Systematic review of nebulized antibiotics in cystic fibrosis: evolution of protocol

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INTRODUCTION

Sputum colonization with *Pseudomonas aeruginosa* (PA) leads to pulmonary decline in cystic fibrosis (CF)¹. The results of the first randomized controlled trial (RCT) indicating possible clinical benefit for nebulized anti-pseudomonal antibiotic therapy were published in 1981². These encouraging results led to the widespread use of this therapeutic intervention in CF clinics across the world. Subsequently, however, a more controversial picture began to emerge from further trials (both RCTs and non-RCTs)³. Pharmacological evidence further reinforced this controversy: when radiolabelled, only about 7% of a standard 120 mg dose of nebulized tobramycin could be traced to the patient's lungs, with a further smaller proportion being delivered to the lung periphery (the proposed site of anti-bacterial effect)^{4,5}. Given this restricted delivery, the expected tobramycin concentration of the lower respiratory fluid is likely to be below the minimum bactericidal concentrations for tobramycin required to achieve PA-killing in CF sputum *in vitro*⁶. This realization, together with our knowledge of the significant demands placed by nebulized anti-pseudomonal antibiotic therapy on the patient and the service³, led us to study the possibility of introducing meta-analysis to this area of CF, in order to critically evaluate the evidence in favour of nebulized anti-pseudomonal antibiotic therapy use.

EVOLUTION OF METHODOLOGY FOR META-ANALYSIS IN CF

When we started work on this project 4 years ago, the Cochrane Collaboration was at an early stage of its development. While the Collaboration was eager to provide us with telephone support and gave us the Data Analysis in

Clinical Medicine software (a fore-runner of the current Revman package) free of charge, the current infrastructure for support had not developed. With support from SO, MS started her early experiments, merging little snapshots of data from one or two RCTs in this field. We soon realized that, although there was conflict between the conclusions of individual nebulized anti-pseudomonal antibiotic therapy trials, it was possible to combine data from a number of RCTs on nebulized anti-pseudomonal antibiotic therapy in order to conclude on efficacy. We worked through a year (1994) when search strategies were undergoing a process of rapid evolution. Lefebvre described the Cochrane search strategy the same year⁷, which we adopted as far as possible. Candidate studies were identified from *Medline*, *Current Contents*, bibliographies of textbooks, reviews, editorials, conference proceedings and personal communications. RCTs were quality scored before listing for meta-analysis. Non-RCTs were used to draw up a table of descriptive analyses. Details of our search strategy and method for quality scoring have been described³.

Therapeutic end-points for comparison were defined after an initial review of literature. They were as follows:

- The number of pulmonary exacerbations requiring treatment with systemic antibiotics
- The number of patients with altered respiratory pseudomonas load
- Alteration in spirometric lung function (forced expiratory volume (FEV₁) and forced vital capacity (FVC)), providing a measure of overall effect
- Alteration in the number of patients with pseudomonas species in sputum resistant to the nebulized antimicrobial
- Increase in auditory, renal and respiratory side effects reported during the course of therapy.

For dichotomous outcome measures, we calculated the exact likelihood estimate of the common odds ratio and its associated 95% confidence intervals (CI). For continuous outcome measures (i.e. lung function), the overall effect of treatment (with 95% CI) was calculated as the mean difference in normalized FEV₁ and FVC within an individual

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Table 1 Clinical heterogeneity. The characteristics of the randomized controlled trials listed for the meta-analysis. The quality index ranges from 0 (lowest) to 1 (highest). (Reproduced from Ref 3 by permission of the BMJ Publishing Group.)

<i>Trial</i>	<i>Study design</i>	<i>No. of patients</i>	<i>Antibiotics used</i>	<i>Duration of intervention</i>	<i>Quality index</i>	<i>Daily cost of drugs (£ sterling)</i>
Hodson, 1981 (1)	Cross-over	20	Carb+gent	6 months	0.8	3.60
Jenkins, 1985 (2)	Cross-over	30	Amikacin	3 weeks	0.7	20.23
Jensen, 1987 (3)	Parallel	40	Colistin	90 days	0.9	4.20
Stead, 1987 (4)	Cross-over (3-period)	18	Carb+gent or ceft	4 months	0.8	3.60 (carb+gent) 30.00 (ceft)
Ramsey, 1993 (5)	Cross-over (3-period)	71	Tobramycin	28 days	1.0	61.18

Carb=carbenicillin, gent=gentamicin, ceft=ceftazidime

Table 2 Typical odds ratios and pooled rate differences [95% confidence intervals (CI) in brackets] for dichotomous outcome measures on meta-analysis of all suitable randomized controlled trials. If 95% CI include unity, the results are not significant. Thus nebulized antibiotics significantly decrease respiratory *Pseudomonas* (Ps) load, reduce the frequency of pulmonary exacerbations requiring systemic antibiotics and do not encourage the development of resistant respiratory *Pseudomonas* strains (however, note the possibility of type II error). (Reproduced from Ref 3 by permission of the BMJ Publishing Group)

<i>Outcome measures</i>	<i>O/T:O/C</i>	<i>Typical odds ratio</i>	<i>Pooled rate difference</i>
Subjects with pulmonary exacerbations treated with systemic antibiotics	16/85 : 31/78	0.37 (0.19 to 0.74)	-0.22 (-0.35 to -0.09)
Subjects with decreased respiratory Ps load	12/81 : 74/74	0.09 (0.03 to 0.32)	-0.22 (0.50 to -0.07)
Subjects with Ps strains resistant to nebulized antibiotic	8/73 : 2/65	3.56 (0.98 to 12.88)	0.06 (-0.02 to 0.15)

O=No. positive for outcome; T=No. treated; C=No. of controls

Table 3 Overall effect of nebulized anti-pseudomonal therapy on respiratory function. Results are presented as percentage change with standard errors of the mean (SEM) and 95% confidence intervals (CI). Nebulized antibiotics are shown to exert a significant beneficial effect on spirometric lung function. As study 4 includes two different antibiotic protocols, 4.1 represents the overall effect with ceftazidime and 4.2 with carbenicillin and gentamicin. (Reproduced from Ref 3 by permission of the BMJ Publishing Group)

<i>Trial code</i>	<i>Normalized FEV₁ (% mean predicted)</i>		<i>Normalized FVC (% mean predicted)</i>	
	<i>Mean change (SEM)</i>	<i>95% CI</i>	<i>Mean change (SEM)</i>	<i>95% CI</i>
3	6.0 (3.6)	1.1 to 14.5	11.0 (4.6)	1.9 to 20.1
4.1	17.0 (27.7)	-37.3 to 71.4	9.4 (16.7)	-23.4 to 42.2
4.2	17.0 (29.2)	-40.3 to 74.3	10.2 (17.7)	-24.5 to 44.9
5	9.7 (2.5)	4.8 to 14.6	6.2 (2.5)	1.3 to 11.0
Pooled effect	8.6 (2.0)	4.6 to 12.6	7.3 (2.1)	3.1 to 11.5

FEV₁=forced expiratory volume; FVC=forced vital capacity

trial and the weighted mean difference (WMD) across trials. The costs of alternative protocols of nebulized anti-pseudomonal therapy were also estimated.

RESULTS OF THE META-ANALYSIS

Our search strategy (listed in detail in Ref 3) yielded 172 references for 1966–1975, 641 for 1976–1983, 832 for 1984–1990 and 740 for 1991–1995. These references were then manually searched. A total of 14 clinical studies on nebulized antibiotic therapy in CF were identified. Five

RCTs (with acceptable quality indices, ranging from 0.7 to 1.0) were found (Table 1). Nine trials were unsuitable for meta-analysis, usually because lack of appropriate randomization or inadequate outcome description. Individual RCTs showed lack of statistically significant effect for many of the outcome measures. When subjected to meta-analysis, however, the pooled effect of nebulized anti-pseudomonal antibiotic therapy identified statistically significant benefit for respiratory pseudomonal load, number of pulmonary exacerbations requiring systemic antibiotic therapy (Table 2) and lung function (FEV₁ in 1 and FVC) (Table 3). For

example, while studies 1, 4 and 5 show lack of effect and study 3 suggests beneficial effect on the number of pulmonary exacerbations requiring treatment with systemic antibiotics, the pooled effect clearly demonstrates statistically significant benefit (see Table 2). The odds ratios (with 95% CI) for individual clinical trials have been plotted elsewhere³. Table 2 presents the pooled odds ratios for the comparison of dichotomous outcome measures across trials, while Table 3 presents the overall effect (defined as the mean difference in normalized FEV₁ and FVC within an individual trial and the weighted mean difference across trials) for the comparison of continuous outcome measures across trials. No major side-effects with nebulized anti-pseudomonal antibiotic therapy were found, although a trend towards an increase in resistance to sputum PA was noted³.

THE NEED TO PROGRESS TO A UNIFIED COCHRANE COLLABORATION PROTOCOL

The meta-analysis summarized above may have provided a new perspective to CF management. However, techniques for systematic reviewing are constantly being improved. It is necessary to define outcome measures before the review process, in order to study the effect of an intervention more objectively. Because we were only feeling our way along during the initial meta-analysis, this procedure was not fully implemented: we drew up our list purely on the basis of our knowledge of outcome measures derived from an initial review of the literature. A standardized method for quality scoring of trials has been adopted by the Cochrane CF Group; to maintain conformity with other reviews, this method requires to be adopted for any updated version of our review. The protocol for review follows a standardized format (see Appendix). Unless this format is followed by all reviewers, reviews will no longer be comparable. A meta-analysis for a scientific journal like *Thorax*³ is written with a scientific and clinical audience in mind. The Cochrane Database for Systematic Reviews is, however, meant to be accessible to a more general audience, which includes patients and their carers. Finally, data from new RCTs will be available with time, and the systematic review will need to be regularly updated; the Cochrane database provides a mechanism for such regular updating. For all these reasons, we have felt it important to adapt our review to the Cochrane format. Based on the above, we have recently developed a protocol for a systematic review of nebulized anti-pseudomonal antibiotic therapy in CF, which has been included in the Cochrane Database for Systematic Reviews, following peer review. The protocol, laid out in standard Cochrane format, shows the rigorous procedure that is currently followed for such reviews, providing an interesting contrast to the flexible, perhaps innovative, but non-

standardized approach of the meta-analysis described above. We will present the Cochrane version of our protocol below, to allow the reader to study this contrast.

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APPENDIX

Nebulized anti-pseudomonal antibiotic therapy in CF

Cover sheet

Short title: Nebulized antibiotic therapy in CF
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Conflict of interest

None

Background

Fifty years ago¹, it occurred to a chest physician that airway infections may be better treated if antibiotics were administered as tiny liquid particles via nose and mouth during breathing, rather than by swallowing or as injections, the more conventional routes for administration. Now many cystic fibrosis (CF) patients are treated with inhaled (usually referred to as nebulized, because the drug is administered via a nebulizer, where air under high pressure breaks antibiotic solution into a fine mist) antibiotics. This treatment takes in total around 20–30 min to administer everyday. The daily cost (to the National Health Service) is variable, ranging between £3–£60/day.

Patients with CF often develop a long-term respiratory infection with a particular bacteria (*Pseudomonas* species). These infections are long-standing, difficult to treat, and associated with worsening respiratory symptoms and poor lung function². Most CF units intensify anti-bacterial management following first respiratory isolation of *Pseudomonas*; intravenous, oral and nebulized anti-pseudomonal antibiotics are used in varying combinations. In addition, drugs other than those with direct antibacterial effect (e.g. steroids, which alter the inflammatory response to *Pseudomonas*) may be used to treat the effects of respiratory *Pseudomonas* infection.

Nebulized anti-pseudomonal antibiotics (henceforth referred to as nebulized antibiotics, since anti-pseudomonal antibiotics are by far the commonest variety of antibiotics used and are the subject of this review) are widely used for the treatment of CF patients. For example, over one-third of 968 patients enrolled in the US Pulmozyme (rhDNase) study³ and 48% of CF patients attending an Irish clinic were noted to be on long-term nebulized antibiotics⁴. There is, however, limited consensus on effectiveness, reflecting the small number of trials, with small sample sizes, varying designs and methodological problems.

There are real and potential negative aspects for the use of nebulized antibiotics. The drugs and equipment have a financial cost, there is an additional treatment burden for patients, together with the potential for drug-induced adverse effects (either by direct drug effect, or through the emergence of drug-resistant strains).

Objectives

The objective of this review is to determine whether nebulized antibiotic therapy improves the outcome of patients with CF. We wish to test the following hypotheses:

- 1 Nebulized antibiotic therapy improves lung function (FEV₁ and FVC)
- 2 Nebulized antibiotic therapy reduces the number of respiratory exacerbations requiring treatment with systemic antibiotics
- 3 Nebulized antibiotic therapy use does not lead to increased resistance in respiratory tract *Pseudomonas* strains to the nebulized anti-pseudomonal used in each RCT
- 4 Nebulized antibiotic therapy use does not lead to a local allergic reaction to antibiotics, or to renal or auditory impairment.

Materials and methods

Criteria for considering studies for this review.

Types of studies We will aim to identify all randomized and pseudo-randomized clinical trials (published or unpublished) where nebulized antibiotics have been compared to placebo in patients with CF.

Types of participants Children and adults with defined CF, diagnosed clinically and by sweat/genetic testing, including all ages and all degrees of severity. Patients at all stages of pulmonary deterioration will be included.

Types of intervention Nebulized antibiotic at any dose for a period of at least 3 months.

Types of outcome measures

- (a) Alteration in lung function (FEV₁ and FVC)
- (b) Number of respiratory exacerbations requiring treatment with systemic antibiotics
- (c) Development of resistant respiratory tract *pseudomonas* strains to the nebulized anti-pseudomonal used in each RCT
- (d) Antibiotic-related local allergic or infective (e.g. fungal) disease, renal or auditory impairment. Any index of renal impairment, including creatinine clearance, random serum creatinine and/or urea levels will be considered
- (e) Weight
- (f) Quality of life
- (g) Survival or age at death

Outcome data will be grouped into those measured at 1, 3, 6 and 12 months and annually thereafter. If outcome data

are recorded at other time periods then consideration will be given to examining them as well.

Search strategy for identification of studies All publications describing RCTs of the use of nebulized antibiotics in CF will be identified through detailed computerized searches for *Medline* from 1985—present (using the search strategy described in the *Cochrane Handbook*, Section V, Appendix 2) and *Embase* 1985—present. Unpublished work will be identified through the searching of the abstract books of the three major CF conferences, the International CF conference, the European CF conference and the North American CF conference. Additional RCTs will be found from reference lists. All these references to trials will be obtained from the specialist CF register held by the editorial base of the Cochrane CF group, the search strategy for this register is described in detail in the module of the Cochrane group.

In addition, full text searching of the *Journal of Pediatrics* from 1988–1997 will be undertaken.

Methods of review

Trials will be listed, and then reviewed by all three reviewers, SM, GR and MS, using a standard data acquisition form. The methodological quality of each trial will be assessed by each reviewer. Specifically, reviewers will examine details of the randomization method, whether the trial was blinded, whether intention to treat analyses were possible from the available data, and if the number of patients lost to follow-up or subsequently excluded from

the study was recorded. Data will be individually extracted by each reviewer. The reviewer will then calculate the pooled estimate for treatment effect for each of the outcomes listed. For continuous outcome measures, the overall effect of treatment will be calculated as the mean difference within an individual trial and the weighted mean difference across trials. Disagreement will be resolved by consultation between all three reviewers.

Description of studies

Methodological quality of included studies

Results

Discussion

References

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