de \textit{Pseudomonas aeruginosa} chez des enfants atteints de mucoviscidose}

\textbf{CONTEXTE :} La mucoviscidose touche les appareils digestif et respiratoire. La maladie évolue vers une détérioration du fonctionnement pulmonaire en raison d’une colonisation des tissus par \textit{Pseudomonas aeruginosa}, et le traitement suppressif ne fait pas consensus. On utilise déjà le colistiméthate en aérosol à cette fin, mais il reste encore à en déterminer la dose et la durée optimales.

\textbf{BUT :} L’étude avait pour but de comparer l’efficacité de deux doses de colistiméthate en aérosol (30 mg contre 75 mg, deux fois par jour) en vue de la suppression de \textit{P} \textit{aeruginosa} chez des enfants atteints de mucoviscidose et sujets à une colonisation épisodique.

\textbf{MÉTHODE :} Une étude de cohorte, comportant à la fois un volet historique (30 mg) et un volet prospectif (75 mg), a été menée de 1999 à 2003. La collecte de données s’est faite à partir de l’examen de dossiers médicaux.

\textbf{RÉSULTATS :} Quatre-vingt-onze patients ont été retenus dans le groupe rétrospectif, pour un total de 111 cures, et vingt patients ont été sélectionnés dans le groupe prospectif, pour un total de 20 événements. Aucun écart statistiquement significatif n’a été relevé en ce qui concerne le taux de suppression de \textit{P} \textit{aeruginosa} au bout de 28 jours et de 90 jours, quelles que soient la dose de colistiméthate ou la durée du traitement. Cependant, il est ressorti un écart statistiquement significatif (P=0.004) entre la 1re journée et la 90e journée dans tous les sous-groupes analysés (peu importe la dose de médicament ou la durée du traitement) pour ce qui est de la capacité vitale forcée seulement. Dans le groupe de patients chez qui il y avait eu suppression de la bactérie au bout de 28 jours (après 3 semaines de traitement par le colistiméthate), une nouvelle infection est apparue chez 50 % des patients au bout de 5,75 mois en moyenne, indépendamment de la dose administrée, dans le groupe de patients chez qui il y avait eu suppression de la bactérie au bout de 90 jours (après 15 semaines de traitement par le colistiméthate), une nouvelle infection est apparue chez 50 % des patients concernés (14) au bout de 7,3 mois en moyenne (P=0.28).

\textbf{CONCLUSION :} Il n’y a aucune différence d’efficacité entre la dose de 30 mg et de 73 mg de colistiméthate en vue de la suppression de \textit{P} \textit{aeruginosa} chez des enfants atteints de mucoviscidose et sujets à une colonisation épisodique.

\textbf{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 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}
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 non-typeable *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 referred 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 parameters. 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 χ² test was used. Change in pulmonary function was evaluated using 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 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 size and power of 80%, the present study would have been able to detect a difference of 33% or more between the two groups.

| 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 (8.6) | | |
| 4 | 1 (1.3) | | |
| Male sex, % | 61 | 50 | NS |
| Age, years | | | |
| Mean ± SD | 6.3±4.2 | 8.8±4.2 | NS |
| Median (interval) | 5.9 (3.3–15.7) | 9.3 (2.0–16.7) | |
| Weight, kg | | | |
| Mean ± SD | 22.2±13.2 | 27±13.0 | NS |
| Median (interval) | 19.2 (4.8–64.4) | 24.1 (11.5–58.4) | |
| Height, cm | | | |
| Mean ± SD | 110.2±27.4 | 123.9±13.0 | NS |
| Median (interval) | 107.8 (55.7–169.5) | 124.5 (61.90–163.4) | |

NS Not significant
Forced expiratory flow during 25% to 75% of FVC (% of predicted value)

Eradication rate

Forced expiratory volume in 1 s (% of predicted value)

Table 2

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

<table>
<thead>
<tr>
<th></th>
<th>Retrospective study group†</th>
<th>Prospective study group‡</th>
<th>p‡</th>
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</thead>
<tbody>
<tr>
<td>FVC (% of predicted value)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Day 1 (n=76)</td>
<td>99.1±12.7</td>
<td>99.3±11.5</td>
<td>0.967</td>
</tr>
<tr>
<td>Day 90 (n=76)</td>
<td>101.4±12.7</td>
<td>104.8±10.2</td>
<td>0.325</td>
</tr>
<tr>
<td>Day 90 – day 1 (n=76)</td>
<td>2.3±9.5</td>
<td>5.6±8.8</td>
<td>0.220</td>
</tr>
<tr>
<td>Forced expiratory volume in 1 s (% of predicted value)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Day 1 (n=76)</td>
<td>94.0±14.7</td>
<td>90.4±13.0</td>
<td>0.372</td>
</tr>
<tr>
<td>Day 90 (n=76)</td>
<td>94.7±14.3</td>
<td>94.4±12.4</td>
<td>0.957</td>
</tr>
<tr>
<td>Day 90 – day 1 (n=76)</td>
<td>0.7±11.9</td>
<td>4.1±8.2</td>
<td>0.284</td>
</tr>
<tr>
<td>Forced expiratory flow during 25% to 75% of FVC (% of predicted value)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 (n=76)</td>
<td>88.2±37.7</td>
<td>68.1±29.4</td>
<td>0.052</td>
</tr>
<tr>
<td>Day 90 (n=76)</td>
<td>86.8±38.3</td>
<td>75.2±24.0</td>
<td>0.252</td>
</tr>
<tr>
<td>Day 90 – day 1 (n=76)</td>
<td>−1.3±26.1</td>
<td>7.1±22.5</td>
<td>0.242</td>
</tr>
<tr>
<td>Eradication rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 28 (n=127)</td>
<td>55.1%</td>
<td>55%</td>
<td>NS</td>
</tr>
<tr>
<td>Day 90 (n=129)</td>
<td>50%</td>
<td>52.6%</td>
<td>NS</td>
</tr>
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</table>

*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 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 antibiotic regimens, 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 tests may be attributed to the absence of those measurements (for example, other medications, such as recombinant dornase-alpha 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 \( P. \text{aeruginosa} \), 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 \( P. \text{aeruginosa} \) in children with CF and intermittent colonization. The optimal antibiotic regimen for early \( P. \text{aeruginosa} \) 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

21. ME Hodson, CG Gallagher, JR Goven. 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.
39. National Committee for Clinical Laboratory Standards. Method for dilution antimicrobial susceptibility tests for bacteria that grow
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