

Nebulised antipseudomonal antibiotic therapy in cystic fibrosis: a meta-analysis of benefits and risks

S Mukhopadhyay, M Singh, J I Cater, S Ogston, M Franklin, R E Olver

Abstract

Background – To establish the benefits and risks of nebulised antipseudomonal antibiotic therapy in cystic fibrosis the results of relevant randomised controlled trials were combined.

Methods – The therapeutic end points compared were (a) number of pulmonary exacerbations requiring treatment with systemic antibiotics, (b) measurable alteration in respiratory tract pseudomonal load, (c) alteration in lung function on spirometric assessment, (d) development of resistance in respiratory tract *Pseudomonas* strains to the nebulised antipseudomonal used in each randomised controlled trial, and (e) renal and auditory impairment.

Results – Five studies were suitable for meta-analysis, eight others could not be included because of inadequate outcome description or the lack of appropriate randomisation. Meta-analysis shows benefit for nebulised antipseudomonal antibiotic therapy with no demonstrable adverse effect other than a possible increase in *in vitro* antibiotic resistance of *Pseudomonas aeruginosa* of the respiratory tract.

Conclusions – Although inferences drawn from individual randomised controlled trials concerning the benefits and risks of this form of therapy are conflicting, pooled effect size establishes benefit with nebulised antipseudomonal antibiotic therapy and emphasises its relevance to the integration of information in other areas of controversy relating to the treatment of this disease.

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Sputum colonisation with *Pseudomonas* species is associated with a decline in respiratory function in patients with cystic fibrosis.¹ Since 1981, 14 published studies have attempted to evaluate the effect of nebulised antipseudomonal antibiotics on respiratory status in children and adults (7-42 years of age) with *Pseudomonas* colonisation of the respiratory tract.²⁻¹⁵ Smallness of sample size, variability of study design, and the possibility of carryover effect in randomised controlled trials have confounded efficacy and safety estimates, resulting in limited areas of consensus in this field.^{6,16,17} In this study we have used the statistical technique of

meta-analysis to combine the results of these randomised controlled trials in order to increase statistical power to improve estimates of effect.

Methods

SEARCH STRATEGY

We followed a search strategy defined by the UK Cochrane Centre for optimal recall of randomised controlled trials.^{18,19} The strategy is formatted for search using the SilverPlatter version 3.10 which was adapted for the Medline database on CD-ROM from CD-Plus using Ovid search software. The main difference is that the SilverPlatter operator "near" (denoting terms within the same sentence) does not exist in the Ovid search software. We used instead the Ovid proximity operator "adjn" where two terms are within "n" words of each other. We therefore replaced the SilverPlatter search statements (clin* near trial*) in titles (TI) or abstracts (AB) with the Ovid statement (clinical\$ adj2 trial\$).tw and the SilverPlatter statement (singl* or doubl* or trebl* or tripl*) near (blind* or mask*) in TI or in AB, with the Ovid statement ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).tw. Other statements such as (clin\$ adj3 trial\$).tw and (singl\$ adj2 blind\$).tw were tested but the additional references retrieved were all either irrelevant or already retrieved by other search statements. The higher the value of "n" in the operator "adjn", the slower the search, therefore in the interests of speed and relevance we opted for the search statements above. A new publication type, "controlled clinical trial", introduced by the National Library of Medicine in January 1995 was added to the second stage of the search. Stage IV of the strategy searches for papers on cystic fibrosis which are not animal only studies and combines this search with stages I, II, and III in turn. The search was conducted in April 1995 and looked back as far as 1966. The complete search strategy is given in the Appendix. Searches of *Current Contents*, bibliographies of textbooks, reviews, editorials, international cystic fibrosis conference proceedings and personal communications supplemented the above. Where the published information on randomised controlled trials was inadequate for meta-analysis, retrieval of unpublished data was attempted by writing letters to first authors. Only randomised controlled trials were considered for meta-analysis. Non-randomised controlled trials were used to draw up a table of descriptive analyses.

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Table 1 Clinical heterogeneity: characteristics of the randomised clinical trials listed for the meta-analysis

Trial (code no.)	Study design	No. of patients	Antibiotics used	Duration of intervention	Quality index	Daily cost of drugs (£ sterling)
Hodson ³ (1)	Crossover	20	Carbenicillin + gentamicin	6 months	0.8	3.60
Jenkins ⁵ (2)	Crossover	30	Amikacin	3 weeks	0.7	20.23
Jensen ⁴ (3)	Parallel	40	Colistin	90 days	0.9	4.20
Stead ³ (4)	Crossover (3-period)	18	Carbenicillin + gentamicin or ceftazidime	4 months	0.8	3.60 (carbenicillin + gentamicin) 30.00 (ceftazidime)
Ramsey ⁶ (5)	Crossover (3-period)	71	Tobramycin	28 days	1.0	61.18

The quality index ranges from 0 (lowest) to 1 (highest) (see Methods).

QUALITY INDEX

The randomised controlled trials were listed and evaluated on a quality score²⁰ based on the following five parameters:

1. Adequate description of patient groups in terms of age, sex, sweat electrolyte criteria for diagnosis of cystic fibrosis, and documentation of respiratory tract colonisation with *Pseudomonas* species.
2. Adequate description of intervention in terms of name and dose of drug/placebo, duration of administration, and characterisation of delivery apparatus.
3. Adequate assessment of outcomes by clinical assessment, lung function studies, audiometry, and renal function monitoring.
4. Outcome assessment on patients completing the study and details of withdrawals or drop-outs.
5. Adequate description of the effects of intervention on all measures of outcome.

Scores of 0, 1 or 2 were assigned for each parameter giving a maximum attainable score of 10. A quality index²¹ was determined by dividing the score attained by the maximum attainable and could thus range from 0 to 1 (table 1).

THERAPEUTIC END POINTS FOR COMPARISON

The following outcome measures, defined after an initial review of the literature, were studied in order to evaluate the efficacy and safety of nebulised antibiotic treatment in cystic fibrosis:

1. The number of pulmonary exacerbations requiring treatment with systemic antibiotics.
2. The number of patients with altered respiratory *Pseudomonas* load.

3. Alteration in spirometric lung function (forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC)) providing a measure of overall effect, as defined below.

4. Alteration in the number of patients with *Pseudomonas* species in sputum resistant to the nebulised antimicrobial treatment.

5. Increase in auditory, renal and respiratory side effects reported during the course of treatment.

ESTIMATE OF COST

The costs of alternative protocols of nebulised antipseudomonal therapy were also estimated (expenses for active drug alone as incurred by Pharmacy, Tayside Health Board, UK; prices correct for May 1994).

STATISTICAL METHODS

Dichotomous outcome measures

With the use of appropriate software²² two techniques for pooling the data were assessed. The first was the exact likelihood estimate of the common odds ratio and its associated 95% confidence intervals (CI). This method assumes a fixed treatment effect across the studies with variation in observed outcomes caused only by sampling error. It is open to criticism on the grounds that, if the accompanying exact test of heterogeneity is statistically significant, the validity of the pooled estimate can be questioned.²³ An alternative method proposed by DerSimonian and Laird was therefore also used; this technique makes no assumption about the constancy of effect and incorporates a measure of interstudy variability into the pooled estimate.²⁴

Continuous outcome measures

The overall effect of treatment (with 95% CI) was calculated as the mean difference in normalised FEV₁ and FVC within an individual trial and the weighted mean difference (WMD) across trials.²⁵

Results

The above search strategy yielded 172 references for 1966–75, 641 for 1976–83, 832 for 1984–90, and 740 for 1991–5. These were then manually searched. A total of 14 clinical studies on nebulised antibiotic therapy in cystic fibrosis were identified. Table 1 lists the characteristics of the randomised controlled trials (n = 5) suit-

Table 2 Studies excluded from the meta-analysis, reason(s) for exclusion, with a descriptive analysis of conclusions in relation to the measures of outcome addressed in the meta-analysis

Study list	Reason for exclusion	No. of patients	Outcome measures				
			1	2	3	4	5
Wall ¹⁰	NR	9	+	-	-	-	-
Kun ⁹	NR	33	0	0	+	+	-
Franz ¹⁴	NR	28	+	0	0	0	0
Nathanson ¹¹	IOD	7	0	-	-	0	0
Wang ¹²	Retrospective	107	0	++	0	++	0
Stroobant ¹⁵	IOD	21	+	0	-	+	-
Carswell ¹⁸	NR	6	0	-	+	+	-
Steinkamp ⁷	NR	14	+	-	+	+	-
Maclusky ¹³	NR, no placebo	27	+	-	+	++	-

NR = non-randomised; IOD = inadequate outcome description.

0 = outcome not addressed, - = opposes, + = supports, ++ = strongly supports the conclusion that nebulised antipseudomonal therapy leads to: (1) reduction in the number of episodes in hospital to treat respiratory exacerbations with intravenous antibiotics; (2) greater numbers of subjects with measurably decreased load or eradication of *Pseudomonas* species in the sputum; (3) improvement in spirometric lung function; (4) greater numbers of subjects with respiratory tract *Pseudomonas* species resistant to the administered antipseudomonal treatment; (5) renal and auditory impairment.

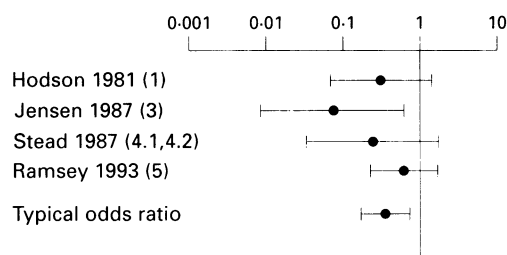


Figure 1 Individual and pooled (typical) log odds ratios with 95% confidence intervals of nebulised antipseudomonal drugs and pulmonary exacerbations requiring treatment with intravenous antibiotics. The typical odds ratio shows a statistically significant beneficial effect for nebulised antipseudomonal therapy on the number of patients developing pulmonary exacerbations who require treatment with intravenous antibiotics.

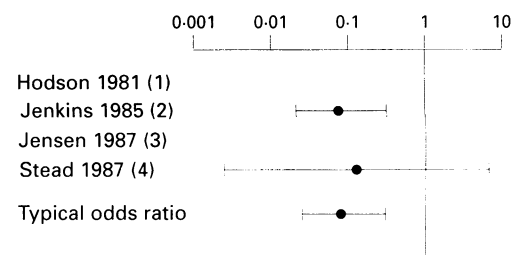


Figure 2 Individual and pooled (typical) log odds ratios with 95% confidence intervals of nebulised antipseudomonal drugs and decrease in respiratory *Pseudomonas* load. The typical odds ratio shows a statistically significant beneficial effect for nebulised antipseudomonal therapy on the number of subjects with a decrease in respiratory *Pseudomonas* load. Odds ratios could not be calculated for studies 1 and 3: there was no difference between "experiment" and "control" limbs.

able for meta-analysis, together with the daily cost of drugs for individual antipseudomonal antibiotic protocols. Further data for study 5 were presented in a subsequent letter²⁶ which was appended to the parent study. The quality index of the included trials ranged from 0.7 to 1.0. Nine trials were unsuitable for meta-analysis, the most common faults being non-randomisation or inadequate outcome description; table 2 gives the reasons for exclusion, together with descriptive analyses of the outcome measures for these studies. Tables 3 and 4 show the results of statistical analysis of pooled outcome measures. Figures 1–3 present the individual and pooled log odds ratios in graphical form.

EFFECT ON PULMONARY EXACERBATIONS

Whilst studies 1, 4, and 5 show lack of effect, study 3 suggests beneficial effect with nebulised antipseudomonal therapy on the number of

patients developing pulmonary exacerbations requiring treatment with systemic antibiotics (fig 1). The pooled effect clearly demonstrates statistically significant benefit (fig 1; table 3). Study 2 does not assess this measure of outcome and hence cannot be included in the meta-analysis.

EFFECT ON RESPIRATORY PSEUDOMONAL LOAD

Study 2 suggests a decrease in respiratory pseudomonal load following nebulised antipseudomonal therapy whilst studies 1, 3, and 4 show no such effect. The pooled effect is significant (fig 2; table 3). As a decrease in pseudomonal load in the sputum had not been documented on an individual patient basis, study 5 could not be included in this analysis.

EFFECT ON SPIROMETRIC LUNG FUNCTION ASSESSMENT

Spirometric lung function improved in two of the three studies (studies 3 and 5) suitable for meta-analysis; the pooled effect is significant (table 4). Study 1 does not provide standard deviations or standard errors of the mean for its data; study 2 does not evaluate spirometric lung function as a measure of outcome and hence cannot be included in the meta-analysis.

EFFECT ON PSEUDOMONAS RESISTANCE

Information on the number of subjects with tobramycin-resistant strains of *Pseudomonas aeruginosa* before and after active drug or placebo was not available from study 5, thus necessitating its exclusion from this meta-analysis. Studies 1–4 qualify for meta-analytic assessment of the increase in the number of subjects with *Pseudomonas* species in sputum resistant to the nebulised antipseudomonal used. The odds of developing resistance were increased almost fourfold, but the results were consistent with no increase and a 12-fold increase and narrowly failed to achieve significance (fig 3; table 3).

OTHER SIDE EFFECTS

Mild chest tightness (three cases) and a bad taste in the mouth (four cases) are the only undesirable side effects described, with no

Table 3 Typical odds ratios and pooled rate differences with 95% confidence intervals (CI) for dichotomous outcome measures on meta-analysis of all suitable randomised clinical trials

Outcome measures	O/T:O/C	Typical odds ratio (95% CI)	Pooled rate difference (95% CI)
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 <i>Pseudomonas</i> load	12/81:74/74	0.09 (0.03 to 0.32)	-0.22 (-0.50 to -0.07)
Subjects with <i>Pseudomonas</i> strains resistant to nebulised antibiotic	8/73:2/65	3.56 (0.98 to 12.88)	0.06 (-0.02 to 0.15)

If 95% CI include unity, the results are not significant. Thus, nebulised antibiotics significantly decrease respiratory *Pseudomonas* load, reduce the frequency of pulmonary exacerbations requiring systemic antibiotics, and do not encourage the development of resistant respiratory *Pseudomonas* strains (however, see text). O = number positive for outcome; T = number treated; C = number of controls.

Table 4 Overall effect (defined in text) of nebulised antipseudomonal therapy on respiratory function

Trial code	Normalised FEV ₁ (% mean predicted)		Normalised FVC (% mean predicted)	
	Mean (SE) change	95% CI	Mean (SE) change	95% CI
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

Results are presented as mean (SE) percentage change and 95% confidence intervals (CI). Nebulised 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.

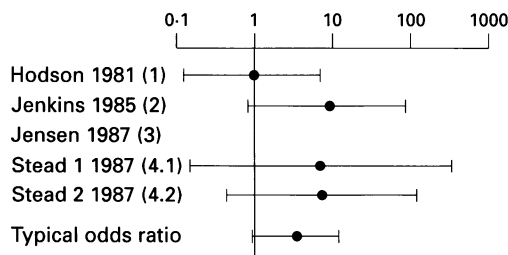


Figure 3 Individual and pooled (typical) log odds ratios with 95% confidence intervals of nebulised antipseudomonal drugs and the development of respiratory *Pseudomonas* strains resistant to the administered nebulised drug. 95% confidence intervals for the typical odds ratio just cross the unity odds ratio line; this is consistent with the hypothesis that a type II error persists in the relationship between nebulised antipseudomonal therapy and the number of subjects with respiratory *Pseudomonas* strains resistant to the administered nebulised drug. Information from study 4 allows the effects on this outcome measure of the ceftazidime (4.1) versus the carbenicillin and gentamicin (4.2) combinations in study 4 to be shown separately. An odds ratio could not be calculated for study 3 as there was no difference between "experiment" and "control" limbs.

reported effect on renal (serum creatinine and urinary creatinine clearance) and auditory (conventional audiometry) function.

Discussion

In this study we have applied the statistical technique of meta-analysis to integrate quantitatively the results of randomised controlled trials evaluating nebulised antibiotic therapy in cystic fibrosis in an attempt to answer specific questions regarding the efficacy and safety of this form of treatment, which is used widely in the treatment of respiratory deterioration associated with *Pseudomonas* colonisation in cystic fibrosis.²⁷ Appropriate enquiries of cystic fibrosis physicians in the UK together with Medline searches combining "meta-analysis" or "systematic review" with "cystic fibrosis" yielded no results; thus information available to us at the time of writing indicates that this is the first systematic review on this subject. By combining the results of randomised controlled trials meeting the criteria for inclusion in the meta-analysis we have demonstrated the clear benefit of nebulised antipseudomonal antibiotics, with reductions in pulmonary exacerbations (fig 1; table 3), respiratory pseudomonal load (fig 2; table 3), and improvement in spirometric lung function (table 4). Although odds ratios and pooled rate differences for the effect of nebulised antibiotic treatment on *in vitro Pseudomonas* resistance included unity, and therefore failed to demonstrate significance, there remains the possibility of a type II error (fig 3; table 3). Antibiotic resistance in *Pseudomonas aeruginosa* is, however, often temporary and resistant strains usually grow slowly, produce small colonies, and lose the ability to produce important virulence factors such as elastase.²⁸ Current microbiological evidence thus dissociates the development of *in vitro* pseudomonal resistance from adverse clinical outcome in cystic fibrosis. This is in line with the conclusions of this meta-analysis, demonstrating clinical benefit in the face of a possible increase in

in vitro Pseudomonas resistance. The quality index is presented to allow comparison between randomised controlled trials in cystic fibrosis; they do not influence study inclusion. Cystic fibrosis is a well defined area of clinical research. Almost all relevant studies have been presented at regular international meetings over the period in which nebulised antibiotic therapy has evolved. Given the dearth of randomised controlled trials of nebulised antibiotics, it is very unlikely that one would go unpublished (at least as an abstract); consequently publication bias is much less likely to present as a major confounder in this field.

Even the recently reported multicentric (seven US centres) randomised controlled trial of nebulised tobramycin⁶ could not recruit more than 71 subjects, falling much below the figure of 500 recommended by the Cystic Fibrosis Foundation Consensus Conference report as the minimum number of subjects required for premarketing clinical trials to allow for imbalances in patient characteristics that are not amenable to adjustments in analysis.²⁹ The last few years have witnessed the introduction of novel pharmacological interventions which may delay the inexorable decline phase of cystic fibrosis by promoting chloride efflux with uridine triphosphate,³⁰ improving mucolysis with recombinant DNase,³¹ neutralising intraluminal proteolytic enzyme activity with aerosolised α_1 -anti-trypsin³² or recombinant secretory leuko-protease inhibitor.³³ "Gene therapy" could, in the foreseeable future, evolve as a therapeutic strategy directed towards arresting or circumventing the basic defect. Adequate sample size will be of crucial importance in order to demonstrate the biological or clinical efficacy of these interventions. Nevertheless, small sample size, particularly in the face of increasing complexity of outcome measures – for example, those based on infant pulmonary function tests, serial computed tomographic scanning of the chest, or bronchoalveolar lavage for markers of inflammation – may continue to confound estimates of effect. As long as there remains in cystic fibrosis this major shortfall in the number of subjects recruitable for individual randomised controlled trials, combining results of multiple small randomised controlled trials by meta-analysis will improve estimates of effect, thus making it a useful technique for evaluating the effectiveness of therapeutic interventions. This paper demonstrates its use in establishing the beneficial effect of nebulised antipseudomonal antibiotics, identifies areas for further study, and emphasises the relevance of meta-analysis in integrating information in other controversial areas of cystic fibrosis management in order to achieve consensus.

Appendix

STAGE I

- 1 randomised controlled trial.pt.
- 2 randomised controlled trials/
- 3 random allocation/
- 4 double-blind method/
- 5 single-blind method/
- 6 1 or 2 or 3 or 4 or 5

STAGE II

- 7 clinical trial.pt.
- 8 controlled clinical trial.pt.
- 9 exp clinical trials/
- 10 (clinical\$ adj2 trial\$).tw.
- 11 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).tw.
- 12 placebos/
- 13 placebo\$.tw.
- 14 random\$.tw.
- 15 research design/
- 16 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
- 17 16 not 6

STAGE III

- 18 comparative study/
- 19 exp evaluation studies/
- 20 follow-up studies/
- 21 prospective studies/
- 22 (control\$ or prospectiv\$ or volunteer\$).tw.
- 23 18 or 19 or 20 or 21 or 22
- 24 23 not (6 or 17)

STAGE IV

- 25 cystic fibrosis/
- 26 limit 25 to human
- 27 limit 26 to animal
- 28 limit 25 to animal
- 29 28 not 27
- 30 25 not 29
- 31 30 and 6
- 32 30 and 17
- 33 30 and 24

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