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REVIEW

Inhalation of antibiotics in cystic fibrosis

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Inhalation of antibiotics in cystic fibrosis. D.J. Touw, R.W. Brimicombe, M.E. Hodson, H.G.M. Heijerman, W. Bakker. ©ERS Journals Ltd 1995.

ABSTRACT: Aerosol administration of antipseudomonal antibiotics is commonly used in cystic fibrosis. However, its contribution to the improvement of lung function, infection and quality of life is not well-established. All articles published from 1965 until the present time concerning the inhalation of antibiotics in cystic fibrosis were collected by computerized literature search and analysed.

Effective aerosol delivery is compromised by nebulizers with limited capacity to produce particles in the respirable range. Twelve studies concerning maintenance treatment were published. Four uncontrolled studies evaluating antibiotic aerosol maintenance treatment in stable patients indicated a beneficial effect in terms of reducing the number of hospital admissions. Eight placebo-controlled studies were found; six of these showed a significant improvement of lung function in the treatment group. Four studies showed a reduction of the number of hospital admissions. In some studies, there was a considerable negative effect of the nebulized placebo solution on the outcome, probably due to the improper choice of its osmolarity. Studies with antibiotic aerosols as adjunct to intravenous therapy in cystic fibrosis patients with an acute exacerbation showed no enhancement of the clinical effects of the intravenous antibiotic by the aerosol; sputum colony counts, however, were lower. Toxicity studies carried out so far have shown no renal or ototoxicity; however, long-term toxicity studies still have to be performed using higher dosages. Introduction or selection of resistant bacteria is relatively rare, but remains a matter of concern.

Aerosol maintenance treatment with an appropriate antibiotic in high enough dosage can be recommended for patients with cystic fibrosis chronically infected with *P. aeruginosa*, and may improve lung function and reduce the number of hospital admissions due to an acute exacerbation.

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Cystic fibrosis (CF) is the most common potentially fatal inherited disease in Western countries. It is associated with an abnormality in the transport of chloride ions across the epithelial membranes of exocrine glands, which causes a diminished water content of their secretions [1, 2].

Early pulmonary changes in CF are inflammatory and noninfective [3]. Morphological changes of dilatation and hypertrophy of the bronchial glands are followed by mucous plugging. This viscid mucus in the airways allows bacterial colonization, with consequent infection of the respiratory tract, contributing to ongoing tissue damage. The chronic airway infection is assumed to maintain a vicious circle, where inflammation leads to progressive destruction of pulmonary tissue, which in turn facilitates infection. *Haemophilus influenzae* and *Staphylococcus aureus* are usually the first pathogens encountered in childhood. As the lung disease progresses, colonization by *Pseudomonas aeruginosa* will follow. After a period of intermittent colonization with *P. aeruginosa* the colonization will become chronic in most CF patients, and will be virtually impossible to eradicate [4]. Over 60% of Pseudomonas isolates from CF patients have a mucoid colony morphology, which is associated with poor response to antibacterial therapy and deterioration in lung function [5].

Prognosis of CF is determined by the progression of the pulmonary disease. It has improved dramatically over the last few decades, mainly due to a higher efficacy of antibiotic treatment. Antibiotic treatment is the mainstay of present respiratory therapy. It should, however, be used in conjunction with chest physiotherapy, bronchodilators, and other agents to promote bronchial clearance when appropriate. Traditionally, only exacerbations have been treated with 2–3 week antibiotic courses. *H. influenzae* and *S. aureus* can usually be treated effectively with oral antibiotics. In case of an exacerbation due to *P. aeruginosa*, oral antibiotic treatment can be given with fluoroquinolones [6]. Intravenous antipseudomonal treatment is needed in case of resistance to fluoroquinolones.

The notion that the persisting chronic airway infection leads to progressive destruction of pulmonary tissue has urged clinicians to give adequate maintenance treatment

between exacerbations. Maintenance treatment for *H. influenzae* and *S. aureus* can be effectively administered orally [7]. Patients treated this way had greater well-being and fewer hospital admissions [7]. The distinction between intermittent colonization with *P. aeruginosa* and chronic infection is important because early treatment of the intermittent colonization may postpone or even prevent the development of a chronic infection, as will be discussed later on. In CF patients with chronic Pseudomonas infection, it has been demonstrated that antibiotic therapy leads to a decreased bacterial load in the lungs, together with improvement in lung function [8]. Because of rapid development of resistance, maintenance treatment with fluoroquinolones for Pseudomonas infections is not a realistic option. Therefore, several CF centres treat patients chronically infected with *P. aeruginosa* with intermittent courses of intravenous anti-pseudomonal antibiotics [4, 9].

An interesting option for maintenance treatment of patients chronically infected with *P. aeruginosa* is the use of inhaled antibiotics. When an aerosolized antibiotic is inhaled, theoretically, effective local concentrations can be obtained and antibiotics can be administered without the problems usually seen when they are administered intravenously [10]. Aerosol administration of antibiotics has been used since the 1940s [11]; however, its contribution to the improvement of lung function, infection and quality of life is not well-established. The aim of this review is to evaluate the efficacy and side-effects of aerosolized antibiotics in CF. We therefore summarized all published literature on the inhalation of antibiotics in CF.

Antibiotic delivery during aerosolization

Although aerosol delivery of antibiotics had taken place since the 1940s, until 1985 surprisingly little information existed on the output characteristics of nebulizers and on the nebulization of antibiotic solutions.

Aerosols are subject to impaction and gravitational sedimentation [12]. Impaction occurs, mainly with larger particles, whenever the transportation is fast and changes direction, or is turbulent. Impaction, therefore, will take place in the upper airways (mouth, pharynx and larynx) and large airways of the lung down to 2 mm in diameter. Sedimentation is a time dependent process, in which small aerosol particles settle in the airways under the influence of gravity. This takes place in the small airways and alveoli. Generally, particles greater than 8 µm in diameter will impact, and particles of 1–8 µm in diameter may be deposited by impaction and sedimentation in large and in small airways and in alveoli [12, 13]. Particles less than 1 µm in diameter may not be deposited at all [12].

Therapeutic aerosols are usually heterodisperse, *i.e.* they comprise particles of different size. Their behaviour is best described by the mass median aerodynamic diameter (MMAD). Half of the aerosol mass is contained in particles smaller, and the other half of the aerosol mass is contained in particles larger, than the MMAD [14]. It is assumed that the MMAD for aerosols should not be greater than 5 µm if sedimentation in the smaller airways and alveoli is required. To adequately treat the pulmonary lesion in CF, where involvement begins in the smaller bronchioles and extends towards the bronchi, the nebulizer should produce particles in the range 1–5 µm [13]. However, there is a wide variation between different nebulizers in the mean size and range of sizes of particles generated [14, 15]. Apart from particle diameter, osmolarity is important for several reasons. Firstly, therapeutic aerosols may be hygroscopic and absorb water within the respiratory tract and, subsequently their size will increase; therefore, their aerodynamics cannot be fully predicted. Secondly, bronchial secretions are iso-osmolar. If large amounts of hypotonic or hypertonic solutions are added to them, mucosal irritation may occur [13].

There are also factors relating to the apparatus and the patient determining the efficacy of therapeutic aerosols. Antibiotics are usually aerosolized by nebulizing a solution of the drug, although dry powder inhalation has also been reported [16, 17]. A nebulized aerosol can be produced by an air jet or by ultrasonic sound waves. In jet nebulizers, particle size is inversely related to the gas flow rate [14], whereas in ultrasonic nebulizers, below 2 MHz, particle size is related to the wave length of the capillary waves produced on the surface of the liquid [18]. NEWMAN *et al.* [19] have evaluated several commercially available jet nebulizers for use with gentamicin solution. Aerosol output, droplet size and nebulization time were assessed. They found a 10 fold difference between the most and the least efficient delivery system. Efficiency increased with airflow rate and volume to be nebulized. At airflow rates of 12 $L \cdot min^{-1}$ and an antibiotic solution volume of 4 mL, only 2 out of the 4 nebulizers tested produced 37–44% of the gentamicin dose in respirable (*i.e.* <5 µm diameter) droplets [19]. Another advantage of a high airflow is a reduction of nebulization time. For example, the nebulization time decreased from 17–25 min at 6 $L \cdot min^{-1}$ to 9–19 min at 12 $L \cdot min^{-1}$ for the nebulizers tested. The same authors evaluated the aerosolization of 1 g carbenicillin in 3–4 mL water by different nebulizers and compressors [20]. There was a wide range in the output of respirable carbenicillin (200–600 mg) and in nebulization time (18–50 min). The authors also found an increase of the carbenicillin concentration in the container during aerosolization due to a preferential evaporation of the solvent.

To quantify the deposition of aerosols in the airways, several radioaerosol studies have been performed [21, 22]. ^{99m}Tc labelled solution was aerosolized using a jet-nebulizer. MMAD was in the respirable range. Mean pulmonary deposition varied between 6.6–9% of the amount placed in the nebulizer [21, 22], whereas 50% remained attached to the wall of the nebulizing system [21]. Mean peripheral deposition was 16%, and was inversely correlated with forced expiratory volume in one second (FEV_1) [22]. Sputum levels of gentamicin were poor predictors for the efficacy of the nebulizers tested; high sputum levels were associated with proximal deposition and distribution in a small sputum volume

and, thus, the therapeutic effect may not be as great [21]. NEWMAN and co-workers [23] studied the deposition of carbenicillin (1 g in 4 mL) after jet nebulization by a Turret nebulizer operating at 9 $L \cdot min^{-1}$, or by an Inspiron Mini-neb nebulizer operating at 6 $L \cdot min^{-1}$, in seven stable CF patients. The solution was labelled with ^{99m}Tc bound diethylenetriamine penta-acetic acid (DTPA). With the Turret nebulizer (MMAD=3.2 µm) 76% of the aerosol-dose was deposited in the lung, and with the Inspiron nebulizer (MMAD=7.3 µm) this figure was 41%. Due to the larger droplets, the Inspiron nebulizer gave more oropharyngeal deposition. There were no data given on the amount of the solution that reached the patient before deposition.

KUNI *et al*. [24] have shown, using ^{99m}Tc-bound DTPA aerosol in CF patients suffering from an acute exacerbation, that the penetration of an aerosolized solution in the lung is better when aerosolization is preceded by physiotherapy and bronchodilators and is not further improved when intravenous antibiotics are administered. Given the improved lung function tests after adequate intravenous antibiotic treatment, one might also have expected better DTPA aerosol study results. The authors explain this by suggesting that the small airways were not yet cleared of mucus, so that penetration could not have taken place.

BARAN *et al*. [25] studied the concentration of tobramycin in bronchoalveolar lavage fluid (BALF) after inhalation of 80 mg by jet nebulizer (particle size: 75% between 0.5–3 µm). In the first aliquot of BALF, the mean tobramycin concentration was 2 $mg \cdot L^{-1}$ (range 0.1–9.2 $mg \cdot L^{-1}$). Corresponding blood levels were low (<0.1–0.2 $mg \cdot L^{-1}$). The tobramycin concentration in sputum was well above the minimal inhibitory concentration (MIC) for most pathogenic microorganisms. The authors concluded that the high concentrations after deposition may well explain the improvement in selected patients with cystic fibrosis.

In general, aerosol delivery is a very inefficient method of delivering the antibiotic. Even with the most efficient nebulizer, only 10% of the medication is deposited in the lung; the other 90% is either impacted on the oropharynx and swallowed, or exhaled into the surrounding atmosphere.

There are other factors also affecting the deposition of nebulized particles in the respiratory tract. The size of the respiratory tract is important. In general, the smaller the bronchi, *e.g*. due to mucus plugging, the greater is the deposition at any given particle size. But the particles must be small to reach the bronchioles [13]. When a droplet size is too small, deposition may not be accomplished. Deposition may also be a problem in those areas where airflow is minimal, and the sites where infection is presumably greatest. This might limit the therapeutic effectiveness, particularly in patients with an acute exacerbation. This suggests that early anti-pseudomonal treatment with aerosolized antibiotic is needed to limit infection and destruction of pulmonary tissue. Respiratory rate and depth of respiration also influence deposition. In general, more deposition occurs at slower respiratory rates and with deeper breaths [13, 23].

The combination of antibiotics with mucolytics deserves further attention. *In vitro*, mucolytics reduce the viscosity of the sputum [26], whereas *in vivo*, this effect has been questioned [27, 28]. *In vitro* studies have shown that the addition of 1% mesna reduces the minimal inhibitory concentration from azlocillin for *P. aeruginosa* [29]. The addition of 1% N-acetylcysteine to carbenicillin gives the same result [30]. The use of 1% N-acetylcysteine, however, is limited due to its irritating nature, unpleasant taste and aroma. Because the viscosity of the sputum is increased partly due to a high content of deoxyribonucleic acid (DNA) released by leucocytes, the recent introduction of recombinant human deoxyribonuclease (rhDNase) I is an interesting development. Since rhDNase has been found to reduce the viscosity of CF sputum [31], it deserves further investigation to compare the effects of aerosolized rhDNase therapy with nebulized antibiotics. The combination of the two is another interesting option for study, since basic antibiotics, such as tobramycin and colistin, can be precipitated by pulmonary secretions containing DNA [32].

Topics that have not yet received much attention are the output characteristics of ultrasonic nebulizers, the volume fill of the nebulizer, and contamination problems with the exhaled antibiotic. In our experience, nebulization times are much shorter using ultrasonic devices than using jet nebulizers. Ultrasonic nebulizers may theoretically have the disadvantage that the solution will accumulate energy and the temperature will rise, leading to stability problems for heat labile drugs. However, this has not been thoroughly evaluated and it has given no problems in actual practice so far. A small volume to be nebulized leads to unwanted remains of relatively high percentages of the dose in the nebulizer, whereas a large volume leads to smaller percentages of the dose remaining in the nebulizer but to undesirably long nebulization times. Exhaled antibiotics must not contaminate the surroundings of the patient. Either the exhaled antibiotic must be discharged through a tube to the outside air or trapped in a filter.

It can be concluded that for each drug solution to be nebulized the most efficient nebulization system has to be established. It is surprising to note that until the results of the evaluation of the nebulizers discussed above were published, the two nebulizers most commonly used in the UK were the least efficient [14]. Therefore, it is of great importance to make certain that the patient is using the most efficient and cost-effective nebulizer and air compressor system, *e.g*. to use reusable units as they are much cheaper than disposable nebulizers, and to use strong and easy to use compressors and nebulizers, appropriately serviced.

Studies with antibiotic aerosols in stable CF patients

The results of four uncontrolled studies of maintenance treatment with antibiotic aerosols in stable CF patients are summarized in table 1. WALL *et al*. [33] studied the effects of twice daily inhalation of 80 mg tobramycin

Table 1. – Overview of uncontrolled studies of aerosolized antibiotics in stable cystic fibrosis (CF) patients

First author [Ref.]	Year	n	Active aerosol treatment	Study duration Months	Difference from baseline %		
					FEV1	FVC	Hospital admissions
WALL [33]	1983	9	Ticarcillin 1 g *b.i.d.* + tobramycin 80 mg *b.i.d.*	5–15	No change		Reduced*
LITTLEWOOD [34]	1985	7	Colistin 500,000 U *b.i.d.*	3–14			
STEINKAMP [35]	1989	14	Tobramycin 80 mg *b.i.d.*	11–38		+4.2	Reduced
SMITH [36]	1989	24	Tobramycin 600 mg *t.i.d.*	3	+14	+4	

[Ref.]: reference number; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FEF: forced expiratory flow. *: $p<0.05$, compared to baseline.

and 1 g ticarcillin in nine CF patients, during 5–15 months. Most of the patients showed no significant change in FEV1. There was, however, a striking decrease in the number of hospital admissions due to exacerbations during the study period. During a period of 89 patient-months before the study, this group of patients had 31 admissions compared to 5 admissions within a comparable period during the study. LITTLEWOOD *et al*. [34] studied the effects of inhaled colistin, in seven CF patients, on *P. aeruginosa* colonization. After 3–14 months of inhalation therapy, a significant reduction of positive Pseudomonas cultures was found. Data on lung function or hospital admissions were not given. STEINKAMP *et al*. [35] evaluated the effect of twice daily inhalation of 80 mg tobramycin by jet nebulizer, in 14 patients chronically infected with *P. aeruginosa*, during 11–38 months. The forced vital capacity (FVC) increased by 4.2% compared to baseline (not significant) and the ratio weight for height (body weight/height) increased by 2.9%. Compared to historical control data, a mean decrease of FVC by 5.7% of predicted over a year was halted. During the study, the sputum cultures of two patients became negative for *P. aeruginosa*. SMITH *et al*. [36] studied the effects of inhalation of tobramycin, 600 mg *t.i.d.*, on lung function in 24 CF patients. During the 3 month study period, FEV1 and FVC increased 18 and 11%, respectively, in the first 2 weeks. At the end of the study period, FEV1 and FVC were still 14 and 4% increased, respectively, compared to baseline. The authors did not discuss this finding, but the decrease of lung function after the initial increase might be the result of either decreasing compliance, development of resistance to tobramycin, or the selection of resistant microorganisms. At the beginning of the study, 14 out of 20 Pseudomonas isolates were susceptible (MIC ≤ 4 mg·L^{-1}) to tobramycin compared to only four isolates at the end of the study. Follow-up cultures after completion of the study showed a return to susceptibility of all isolates after 1 yr. Quantitative culture of the sputum showed a 1,000 fold decrease of the average *P. aeruginosa* density in the first 2 weeks, suggesting a therapeutic effect.

The results of eight placebo-controlled studies of antibiotic aerosols in stable CF patients are summarized in table 2. HODSON *et al*. [37] published a placebo-controlled study on the effectiveness of aerosolized antibiotics in CF. Aerosolized carbenicillin 1 g and gentamicin 80 mg *b.i.d.* was compared with a normal saline solution for 6 months. Lung function parameters increased significantly in the active treatment group and the number of hospital admissions was reduced. NOLAN *et al*. [38] compared the effect of aerosolized cephaloridin with placebo. Lung function decreased compared to baseline, suggestive of no effect by cephaloridin. This was probably caused by the fact that cephaloridin has no activity against *P. aeruginosa*, whereas more than 90% of the patients studied were infected with *P. aeruginosa*. KUN *et al*. [39] studied the effect of 20 mg aerosolized gentamicin 20 mg *b.i.d.* In the active treatment group, lung functions tended to be better and the total number of in-hospital days was reduced compared to placebo. Changes were small and did not reach significance, possibly due to the small doses of gentamicin aerosolized. CARSWELL *et al*. [40] studied the effects of a combined antistaphylococcal/antipseudomonal regimen with oral flucloxacillin and nebulized tobramycin against double placebo in a cross-over design. At the end of the active treatment period lung function was better than at the end of the placebo period. Because of the chosen design, the results cannot be attributed to inhalation therapy alone. STEAD *et al*. [41] compared the effects of aerosolized ceftazidime alone, and a combination of aerosolized gentamicin and carbenicillin, to aerosolized saline in 18 patients in a randomized, cross-over design. In both active treatment groups, lung function improved and the number of hospital admissions decreased compared to placebo. There was no difference between either active treatment regimens on improvement of the lung function. JENSEN *et al*. [42] studied the effects of aerosolized colistin in 40 patients. Twenty patients received colistin and 20 comparable controls received placebo. Twenty nine patients completed the 3 months study, 18 in the colistin group and 11 in the placebo group. The high rate of drop-outs in the placebo group was partly due to

Table 2. – Overview of placebo-controlled studies of aerosolized antibiotics in stable cystic fibrosis (CF) patients

First author [Ref.]	Year	n	Design	Active aerosol treatment	Control aerosol treatment	Study duration Months	Difference between active aerosol and control %				Difference between active aerosol and baseline %			
							FEV_1	FVC	FEF	Hosp. adm.	FEV_1	FVC	FEF	Hosp. adm.
Hodson [37]	1981	20	Cross-over	Carbenicillin 1 g *b.i.d.* + gentamicin 80 mg *b.i.d.*	Placebo (hypertonic NaCl)	6	+20##	+15**	+14##	Red.				
Nolan [38]	1982	47	Parallel	Cephaloridin 500 mg *b.i.d.*	Placebo	24	-0.9	0.5	1.7		-3.7	-2.0	-0.7	
Kun [39]	1984	29	Cross-over	Gentamicin 20 mg *b.i.d.*	Placebo	12	+15		+35	Red.	+5		+23	
Carswell [40]	1987	6	Cross-over	Flucloxacillin 25 $mg \cdot kg^{-1}$ *b.i.d.*, tobramycin 40 mg *b.i.d.*	Placebo	1	+5*	+4	+4					
Stead [41]	1987	18	Cross-over, three arms	Ceftazidime 1 g *b.i.d.*	Placebo (3.5% NaCl)	4	+15**	+9	+8**	Red.	+32	+20	+13	Red.
				carbenicillin 1 g *b.i.d.* + gentamicin 80 mg *b.i.d.*	Placebo (3.5% NaCl)	4	+15##	+8*	+7*	Red.	+32	+20	+13	Red.
Jensen [42]	1987	40	Parallel	Colistin 1 million U *b.i.d.*	Placebo	3	+6	+11*			-7	-11		
MacLusky [43]	1989	27	Parallel	Tobramycin 80 mg *t.i.d.*	Placebo (0.9% NaCl)	32	+7.8***	+5.4*	+10.8*	Red.	+0.7	+0.2	+0.9	Red.
Ramsey [44]	1993	66	Cross-over	Tobramycin 600 mg *t.i.d.*	Placebo (0.45% NaCl)	1	+4.3#	+2.52	+6.4##					

*: $p<0.05$; **: $p<0.02$; ***: $p<0.01$; #: $p<0.002$; ##: $p<0.001$, compared to control. Hosp. adm.: hospital admissions; Red.: reduction in number of hospital admissions.

a deterioration of the lung function, requiring intravenous antipseudomonal therapy. At completion of the study, patients in the colistin group had a better lung function than patients in the control group, but lung function tests in both treatment groups were worse compared to baseline. Colistin, thus, only slowed the deterioration of the lung function and gave a reduction in acute exacerbations. MACLUSKY *et al.* [43] studied the effects of aerosolized tobramycin. Fifteen patients received the active treatment and 12 patients received placebo. The active treatment showed no deterioration in the lung function compared to baseline, whilst lung function in the placebo group worsened. However, the number of hospital admissions in both groups were comparable.

RAMSEY *et al.* [44] studied the effects of tobramycin, 600 mg *t.i.d.*, given by ultrasonic nebulizer. Seventy one patients were enrolled and 66 patients completed the study. Patients were randomized into two groups. Group one received tobramycin, 600 mg *t.i.d.*, for 28 days followed by half strength physiological saline (placebo *t.i.d.*,) for 56 days. Group 2 received placebo *t.i.d.* for 28 days followed by tobramycin, 600 mg *t.i.d.*, for 56 days. Lung function tests and quantitative culture of sputum were carried out. Results were analysed at the end of the first 28 day period (parallel analysis) and at the end of the study (cross-over analysis). Parallel analysis showed an improvement in FEV1 by 9.7%, FVC by 6.2%, and forced expiratory flow in the mid vital capacity (FEF) by 13% compared to placebo. Cross-over analysis showed an improvement of FEV1 by 4.3%, FVC by 2.5% and FEF by 6.4%. The effect of the active treatment on lung function in the parallel analysis was about double the effect of the active treatment on the lung function in the cross-over analysis. As a possible explanation, a carry-over effect was suggested. However, only the FEV1 showed a significant carry-over effect. Scrutinizing the results of changes in the lung function, a negative effect from the placebo solution (0.45% sodium chloride) on the lung function cannot be excluded. FVC decreased in the first placebo period of 28 days by about 5%, FEV1 decreased by about 6%, and FEF decreased by about 6%. These decreases are far greater than the estimated annual decline in lung function of most patients with CF of approximately 3.5% [15]. As will be outlined in the next paragraph, non-isotonic solutions may lead to a decrease of the lung function, which makes the interpretation of the effects of the active treatment difficult. Emergence of tobramycin-resistant strains of *P. aeruginosa* occurred in 14 out of 71 patients, and was equally distributed over the placebo and active treatment groups [45, 46].

The concept of early antibiotic treatment to postpone or to prevent Pseudomonas colonization from becoming a chronic infection has been studied by VALERIUS *et al.* [47]. They conducted a placebo-controlled study on the effects of oral ciprofloxacin combined with aerosolized colistin whenever *P. aeruginosa* was isolated from the sputum of CF patients. During the study period (27 months), treated patients showed significantly fewer chronic infections with *P. aeruginosa* than untreated patients. This finding indicates the value of early treatment of *P. aeruginosa* whenever cultured in CF.

Interpretation and comparison of these studies is difficult because of the different designs, the wide range in the amount of the antibiotic used, and the possible carry-over effects in cross-over studies. Despite these methodological difficulties, most of the studies showed improved lung function or slowing of the deterioration of lung function in the active treatment group compared to placebo. Additionally, most studies report a reduction in the number of hospital admissions. The emergence of resistant Pseudomonas strains was, as expected, observed but mostly transient. The choice of the appropriate antibiotic should, in principle, be guided by sputum culture. The optimal dose to be aerosolized for the different antibiotics has yet to be established. Early aerosol treatment in conjunction with systemic treatment seems to delay the development of a chronic infection with *P. aeruginosa*. Prolonged aerosol treatment will result in lower sputum counts of *P. aeruginosa*, but as already mentioned, mucoid colonies of *P. aeruginosa* are hard to eradicate [4]. In selected patients, progression of the pulmonary destruction can be slowed by aerosol treatment. Further studies are needed to establish the optimal dose to be aerosolized, and special care must be taken in the choice of placebo solution in controlled studies.

Studies with antibiotic aerosols in addition to intravenous antibiotic therapy in CF patients with an acute exacerbation

In acute exacerbations, the CF patient may be hospitalized or receive home treatment with *i.v.* antipseudomonal antibiotic therapy. Most of the antibiotics which are administered intravenously can also be administered by nebulizer as an adjunct. Clinical studies evaluating the rational use of the combination of *i.v.* and aerosolized antibiotics in acute exacerbations are scarce. HUANG *et al.* [48] have studied several antibiotic regimens with carbenicillin. Seven patients received a regimen consisting of carbenicillin *i.v.* 500 mg·kg^{-1} *q.d.* plus carbenicillin aerosol 500 mg *b.i.d.* The control group (20 patients) received carbenicillin 500 mg·kg^{-1} *q.d. i.v.* only. Therapeutic efficacy was evaluated by changes in the general condition of the patient, frequency and severity of coughing, sleeping respiratory rate, temperature, physical findings, weight gain, roentgenological appearance of the chest, lung function tests and bacteriological studies. In the aerosol group, 4 out of the 7, and in the control group 13 out of the 20, patients improved. The authors concluded that administration of carbenicillin by aerosol combined with its *i.v.* administration did not result in a greater clinical improvement.

STEPHENS *et al.* [49] studied the efficacy of intravenous ticarcillin 300 mg·kg^{-1} *q.d.* and tobramycin 10 mg·kg^{-1} *q.d. versus* intravenous ticarcillin 300 mg·kg^{-1} *q.d.* and tobramycin 10 mg·kg^{-1} *q.d.* plus inhaled tobramycin 80 mg *t.i.d.* in 28 children with CF and an acute exacerbation. Sixteen patients received the combination of

aerosol and *i.v.* therapy, and 12 patients the *i.v.* treatment only. Both groups were comparable in age, Shwachman scores, FEV1, FEF, and sputum colony counts of *P. aeruginosa*. After 2 weeks of therapy, 14 of the 16 patients in the group that received both *i.v.* and aerosol therapy, and 11 of the 12 patients in the *i.v.* only treatment group, were improved and discharged. The three other patients were treated for 21–26 days due to slow improvement. There were no significant differences in the improvement between the two groups. Only the effect of inhaled tobramycin on sputum colony counts was striking. After 14 days, Pseudomonas disappeared from the sputum in 10 out of 16 patients receiving both *i.v.* and aerosol treatment, compared to 3 out of 12 patients who were only treated intravenously. However, this disappearance was only transient; 1–2 months after aerosol therapy, Pseudomonas could be isolated from the sputum in all patients.

SCHAAD *et al.* [50] studied the efficacy of ceftazidime 250 mg·kg^{-1} *q.d.* and amikacin 33 mg·kg^{-1} *q.d.* intravenously *versus* the same regimen plus amikacin aerosol 100 mg *b.i.d.* in 87 patients with CF with an acute exacerbation. Forty three patients were included in the group receiving both *i.v.* and aerosol treatment, and 44 patients in the group receiving *i.v.* treatment alone. Both groups were comparable in age, sex and clinical score. Both groups improved significantly during hospital admission and antibiotic treatment. There were no differences in lung function between the two groups at completion of therapy. The addition of an aerosol treatment resulted in significantly greater eradication of *P. aeruginosa* from the sputum (70 *vs* 41%) for 4–6 weeks after completion of the study.

Based on these studies, it can be concluded that in CF patients with an acute exacerbation the addition of an aerosol treatment to an intravenous regimen consisting of the same antibiotic does not result in a better or a faster rate of clinical improvement. Sputum counts of *P. aeruginosa* may be lower, but this effect is only transient when aerosol treatment is discontinued. However, it is indicated that colony counts of *P. aeruginosa* remain lower for a longer period of time when aerosolization of an antibiotic is given during intravenous treatment and continued afterwards.

Side-effects

Respiratory response to nebulized antibiotic solutions in CF patients

CHUA *et al.* [51] tested the immediate effect of inhaled solutions of different osmolarity on FEV1 in 12 CF patients. Ticarcillin (3,080 mOsm·kg^{-1}) gave the largest fall in FEV1 (-10.7%) compared with normal saline (272 mOsm·kg^{-1}, -4.8%) or tobramycin (248 mOsm·kg^{-1}, -1.2%). The difference between normal saline and tobramycin was not significant. GÖTZ *et al.* [52] tested the immediate effects of inhaled hypo-, iso-, and hypertonic solutions of colistin, diluted with water, 0.45% sodium chloride and normal saline, respectively, in CF patients and volunteers. Mean changes in FEV1 from baseline were: for the hypotonic solution -6.2%; for the hypertonic solution -6.8%; and for the isotonic solution no change. MADDISON *et al.* [53] studied the occurrence of chest tightness in 46 CF patients after inhalation of 2 million units of colistin dissolved in 4 mL normal saline, resulting in a hypertonic solution. Thirty five patients developed a bronchoconstrictor response to colistin. Fifteen patients were intolerant of colistin due to the bronchoconstriction, with a mean fall in FEV1 of 16%. These data indicate that bronchoconstriction can occur due to inhalation of hypo- or hypertonic antibiotic solutions. Therefore, patients should have FEV1 and FVC measurements made before and after nebulization of the antibiotic. If any bronchoconstriction is experienced, measurements should be repeated on a subsequent day, nebulizing bronchodilator before the aerosol antibiotic. In most patients, this will prevent bronchospasm, but in a minority of patients it will not, and in that case either an isotonic solution of the same antibiotic or another antibiotic should be used.

Allergy

Patients have a fairly high rate of allergic reactions to beta-lactam antibiotics; after intravenous administration, many patients become allergic to some [4]. In the studies on aerosol administration of beta-lactam antibiotics reviewed above, no hypersensitivity was reported. However, it seems rational to withhold beta-lactam antibiotics as aerosol in patients with a known allergy. For aminoglycosides, although there used to be much concern about hypersensitivity, allergy is a minor problem [54].

Systemic toxicity

Systemic toxicity is a potential adverse effect of aerosolized antimicrobial agents, particular in the case of the aminoglycosides and colistin. ZACH [55] studied the systemic resorption after inhalation of gentamicin in eight CF patients. The gentamicin dose ranged 120–600 mg. The maximum serum concentration of gentamicin measured, ranged 1.5–4.2 mg·L^{-1}. MUKHOPADHYAY *et al.* [56] studied the ototoxicity following a 400 mg inhalation of tobramycin in 10 patients with CF. Routine pure tone audiometric tests were carried out before and a week after nebulization, and no audiometric abnormalities were detected in any of the patients. Furthermore, serial blood samples were drawn after the inhalation of the aminoglycoside. Tobramycin serum concentrations varied from <0.1 to 2.0 mg·L^{-1} after inhalation. In one patient, a 30 min post-dose serum concentration of 9.9 mg·L^{-1} was measured. In this patient, the serum levels at 15 min post-dose and at 45 min post-dose were 0.3 and 0.9 mg·L^{-1}, respectively. Applying pharmacokinetic principles, such a peak is impossible so that the 9.9 mg·L^{-1} value has to be an analytical or a sampling error [57].

SMITH *et al*. [36] studied the toxicity of 600 mg inhaled tobramycin *t.i.d*. over 3 months in 22 patients with CF [36]. During and after the 3 month study period no renal toxicity, ototoxicity (defined as a decrease of 20 dB or more at any frequency from 250–20,000 Hz in either ear), or vestibular toxicity could be demonstrated. The 24 h urine recovery of tobramycin was 0.15–25 mg (0.008–1.4% of the dose). STEINKAMP *et al*. [35] studied the toxicity after long-term tobramycin aerosol therapy. Fourteen patients received 80 mg of tobramycin aerosol therapy *b.i.d*. for a mean duration of 20 months. No signs of renal or ototoxicity (frequency up to 10,000 Hz) were detected during the study period. Unfortunately, no high tone audiometry was performed. In 50 out of 70 blood samples no tobramycin (*i.e*. <0.1 $mg \cdot L^{-1}$) could be detected; 19 samples showed a serum concentration of 0.1–0.3 $mg \cdot L^{-1}$; and in one sample, drawn 1 h after inhalation, the concentration was 0.4 $mg \cdot L^{-1}$.

MACLUSKY *et al*. [43] studied the toxicity of aerosolized tobramycin (80 mg *t.i.d*.) in 15 patients for 32 months. At the end of the study period, there was no significant trend from baseline for serum creatinine or blood urea nitrogen. All tobramycin serum concentrations measured were less than 1 $mg \cdot L^{-1}$ except for two blood samples (5.8 and 6.5 $mg \cdot L^{-1}$). These high levels were unexplained and attributed to analytical errors.

From the few studies available, it can be concluded that at moderate daily doses (up to 240 mg aerosolized daily) no significant amount of the aminoglycoside nebulized is absorbed systemically, and hence no serious adverse effect on renal, hearing or vestibular function is to be expected, although a striking difference is noted in amount absorbed between gentamicin and tobramycin. At higher daily doses, as used in the studies by SMITH *et al*. [36] and RAMSEY *et al*. [44] (1,800 mg aerosolized) long-term safety studies still have to be carried out. Inhalation is very ineffective with maximally 10% deposition in the lung, therefore large amounts of the aerosolized antibiotics will be swallowed. So far, no studies have been performed on the effects on the gastrointestinal flora during chronic administration.

Drug resistance

Development of resistant Pseudomonas strains or the selection of multiresistant microorganisms is a matter of concern in chronic aerosol treatment. Treatment of an acute exacerbation with intravenous antibiotics may also induce selection of multiresistant strains. Continuous antibiotic administration is feared to have a major impact on the bacterial ecology; it may allow overgrowth of resistant bacteria. The development of antibiotic resistance may cause difficulties in the use of systemic antibiotics during future episodes of acute respiratory deterioration [43]. The occurrence of overgrowth with *Aspergillus fumigatus* is a matter of concern; however, data on this issue are lacking.

Various authors, who have performed trials with nebulized antibiotics in CF patients, have evaluated the emergence of resistant Pseudomonas species in the sputum of their patients before, during and after treatment (table 3). Most studies show little emergence of antibiotic resistant Pseudomonas strains compared to placebo aerosol courses [42, 58], but in some studies as much as 30% resistance is noted [36, 43]. Culture of resistant microorganisms was usually not associated with a poor response to treatment [35, 36, 41, 43]. In most cases, the isolation of resistant microorganisms was transient, indicating that the selection of resistant strains did not result in a major change in the bacterial ecological equilibrium. Frequent changing from one antipseudomonal

Table 3. – Overview of emergence of resistance or selection of resistant strains during aerosolization of antibiotics

First author	[Ref.]	Year	Antibiotic	Duration months	Development of resistance
HODSON	[37]	1981	Carbenicillin+ gentamicin	6	Active: 3/20 resistant Placebo: 3/20 resistant
KUN	[39]	1984	Gentamicin	24	Active: 3/25 resistant Placebo: 2/25 resistant
CARSWELL	[40]	1987	Tobramycin	1	Active: 2/6 resistant Placebo: 1/6 resistant
STEAD	[41]	1987	Ceftazidim Carbenicillin+ gentamicin	4	Not stated
JENSEN	[42]	1987	Colistin	3	No resistant Pseudomonas, no superinfection
STEINKAMP	[35]	1989	Tobramycin	20	Active: 5/21 resistant
SMITH	[36]	1989	Tobramycin	3	Active: 6/21 resistant
MACLUSKY	[43]	1989	Tobramycin	32	Active: 4/14 resistant Placebo: 0/12 resistant
RAMSEY	[44]	1993	Tobramycin	1	Active: 2/71 resistant Placebo: 0/71 resistant Active: 1/71 *Burkholderia cepacia* Placebo: 2/71 *B. cepacia* Active: 4/71 *Xanthomonas maltophilia* Placebo: 2/71 *X. maltophilia*

antibiotic to another (*e.g.* from tobramycin to colistin and *vice versa*) may be an interesting option to prevent a permanent change to antibiotic resistant flora. However, *in vitro* resistance is not invariably associated with a poor response, so in the case of clinical efficacy the antibiotic may very well be continued. In practice, the emergence of resistant microorganisms during aerosolization of colistin is extremely rare (N. Høiby, personal communication). Although there are no studies comparing colistin and tobramycin, one may speculate that, provided the efficacy of the two antibiotics is similar, colistin is to be preferred because of the rare occurrence of resistance. Moreover, in the case of an exacerbation with the emergence of resistance for colistin, tobramycin is still available for intravenous use, whereas the reverse is not advisable because of the toxicity of parenteral colistin.

Another microbiological complication may be the introduction of antibiotic resistant microorganisms by the use of contaminated aerosol solutions [59]. A British survey on the hygiene of nebulizer use in 1990 revealed that in 39% of the 74 wards interviewed, the drug delivery unit was not cleaned or changed between drug doses [60]. This survey was not confined to nebulization of antibiotics or CF centres. Another study found that over one third of nebulizers in domiciliary practice were contaminated with bacteria [61]. In this study, the contaminating flora were predominantly Gram-positive microorganisms.

Burkholderia cepacia (formerly known as *Pseudomonas cepacia*) infection is especially feared in CF units, as in some patients this may lead to a rapid deterioration of lung function and possibly even septicaemia. *B. cepacia* is usually resistant to beta-lactam antibiotics, aminoglycosides, choramphenicol and colistin. Nosocomial outbreaks of *B. cepacia* have been described due to a contamination of mechanical ventilators [62, 63]. NELSON *et al.* [64] were able to demonstrate that indirect transmission of *B. cepacia* between CF patients was possible by contaminated environmental surfaces. The nebulizers in this case were not contaminated. BURDGE *et al.* [65] described how, in their centre for adult CF patients, the use of nebulizers and humidifier treatment was complicated by the transmission of *B. cepacia*. Bacteriological sampling from the reservoirs of the nebulizers showed contamination by *B. cepacia*. This study underscores traditional concerns regarding the potential role of respiratory therapy equipment as a mode for microbial spread, and reinforces the need for proper and routine cleaning and drying of the equipment as well as restriction of the use of the inhalation equipment to just one patient. The nebulizer should be cleaned and dried after each nebulization. It should be disinfected frequently.

Conclusion

Aerosol delivery of antibiotics to CF patients who have Pseudomonas colonization in the lung seems attractive as maintenance treatment. Studies carried out so far have shown that the administration of an antibiotic aerosol to stable patients can reduce the number of exacerbations and hospital admissions. The annual decrease of lung function seems to be slowed or even halted. There are data suggesting that the early treatment of intermittent colonization of *P. aeruginosa* by the combination of a systemic antibiotic and the inhalation of an antibiotic may delay the onset of chronic *P. aeruginosa* infection. Since this approach may play an important role in future, it deserves further attention. Aerosol treatment, when added to an intravenous treatment in patients with an acute exacerbation does not appear to enhance the therapeutic effects of the intravenous treatment; how-ever, it enhances the reduction of sputum counts of *P. aeruginosa*. Therefore, studies of the effects of maintenance aerosolization of an antibiotic after treatment of an acute exacerbation are of interest. In placebo-controlled studies, special attention should be paid to the placebo solution. The antibiotic to be nebulized must, in principle, be chosen based on the resistance pattern of the microorganisms. Patients must be treated with dosages high enough to be effective, but the minimal effective dose still has to be established. Serum concentrations of aminoglycosides after inhalation are low or undetectable, and toxicity studies so far have shown no oto- or renal toxicity. Long-term toxicity studies on higher dosages have not yet been performed. Studies are needed on the effect of chronic aerosol administration on gastrointestinal flora.

The emergence of resistant bacteria in sputum seems to be rare and does not necessarily correlate with a poor response. However, it is undesirable to select resistant bacteria as otherwise useful parenteral antibiotics may be useless for the treatment of an acute exacerbation. More research is warranted into antibiotics not usually used systemically (*e.g.* colistin). It is mandatory to establish the efficacy for each nebulizer/antibiotic combination before using them in clinical practice. Contamination of the aerosol equipment with antibiotic resistant microorganisms is a matter of concern. It has been shown that indirect transmission of microorganisms by this route is possible, and the importance of proper cleaning and drying of all equipment must be emphasized.

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