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Aerosolized antibiotic therapy for chronic cystic fibrosis airway infections: continuous or intermittent?

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Summary
The use of inhaled therapies for chronic respiratory infections in cystic fibrosis represents a substantive treatment burden to patients. In this paper, we review the evidence supporting two commonly used inhaled antibiotic regimens for chronic respiratory infections – continuous vs. intermittent (28 days on followed by 28 days off) therapy. We included trials of good methodological quality and excluded those in which the primary intent was eradication. In total, we included 13 trials (5 of intermittent therapy and 8 of continuous therapy) and summarized their main findings, placing particular emphasis on change in FEV_1, emergence of resistance and patient adherence. What is evident from our review is that both continuous and intermittent inhaled therapies work. Although an intermittent regimen would be intuitively "better" in terms of cost savings and patient tolerability, there is currently a lack of head-to-head trials that compare the same drugs (and dosages) using the two different regimens to make such a recommendation based on robust clinical evidence.

Introduction

The earliest known description of cystic fibrosis (CF) was in 1938 by Dorothy Andersen of the New York Babies Hospital.[1] Since that time, survival from the disease has increased steadily. Only 3% of adults with CF born between 1947 and 1949 could expect to survive to 30 years of age.[2] The median predicted survival from the 2009 UK registry is now 34 years,[3] and the previously predicted survival to >50 years of age for children born in 2000 is now looking realistic, even in the absence of effective therapy to correct the genetic defect.[4]

During the 1970s and 1980s, the main emphasis on CF treatment focused on antibiotics. Although intravenous (IV) access techniques improved and patients lived longer, many became chronically infected with *Pseudomonas aeruginosa*. In the UK, 36% of the CF population is chronically infected with *P. aeruginosa* and 15% with *Staphylococcus aureus*.[3] In the US, the figures are 52% and 51%, respectively.[5]

Reduced levels of chronic *P. aeruginosa* infection have been attributed by some to the aggressive use of nebulized antibiotics, regular microbiological monitoring, prompt antibiotic treatment of first isolates, and intensive use of IV antibiotics when inhaled antibiotics have failed.[6-8] One Belgian center achieved a rate of chronic *P. aeruginosa* of 20.7%, compared with a national average of 48%.[6] In the UK, Lee and colleagues reported a decline in the number of patients with chronic *P. aeruginosa* infection, from 24.5% to 18.1% ($P < 0.05$), which was thought to be the result of these measures.[7] An increase in representation among individuals with a relatively "mild" CF phenotype identified by molecular diagnostic techniques may also have contributed to the observed decrease in prevalence of chronic *P. aeruginosa* infection in the population.

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Continuous vs intermittent therapy: how did we get here?

Three antibiotics are commonly used for inhalation therapy in patients with CF: tobramycin, colistin, and aztreonam. Colistin has been in use in Europe since the 1980s, following studies by Littlewood and colleagues[9] and Jensen and associates.[10] Its use remains widespread, due largely to its tolerability profile and the fact that *P. aeruginosa* resistance is relatively rare.[11] Inhaled tobramycin has been the preferred chronic suppressive therapy against *P. aeruginosa* in North America since the landmark trial by Ramsey and collaborators in 1999.[12] Only one head-to-head comparison of inhaled colistin vs. tobramycin has been conducted to date,[13] and although tobramycin appeared to be more efficacious, the dose of colistin used was 1 MU twice daily, which is only half the maximum recommended dose. Inhaled aztreonam is relatively new to the market, having been granted US Food and Drug Administration (FDA) approval for use in 2010.

The specific reasons for choice of inhaled antibiotic are beyond the scope of this article. A critical question in the selection of a therapeutic regimen of chronic suppressive aerosolised antibiotics for CF is whether to use continuous or intermittent therapy (usually 28-day on/off cycles). If the efficacy and safety of the two approaches were similar, then intermittent therapy would win hands down because of increased convenience and reduced cost. Two other potential advantages, although intuitively sensible, should be accepted only if robust evidence is present – namely, greater adherence to treatment and reduced antimicrobial resistance. Comparison of the two approaches to scheduling is difficult, because historically, a continuous regimen has been used with aerosolised colistin and an intermittent regimen with tobramycin (and lately with aztreonam).

The origin of the 28-day intermittent treatment cycle can be traced back to a trial of 3-times-daily nebulized tobramycin, administered continuously for 3 months. This study was conducted in 22 patients (no control group) in the 1980s.[14] Mean forced expiratory volume in 1 second (FEV_1) improved significantly in these patients at 28 days, but the improvement had diminished by the end of 3 months of treatment and was close to baseline approximately 1 month after treatment ceased. In addition, substantially more bacterial isolates with reduced susceptibility to tobramycin were observed after 3 months of nebulized tobramycin, although this proportion declined over the following year (off treatment). A subsequent randomized, blinded, placebo-controlled, crossover study by Ramsey and colleagues[15] (Table 1) again reported significant improvements in FEV_1 and forced expiratory flow between 25% and 75% of forced vital capacity ($FEF_{25\%-75\%}$) during 28 days of treatment with inhaled tobramycin – improvements that diminished from days 28 to 56 of treatment. There was also an associated decrease in *P. aeruginosa* sputum density by a factor of 100 with tobramycin treatment during the first 28 days, but less of a decline following the first 28 days.[15] Based on these two studies, it was postulated that continued administration of tobramycin beyond 28 days would not result in an increased treatment effect and was more likely to lead to selection for bacterial isolates resistant to tobramycin.[14]

Intermittent therapy has been accepted as "standard of care" by such regulatory agencies as the FDA. It is likely that pharmaceutical companies undertaking clinical trials of new formulations of inhaled antibiotics will be expected to compare their product with intermittent nebulized tobramycin and presumably will adopt an intermittent regimen for the new product, as well for current ongoing trials.

Comparisons of continuous vs. intermittent therapy

Only one trial (Nikolaizik et al., 2008[21]) compared continuous vs. intermittent therapy. Different doses of tobramycin were used in the two treatment arms, rendering comparison difficult. No other head-to-head comparisons of the same dose of inhaled antibiotic administered either continuously or in 28-day on/off cycles have been conducted to date, thus a direct comparison of safety and efficacy (or adherence and antimicrobial resistance) is not possible.

So can we make indirect comparisons? The randomized, controlled trials (RCTs) that have evaluated long-term aerosolised antibiotic therapy in patients with CF have been compared in an exhaustive systematic review, conducted by Ryan and coworkers.[22] These 19 trials (with 1724 participants) found that lung function (as measured by FEV_1) improved and exacerbations of respiratory symptoms were less frequent in the antibiotic-treated group vs. the placebo-treated group.

In this article, we have categorized the RCTs of nebulized antibiotics for chronic suppressive therapy in CF conducted to date according to whether the regimen was intermittent (Table 1) or continuous (Table 2). Table 3 lists trials in which treatment was administered for 28 days only, which cannot be said to be intermittent or continuous, and have been included for comparison. As in the systematic review, RCTs of poor methodological quality or <4 weeks' duration have been omitted and six new studies have been added.[13,18,19,30–32] We have omitted trials in which the intention of therapy was eradication of *P. aeruginosa* (not trials of chronic therapy). Of note, the study of intermittent aztreonam lysine by Oermann and colleagues[18] is a continuation trial of two previous trials: AIR-CF1[19] and AIR-CF2,[20] respectively. The Nikolaizik trial[21] is not included in any of the tables, as it compares continuous and intermittent regimens, and a trial that considered only patients with *Burkholderia cepacia* complex has been omitted as well.[34]

Trials of intermittent therapy

Table 1 illustrates trials of intermittent therapy. These 5 trials have enrolled 1293 participants, with a median treatment duration of 20 weeks (range, 12 to 72 weeks). Whenever FEV_1 was a recorded outcome (not always the primary outcome), these data have been included in the table. Although FEV_1 is not necessarily the most clinically relevant outcome (or the most important to patients), it is objective, has been reported most consistently, and is closely related to prognosis.[35] Hence, it is included as the outcome measure in Table 1, in order to allow comparison between trials. In 3 of the 5 trials, the FEV_1 improved to a significantly greater degree in the active vs. the comparator group. Of the remaining 2 trials, Oermann and associates[18]

Table 1
Studies evaluating intermittent aerosolized antibiotic therapy (28 days on/28 days off)

Study	Year	Drug	Dose (mg)	No. of times per day	Comparator	Randomized participants (N)	Duration (weeks) until final FEV_1	Benefit claimed for active treatment arm (FEV_1)	*P* value
Ramsey et al.[15]	1993	Tobramycin	600	3	Placebo	71	12	FEV_1 % predicted better in active group	<0.001
Ramsey et al.[12]	1999	Tobramycin (TOBI®, Novartis Pharmaceuticals, East Hanover, NJ, USA)	300	2	Placebo	520	20	Active: FEV_1 increased by 10% of predicted; Placebo: FEV_1 declined by 2% of predicted	<0.001
Murphy et al.[16]	2004	Tobramycin (TOBI®, Novartis Pharmaceuticals, East Hanover, NJ, USA)	300	2	Routine care[a]	181 (63 completed the study)[b]	56	Comment: "modest (insignificant) trend towards improvement in percent predicted FEV_1 for the TSI group over the control group observed at weeks 20 and 32" but numbers not reported	Not reported
Chuchalin et al.[17]	2007	Tobramycin (Bramitob®, Chiesi Farmaceutici S.p.A., Parma, Italy)	300	2	Placebo	247	20	Estimated difference of improvement in FEV_1 % predicted between groups = 6.38% favoring active treatment	<0.001
Oermann et al.[18]	2010	Aztreonam lysine	75	2	Aztreonam lysine 75 mg 3 times dailyl	274[c]	72	**At end of cycle 1:** Twice-daily dosing: FEV_1 increased by 4.9% of predicted; 3-times-daily dosing: FEV_1 increased by 8% of predicted. **At end of cycle 9:** Twice-daily dosing: FEV_1 increased by 1.2% of predicted; 3-times-daily dosing: FEV_1 increased by 4.2% of predicted	Not reported

FEV_1, forced expiratory volume in 1 second.
[a] What constitutes routine care not specified in the study methodology; however, control subjects could potentially receive inhaled tobramycin as part of routine care for exacerbations.
[b] Early termination of study attributed to difficulty in enrollment and observation of significant difference between treatment groups with respect to time to first hospitalization.
[c] Participants recruited from those in AIR-CF1[19] and AIR-CF2[20] (see Table 3.) as an extension trial comparing twice-daily vs 3-times-daily dosing with aztreonam, not vs placebo.

Table 2
Studies evaluating continuous aerosolized antibiotic therapy

Study	Year	Drug	Dose	No. of times per day	Comparator	Randomized participants (N)	Duration (months) until final FEV_1	Benefit claimed for active treatment arm (FEV_1)	*P* value
Hodson et al.[23]	1981	Gentamicin Carbenicillin	80 mg 1 g	2 2	Placebo	20	12	Active: Mean FEV_1 at end of treatment = 1.566 L; Placebo: Mean FEV_1 at end of treatment = 1.300 L	<0.001
Nolan et al.[24]	1982	Cephaloridine plus oral cloxacillin	500 mg	2 or 3	Oral cloxacillin only	47	24	Active: FEV_1 decreased by 3.7% of predicted; Placebo: FEV_1 decreased by 2.8% of predicted	Not reported
Kun et al.[25]	1984	Gentamicin	20 mg	2	Placebo	33	24[a]	Active: FEV_1 changed by 0% of predicted; Placebo: FEV_1 decreased by 6% of predicted	<0.03
Nathanson et al.[26]	1985	Gentamicin	80 mg	3	Placebo	7	3	Active: FEV_1 at end of treatment 1.02 L; Placebo: FEV_1 at end of treatment 1.02 L	Not reported
Jensen et al.[10]	1987	Colistin	1 MU	2	Placebo	40	3	Active: FEV_1 decreased by 11% of predicted; Placebo: FEV_1 decreased by 17% of predicted	Not reported
Stead et al.[27]	1987	Ceftazidime alone vs Carbenicillin plus Gentamicin	1 g 1 g 80 mg	2	Saline	18	4	On entry: mean FEV_1 = 1.29 L; Active (ceftazidime): mean FEV_1 = 1.70 L; Active (gentamicin/carbenicillin): mean FEV_1 = 1.70 L; Placebo: mean FEV_1 = 1.48 L	<0.02 <0.01
Day et al.[28]	1988	Colistin	1 MU	2	Saline	14	6	Comment: "FEV_1 decreased significantly during placebo months and maintained during treatment" but no numbers reported	Not reported
MacLusky et al.[29]	1989	Tobramycin	80 mg	2	Saline	27	33	Active: FEV_1 decreased by 0.7% of predicted; Placebo: FEV_1 decreased by 7.1% of predicted	<0.01

FEV_1, forced expiratory volume in 1 second.
[a] Crossover study. Both groups switched treatment arms after 12 months.

Table 3
Studies of 28 days' duration

Study	Year	Drug	Dose (mg)	No. of times per day	Comparator	Randomized participants (N)	Duration (weeks) until final FEV_1	Benefit claimed for active treatment arm (FEV_1)	*P* value
Hodson et al.[13]	2002	Tobramycin (TOBI)	300	2	Colistin 1 MU twice daily	126	4	Active: FEV_1 increased by 6.7% of predicted; Colistin: FEV_1 increased by 0.37% of predicted	0.008
Lenoir et al.[33]	2007	Tobramycin (Bramitob)	300	2	Placebo	59	4	Active: FEV_1 increased by 16% of predicted; Placebo: FEV_1 increased by 2.5% of predicted	0.003
McCoy et al.[20]	2008	Aztreonam lysine (Cayston®, Gilead Sciences, Foster City, CA, USA) AIR-CF2	75	2 or 3	Placebo	211	4	Active: FEV_1 increased by 4.1% of predicted[a]; Placebo: FEV_1 decreased by 2.5% of predicted	0.001
Retsch-Bogart et al.[19]	2009	Aztreonam lysine (Cayston) AIR-CF1	75	3	Placebo	164	4	Difference between active and placebo groups in FEV_1 (change in % predicted from baseline) =10.2%[a]	<0.001
McColley et al.[30]	2010[b]	Fosfomycin/tobramycin for inhalation (FTI)	80/20 vs 160/40	2 vs 2	Placebo	119	FEV_1 not measured	Primary outcome was change in CFU sputum density of CF-associated pathogens	Not reported
Geller et al.[31]	2011	Levofloxacin	120 vs 240 vs 240	1 vs 1 vs 2	Placebo	151	4	240-mg twice-daily group: FEV_1 increased by 6.25% from baseline; Placebo: FEV_1 decreased by 2.36% from baseline	0.003
Wainwright et al.[32]	2011	Aztreonam (AZLI)	75	3	Placebo	157	4	Active: FEV_1 increased by 0.29% from baseline; Placebo: FEV_1 decreased by 2.5% from baseline	0.021

CF, cystic fibrosis; CFU, colony-forming unit; FEV_1, forced expiratory volume in 1 second.
[a] Primary outcome was time to additional antibiotics.
[b] This trial commenced following a 28-day run-in course of inhaled aztreonam.

did not report a statistical test, although the authors did comment that generally there was greater improvement in FEV_1 observed in the 3-times-daily compared with the twice-daily treatment group. The remaining study by Murphy and coworkers[16] was terminated early and did not detect a significant improvement in FEV_1, although the trend appeared to favor active treatment.

Recent trials have used a primary outcome measure that is more relevant to patients. McCoy and coworkers[20] used time to IV antipseudomonal antibiotic use (21 days longer in the group receiving nebulized aztreonam lysine; $P = 0.007$). The primary efficacy endpoint in the study by Retsch-Bogart and colleagues[19] was change in patient-reported respiratory symptoms on the Respiratory Scale of the CF Questionnaire-Revised[36] (9.7-point improvement; $P = 0.001$; a minimum difference of 5 points was set a priori).

Few side effects have been reported in these trials, although tinnitus (a recognized adverse effect associated with tobramycin use) occurred more often in the active group in the largest trial of inhaled tobramycin.[12] Clearly, nebulized antibiotics have the potential to do harm. Along with tinnitus, acute kidney injury has been reported with the use of nebulized tobramycin,[37] although the occurrence is rare. The use of 28-day on/off cycles will reduce lifetime drug exposure, and, hence, the risk for renal toxicity and ototoxicity with nebulized tobramycin use. Furthermore, in animal models, the half-life of aminoglycoside antibiotics in the hair cells of the inner ear is measured in months,[38] so an alternate monthly regimen should allow for improved drug clearance.

So what about antimicrobial resistance? Burns and associates[39] reported the antimicrobial resistance data from the pivotal trial of nebulized tobramycin,[12] using the accepted minimum inhibitory concentration (MIC) breakpoints for parenteral therapy. The percentage of patients with a strain of *P. aeruginosa* having an MIC above the parenteral breakpoint (>16 μg/mL) increased from 13% to 23% among individuals receiving inhaled tobramycin over the 24-week trial (vs. a decrease from 10% to 8% among controls). The parenteral MIC breakpoint used to define resistance may not be relevant in these circumstances, however, as much higher concentrations of antibiotics are achieved by the inhaled route. Hodson and collaborators[13] reported "a small increase" in MIC following 28 days of treatment in tobramycin-treated patients but not in colistin-treated patients, but they presented no data. The study of long-term nebulized aztreonam lysine[18] reported no increase in antimicrobial resistance in either arm, although 3 patients in the times-daily group experienced first isolation of *B. cepacia* after commencing the study therapy. Neither the Burns paper[39] nor the 28-day duration aztreonam lysine trials[19,20] demonstrated an increase in such other pathogens as *B. cepacia* complex, *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans*.

Adherence to (or compliance with) treatment is usually better in clinical trials than in routine practice. Briesacher and colleagues[40] identified 804 patients with CF and determined their adherence to treatment by means of claims made through occupational health insurance plans. The authors concluded that only 7% of patients received ⩾4 cycles of inhaled tobramycin per year ("high adherence"), compared with the 6 cycles prescribed. High adherence was associated with a reduced risk for hospitalization (odds ratio, 0.4; 95% confidence interval, 0.19 to 0.84) compared with low adherence (⩽2 cycles per year). This is very different from the adherence reported in clinical trials. In the studies shown in Table 1, in which adherence has been defined, the definition of satisfactory adherence varies from participants taking 66%[20] to 80%[13] of prescribed doses. With both definitions, adherence was >90%. A Canadian study estimated that about half of the cost of nebulized tobramycin might be recouped because of a reduced requirement for hospital-based and home IV antibiotic treatment.[41] However, poor adherence in routine clinical practice may diminish considerably the economic benefits claimed. In addition, the demand on time is substantial when patients are receiving inhaled antibiotics. Administration time with nebulized tobramycin solution is 15 to 20 minutes, excluding the time required for cleaning and sterilization of the delivery device[42]; this equates to approximately 14 to 18 hours per month. An on/off regimen would save a considerable amount of time every other month; however, whether this would result in improved adherence is not known.

Trials of continuous therapy

In contrast to trials of intermittent therapy, trials of continuous nebulized antibiotics enrolled fewer participants (206 in total; see Table 2). Where FEV_1 was measured, most patients showed an improvement, with the exception of the study by Nolan and associates,[24] in which a slightly larger decrease in FEV_1 % predicted was reported in the active treatment group. However, the authors noted that this did not reach statistical significance.

Although they enrolled fewer participants, these studies were of longer duration (median, 9 months; range, 3 to 33 months) and provided a total of 283 person-years of drug exposure to yield data on adverse effects. The more recent studies of intermittent therapy, however, may include open-label continuation phases to assess long-term safety. Studies of continuous therapy are generally older (1981 to 1989 vs. 1993 to 2010 for studies of intermittent aerosolized antibiotic therapy). Trials in the 1980s were not subject to the same rigorous regulations on reporting adverse events that have applied over the last 2 decades. Nevertheless, in trials of continuous therapy, adverse effects were no more common in the active treatment group than in the comparator group.

In terms of antibiotic resistance, 2 studies did not report on this,[26,28] whereas 4 reported no significant difference.[10,23-25] Of the remaining 2 trials, MacLusky and colleagues[29] reported the development of tobramycin-resistant *P. aeruginosa* in 4 of the 12 active treatment arm patients who were originally infected with sensitive strains, and Stead and coworkers[27] reported the development of *P. aeruginosa* with partial resistance in 3 patients (1 to ceftazidime and 2 to carbenicillin), who regained full sensitivity 1 to 2 months following completion of the trial. Although it may well be that continuous use of some classes of inhaled antibiotics can result in persons with CF becoming refractory to their beneficial effects, in vitro antibiotic susceptibility testing is a notoriously poor method for predicting the efficacy of antibiotics delivered by any route in patients with CF.[43-45] For this reason, use of in

Table 4
Current studies

Agent	Company	Dose	Comparator	Regimen	ClinicalTrials.gov identifier
Aztreonam (AZLI)	Gilead	75 mg 3 times daily	Tobramycin 300 mg twice daily	3 cycles of 28 days on/off	**NCT00757237**
Oral ciprofloxacin plus inhaled colistin	Universitaire Ziekenhuizen, Leuven, Belgium	30 mg/kg/day 2 MU twice daily (continuous for 3 months)	Tobramycin 300 mg twice daily for 28 days	Eradication regimens	**NCT01400750**
Liposomal amikacin (Arikace®)	Insmed	560 mg once daily	Tobramycin 300 mg twice daily	3 cycles of 28 days on/off	**NCT01315678**
Levofloxacin (MP-376)	Mpex Pharmaceuticals	240 mg twice daily	Tobramycin 300 mg twice daily	3 cycles of 28 days on/off	**NCT01270347**
Levofloxacin (MP-376)	Mpex Pharmaceuticals	240 mg twice daily	Placebo	28 days on followed by 28 days off	**NCT01180634**

vitro antibiotic susceptibility tests to predict the relative long-term efficacy of continuous vs. intermittent inhaled antibiotic therapy is problematic.

Single-agent therapy vs rotation of antibiotics

We identified no clinical trials that directly compared a single inhaled antibiotic vs the rotation of antibiotics in patients with CF.

The way forward

From a thorough review of the literature, it is apparent that both intermittent and continuous regimens of aerosolised antibiotics are effective in maintaining lung function and are associated with few adverse effects. Recent studies have shown that aerosolised antibiotics may reduce respiratory symptoms and defer the need for IV antibiotics. A 28-day on/off regimen of nebulized tobramycin is associated with an increase in antimicrobial resistance, but in general, emergence of other pathogens is not seen with either intermittent or continuous therapy. A major confounding factor is the fact that trials of continuous therapy were conducted almost a decade earlier than trials of intermittent therapy. These trials used different antibiotics (gentamicin and beta-lactams, as well as tobramycin) and enrolled far smaller numbers of participants.

There are planned and ongoing studies (Table 4) of other antibiotics, but these generally follow the precedent of intermittent therapy. Clearly what is needed are well-designed and adequately powered RCTs of intermittent vs continuous therapy, using the same dose of the same antibiotic in each arm. The challenges and limitations associated with the designs of such trials are addressed in the article by VanDevanter et al. in this supplement.[46]

Conclusion

Both intermittent and continuous inhaled antibiotics work, although direct comparisons of their efficacy are difficult. The administration of intermittent antibiotics is less time-consuming to patients; however, whether this necessarily means improved adherence is not yet known. It would be easy to assume that adherence would be better with intermittent regimens, although the opposite may also be true if patients do not experience any appreciable deterioration in health during "off" months and therefore feel reluctant to resume treatment at the start of "on" months. The cost of intermittent therapy might be less expensive than that of continuous therapy, although this would be true only when the same drugs (in the same dosage) are compared head to head with both regimens, and we have not identified any trials in which this has been performed. Some evidence suggests that long-term use of inhaled tobramycin is associated with increased resistance; however, given that deterioration in lung function is the main predictor of mortality among individuals with CF, this factor must be taken in the context of the patient's well-being as a whole. In conclusion, additional trials are required before we can base our treatment decisions, at least in terms of scheduling strategy, on good evidence.

Conflict of interest statement

David Lo, MB – no conflict of interest to report.

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