

Tobramycin Solution for Inhalation Reduces Sputum *Pseudomonas aeruginosa* Density in Bronchiectasis

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We conducted a placebo-controlled, double-blind, randomized study to evaluate the microbiological efficacy and safety of inhaled tobramycin for treatment of patients with bronchiectasis and *Pseudomonas aeruginosa*. Patients were randomly assigned to receive either tobramycin solution for inhalation (TSI) ($n = 37$) or placebo ($n = 37$), which was self-administered twice daily for 4 wk and followed by 2-wk off-drug. At Week 4, the TSI group had a mean decrease in *P. aeruginosa* density of 4.54 \log_{10} colony-forming units (cfu)/g sputum compared with no change in the placebo group ($p < 0.01$). At Week 6, *P. aeruginosa* was eradicated in 35% of TSI patients but was detected in all placebo patients. Investigators indicated that 62% of TSI patients showed an improved medical condition compared with 38% of placebo patients (odds ratio = 2.7, 95% confidence interval [CI] 1.1 to 6.9). Tobramycin-resistant *P. aeruginosa* strains developed in 11% of TSI patients and 3% of placebo patients ($p = 0.36$). The mean percent change in FEV₁ percent predicted from Week 0 to Week 4 was similar for the TSI and placebo groups ($p = 0.41$). More TSI-treated patients than placebo patients reported increased cough, dyspnea, wheezing, and noncardiac chest pain, but the symptoms did not limit therapy. Additional study is warranted to further evaluate TSI in bronchiectasis patients.

Bronchiectasis is a chronic disorder of the major bronchi and bronchioles characterized by permanent dilation and destruction (1). The origin of bronchiectasis varies, but the presence of microbial infection and a persistent inflammatory response is typical of the disease. This cycle of infection and inflammation periodically develops into an exacerbation that is characterized by symptoms of fever, purulent sputum, and often, pleurisy and hemoptysis (2, 3). Bacteria commonly isolated from the sputum of patients with bronchiectasis include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* (4–6).

Patients with *P. aeruginosa* exhibit more extensive and severe disease as demonstrated by both radiological and physiological studies (6–8). Although antimicrobial therapy is an important aspect of disease management for patients with bronchiectasis, only a few small clinical studies have evaluated antimicrobial therapies

(5, 9, 10). None was specifically designed to assess treatment regimens for patients with *P. aeruginosa*.

Delivery of an inhaled antibiotic is an appealing alternative to oral or intravenous administration because the antibiotic is delivered in high concentrations directly to the site of infection, eliminating the need for high systemic concentrations and reducing the risk of systemic toxicity (11, 12). These potential benefits have been assessed in patients with cystic fibrosis (CF) who are colonized with *P. aeruginosa* (13–16). Recently, Ramsey and coworkers (17) described the results of large clinical studies in which CF patients treated with tobramycin solution for inhalation (TSI) for three treatment periods of 28 d on-drug and 28 d off-drug had improved lung function, decreased sputum *P. aeruginosa* density, decreased use of intravenous antipseudomonal antibiotics, and decreased number of hospital days. Chronic endobronchial infection with *P. aeruginosa* occurs in both CF and non-CF-related bronchiectasis, although not all therapies that are effective for CF are effective in non-CF patients (18). Therefore, as an initial evaluation of whether TSI might be effective in non-CF patients with bronchiectasis and *P. aeruginosa*, we conducted a placebo-controlled, double-blind, randomized study to test the antimicrobial efficacy of TSI.

METHODS

Patients were recruited from 16 sites across the United States. The institutional review board at each site approved the study protocol and informed consent. After discussing the study with the site investigator, all patients gave informed consent and were screened for eligibility.

Study Design

Patients included in this Phase 2 study had a diagnosis of bronchiectasis confirmed by conventional or high-resolution computed tomography and had grossly purulent sputum containing, at minimum, 10^4 colony-forming units (cfu) *P. aeruginosa* per gram. Patients were excluded if they had cystic fibrosis, a diagnosis of allergic bronchopulmonary aspergillosis, and acute pulmonary process requiring medical intervention as indicated by a new infiltrate on a chest radiograph, significant recent hemoptysis, or had received antibiotics within 2 wk of the screening visit.

Eligible patients were randomly assigned in blocks of two to parallel groups at each study center to receive either TSI or placebo. Patients were not stratified on the basis of any criteria. TSI (TOBI; PathoGenesis Corporation, Seattle, WA) is a nonpyrogenic, preservative-free, pH-adjusted solution designed for inhalation. Each 5-ml dose of TSI contains 300 mg tobramycin and 11.25 mg sodium chloride in sterile water for injection. The placebo, 1.25 mg quinine sulfate in the same excipient, was chosen because its taste is similar to tobramycin. Patients in both treatment groups self-administered the study drug twice daily for 28 d using a PARI LC PLUS jet nebulizer (Pari, Richmond, VA) and a Pulmo-Aide compressor (De Vilbiss, Somerset, PA). Investigators and patients remained blinded to study drug

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assignment until all patients had completed the follow-up visit and data were collected from all study sites.

Study visits were scheduled every 2 wk during the 8-wk study. The first dose of drug was administered at Week 0, 2 wk after screening. Patients visited the clinic for an interim visit at Week 2, for the last day of treatment at Week 4, and for a follow-up visit at Week 6. Patients were withdrawn from the study if they required additional antibiotic treatment at any time during study participation.

At all study visits, vital signs were measured, adverse events were recorded, and a sputum sample was collected for quantitative microbiology and susceptibility testing. At Week 0, before and 30 min after the patient-administered study drug, the forced expiratory volume at one second (FEV₁) was measured by standard American Thoracic Society methodology to monitor airway reactivity (19). Blood was drawn 30 to 60 min after drug administration for analysis of serum tobramycin concentration. At Week 4, airway reactivity was again monitored, a physical examination was performed, and laboratory tests that were performed at screening were repeated. Compliance was measured at Week 4 by counting the number of vials of study drug used.

Serum chemistry, hematology, and serum tobramycin concentrations were performed at a central laboratory. Quantitative sputum bacterial culture and measurement of tobramycin minimum inhibitory concentrations (MIC) for *P. aeruginosa* were performed at a central laboratory (Children's Hospital and Regional Medical Center, Seattle, WA) as described by Burns and coworkers (20). Sputum samples collected at each study visit were shipped on wet ice for receipt within 48 h at the central laboratory.

Endpoints

The primary efficacy endpoint was the change in *P. aeruginosa* density (expressed as log₁₀ cfu/g sputum) from baseline to Week 4. Additional efficacy endpoints included the following: (1) the change in *P. aeruginosa* density from baseline values to Week 2 and to Week 6; (2) an investigator's subjective assessment of change in the patient's general medical condition ("improved" or "not improved") was made and recorded at Week 6; and (3) the percent change in FEV₁ percent predicted and in FVC percent predicted from Week 0 to Week 4. Percent predicted values were calculated by dividing the actual values of FEV₁ or FVC by the values predicted by the Knudson equations for normal, healthy individuals based on sex, age, and height and multiplying by 100 (21). Safety endpoints included the incidence of adverse events, change in serum chemistry and hematology measurements, and airway reactivity.

Each patient's microbiological response was categorized according to whether *P. aeruginosa* was eradicated, reduced by treatment, or did not respond to treatment. *P. aeruginosa* was considered eradicated if (1) *P. aeruginosa* was not detected at Week 6, or if (2) the patient was unable to produce a sputum sample at Week 6 and *P. aeruginosa* was not isolated at Week 4. A patient's response was defined as reduced by treatment if *P. aeruginosa* was recovered from the Week 6 sputum sample but was reduced by at least 2 log₁₀ cfu/g at Week 4 compared with baseline. A patient had no microbiological response if *P. aeruginosa* did not decrease 2 log₁₀ cfu/g at Week 4 or if the patient withdrew from the study.

Statistical Analysis

The sample size calculation was based on 85% power to detect a 1.0 log₁₀ difference in *P. aeruginosa* density between the treatment groups. All patients who received at least one dose of either TSI or placebo (intent-to-treat) were included in the statistical analyses. The groups were compared with respect to the mean change from baseline values in *P. aeruginosa* density using two-sample, two-sided *t* tests. The measurement at Week 0 was used as the baseline value unless unavailable; in that event, the measurement at the screening visit was used. Any result of "no *P. aeruginosa* isolated" was numerically represented as 19 cfu/g, 1 cfu/g below the limit of detection for the quantitative bacterial culture.

The relationship between baseline characteristics and investigator's subjective assessment of patients' general medical condition (improved, not improved) at Week 6 was analyzed using logistic regression. Logistic regression was also used to assess the relationship between general medical condition and change in *P. aeruginosa* density.

Within each treatment group, airway reactivity (percent change in FEV₁ from pre- to post-study drug administration) was analyzed using the Wilcoxon signed rank test.

RESULTS

A total of 125 patients were screened for this study (Figure 1). A majority of the 47 patients who failed screening did so because their sputum contained less than 10⁴ cfu/g *P. aeruginosa*. Seventy-eight patients were randomized and 74 patients received at least one dose of study drug; 37 received TSI and 37 received placebo. Similar numbers of patients in each treatment group withdrew from the study, six of 37 (16%) in the TSI group and eight of 37 (22%) in the placebo group (Figure 1). The treatment groups were similar at baseline values with respect to sex, age, race, *P. aeruginosa* density in sputum, and pulmonary function (Table 1). Both treatment groups adhered to the dosing requirements; 81% of patients in the TSI group and 86% in the placebo group used more than 80% of the drug doses.

At all time points of the study, patients treated with TSI had a significant reduction in sputum *P. aeruginosa* compared with patients treated with placebo (Figure 2). At the end of treatment (Week 4), TSI-treated patients had a mean decrease of 4.54 log₁₀ cfu/g sputum compared with a mean increase of 0.02 log₁₀ cfu/g sputum in patients receiving placebo (*p* < 0.01). After the 2-wk follow-up period (Week 6), the mean reduction observed in the TSI group was smaller than at previous weeks, indicating that some regrowth of the organism had occurred after the cessation of TSI administration. The placebo group had a negligible change in *P. aeruginosa* density at all time points.

At the end of the study (Week 6), more TSI-treated patients (23 of 37, 62%) than placebo-treated patients (14 of 37, 38%) were assessed as having an improved medical condition. The odds that a patient receiving TSI would improve were 2.7 times higher than for a patient who received placebo (95% confidence interval [CI] 1.1 to 6.9). In addition to treatment group, sex was also a significant predictor of clinical improvement; 62% of women were assessed as improved compared with 31% of men (*p* = 0.01). Other baseline characteristics, e.g., whether the patient smoked and baseline FEV₁ were not predictive. Logistic regression analyses performed to evaluate the relationship between clinical improvement and change in *P. aeruginosa* density showed that decreases in cfu/g sputum at Weeks 2 (*p* < 0.01), 4 (*p* < 0.01), and 6 (*p* = 0.04) were significant predictors of improved medical condition.

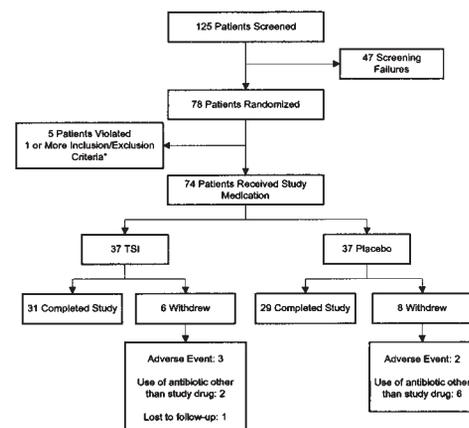


Figure 1. Trial profile. *One patient repeated screening, was randomized a second time, and then received study drug.

TABLE 1
DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic	TSI (n = 37)	Placebo (n = 37)	p Value
Sex			
Female, n (%)	23 (62%)	22 (59%)	1.00*
Age, yr, mean (SD)	66.6 (13.0)	63.2 (13.5)	0.27 [†]
Race			
White, n (%)	36 (97%)	32 (86%)	0.20*
<i>P. aeruginosa</i> log ₁₀ cfu/g sputum, mean (SD)	7.1 (1.4)	6.7 (1.6)	0.33 [†]
FEV ₁ % predicted, mean (SD)	56.2 (21.2)	53.3 (22.1)	0.57 [†]
Duration of bronchiectasis in years, mean (SD)	14.1 (15.4)	18.7 (17.0)	0.23 [†]
Use of bronchodilators, n (%)	30 (81%)	31 (84%)	0.76*
Use of steroids, n (%)	20 (54%)	21 (57%)	0.82*
Use of chest physiotherapy, n (%)	9 (24%)	5 (14%)	0.24*
History of smoking, n (%)	24 (65%)	16 (43%)	0.10*

* Treatment groups were compared using either the chi-square or Fisher exact test.

[†] Treatment groups were compared using two-sample, two-sided *t* tests.

Examination of individual patient's microbiological response showed that one-third (13 of 37) of the TSI-treated patients had *P. aeruginosa* eradicated from their sputum (Table 2). Twelve of these 13 patients were assessed as having an improved medical condition at Week 6. An additional third (12 of 37) showed a reduction of at least 2 log₁₀ in *P. aeruginosa* density at Week 4. Nine of these 12 patients were assessed as improved. The last third (12 of 37) of TSI-treated patients had no microbiological response, and 10 of these patients were not improved. In contrast, 33 of 35 (94%) of the placebo patients had no microbiological response and only two of 35 (6%) had greater than a 2 log₁₀ decrease in *P. aeruginosa* density.

Decreased susceptibility of bacteria to a drug is a common consequence of treating chronically infected patients with antibiotics. In this study, 26% (eight of 31) of TSI patients had *P. aeruginosa* isolates that showed at least a fourfold increase from baseline to Week 6 in the tobramycin MIC compared with 14% (four of 29) of placebo patients (*p* = 0.25, Table 3). Because a resistance breakpoint for administration of aerosolized tobramycin to treat *P. aeruginosa* has not been established, the value for parenteral administration (MIC ≥ 16 μg/ml) (22) was used to determine the number of patients who had resistant *P. aeruginosa* develop during the course of treat-

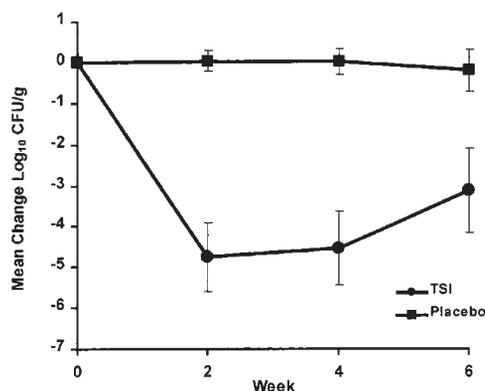


Figure 2. Mean change in sputum *P. aeruginosa* density. Patients received TSI or placebo twice daily between Weeks 0 and 4. In the TSI group, sample sizes were *n* = 37 (Week 0), *n* = 32 (Week 2), *n* = 31 (Week 4), and *n* = 28 (Week 6). In the placebo group, sample sizes were *n* = 37 (Week 0), *n* = 33 (Week 2), *n* = 30 (Week 4), and *n* = 29 (Week 6). The error bars represent 95% confidence intervals.

TABLE 2
MICROBIOLOGICAL RESPONSE CATEGORIES AND INVESTIGATOR ASSESSMENT OF PATIENTS' GENERAL MEDICAL CONDITION

	TSI (n = 37)		Placebo (n = 35)*	
	Improved	Not Improved	Improved	Not Improved
Eradicated [†]	12	1	0	0
Treatment-reduced [‡]	9	3	1	1
No microbiological response [§]	2	10	13	20

* Two patients were not evaluable for microbiological response. One patient, who had *P. aeruginosa* at the screening visit, had a negative culture 2 wk later at the baseline visit. The second patient did not have a sample collected at Week 4. Both patients were assessed as not improved.

[†] No *P. aeruginosa* detected at Week 6.

[‡] *P. aeruginosa* cfu/g decreased at least 2 log₁₀ at Week 4.

[§] *P. aeruginosa* cfu/g did not decrease at least 2 log₁₀ at Week 4 or patient withdrew from the study.

^{||} Includes six TSI and eight placebo patients, respectively, who withdrew from the study.

ment. Four of 36 (11%) patients in the TSI group and one of 32 (3%) patients in the placebo group who began the study with susceptible *P. aeruginosa* had resistant *P. aeruginosa* at their last visit (*p* = 0.36). Three of the four patients in the TSI group who developed resistant *P. aeruginosa* showed no microbiological response. The general medical condition of all four patients was assessed as not improved.

Changes in pulmonary function were not significantly different between the treatment groups. The mean percent change from Week 0 to Week 4 in FEV₁ percent predicted was similar for the TSI and placebo group (-2.2% versus 1.5%, respectively, *p* = 0.41). The mean percent change in FVC percent predicted was also similar for both TSI and placebo groups (-2.8% versus 2.2%, respectively, *p* = 0.19).

Thirty-one of 37 (84%) patients in each treatment group reported at least one adverse event. Respiratory system adverse events were reported by 26 (70%) TSI patients and by 19 (51%) placebo patients. The incidence of dyspnea, chest pain, and wheezing was significantly greater in the TSI group (Table 4). Chest pain appeared to be related to the respiratory system based on investigator comments (e.g., chest tightness and pleuritic pain) and on the treatment interventions (bronchodilators and analgesics). Investigators reported that the adverse events were related to study drug administration for 12 of 15 TSI-treated patients reporting increased cough, for three of 12 patients experiencing dyspnea, for three of the six patients with wheezing, and for three of the seven patients reporting chest pain.

TABLE 3
SHIFT IN TOBRAMYCIN MIC VALUES FROM BASELINE TO WEEK 6

	TSI (n = 31)	Placebo (n = 29)
	n (%)	n (%)
<i>P. aeruginosa</i> , eradicated	13 (42)	0 (0)
<i>P. aeruginosa</i> , persistent*		
MIC decreased ≥ 4-fold	0 (0)	5 (17)
MIC unchanged ± 2-fold	10 (32)	20 (69)
MIC increased ≥ 4-fold	8 (26)	4 (14)

* Patients with *P. aeruginosa* isolated at Week 6.

TABLE 4
INCIDENCE OF ADVERSE EVENTS OCCURRING IN
GREATER THAN 10% OF TSI PATIENTS

Symptom	TSI	Placebo	p Value*
	(n = 37)	(n = 37)	
	n (%)	n (%)	
Patients reporting ≥ 1 adverse event	31 (84)	31 (84)	
Increased cough	15 (41)	9 (24)	0.14
Dyspnea	12 (32)	3 (8)	0.01
Increased sputum	8 (22)	5 (14)	0.36
Chest pain	7 (19)	0 (0)	0.01
Wheezing	6 (16)	0 (0)	0.01
Fatigue	5 (14)	6 (16)	0.74
Hemoptysis [†]	5 (14)	3 (8)	0.45
Fever	4 (11)	6 (16)	0.50

* Treatment groups were compared using the chi-square test.

[†] Mild or moderate, including blood-streaked sputum; no severe hemoptysis occurred in either group.

Patients hospitalized and treated for exacerbation of their pulmonary disease included five patients in the TSI group and one patient in the placebo group ($p = 0.20$). The placebo patient and four of the five TSI patients were treated with additional antibiotics. A tobramycin-resistant *P. aeruginosa* strain was isolated from only one of the TSI patients. The susceptibility test result was reported after hospitalization and after the patient had received two additional courses of nonstudy inhaled tobramycin. None of the other hospitalized TSI patients had treatment-emergent isolation of any other potentially pathogenic tobramycin-resistant organisms. The fifth TSI patient received oral and intravenous corticosteroids but continued to administer TSI while in the hospital. The patient completed the study and *P. aeruginosa* was eradicated from the patient's sputum.

Airway reactivity (percent change in FEV₁ from pre- to post-study drug administration) was not significantly different from zero percent for either the TSI group (mean = -1% Week 0, -3% Week 4) or placebo group (mean = -3% Week 0, -1% Week 4).

Overall, no clinically significant changes in laboratory values, including blood urea nitrogen (BUN) and creatinine, occurred in patients in either treatment group. The median tobramycin concentration in serum of TSI-treated patients measured 30 to 60 min after drug administration was 0.54 $\mu\text{g/ml}$ and ranged from the lower limit of detection (0.18 $\mu\text{g/ml}$) to 2.64 $\mu\text{g/ml}$.

DISCUSSION

Previous reports suggested that the presence of *P. aeruginosa* in patients with bronchiectasis is associated with increased disease symptoms and a worsened prognosis (6, 7). The use of nebulized antibiotics for the management of *P. aeruginosa* has been advocated for patients with bronchiectasis (12, 23). Orriols and colleagues recently published a small study that suggested that inhaled ceftazidime and tobramycin reduced disease severity in non-CF patients with bronchiectasis (24). The study reported here presents a quantitative evaluation of sputum *P. aeruginosa* during the course of inhaled antibiotic therapy and relates the data to the physician's assessment of the patients' medical condition.

Some earlier small studies of oral and inhaled antibiotics in non-CF bronchiectasis have shown eradication of *P. aeruginosa* but no studies have included quantitative microbiology (9, 10, 12, 24). Aerosolized tobramycin in a large CF study showed an aver-

age reduction of 1.7 to 2.0 log₁₀ cfu/g with a rebound to baseline values 2 wk after cessation of therapy (17). In this study, the marked decline in the sputum density of *P. aeruginosa* was 2 to 3 log₁₀ greater than in the CF study and was noted as early as 2 wk after treatment began. Additionally, 35% of the patients treated with TSI had no detectable *P. aeruginosa* 2 wk after therapy was discontinued. Moreover, the significant decrease in bacterial load was associated with an improved medical condition in these patients.

We did not observe improvement in FEV₁ for patients in the TSI group compared with patients in the placebo group, which is consistent with observations of others (4, 10, 12, 24). Tsang and coworkers (25) reported that patients with bronchiectasis who received longer-term antibiotic therapy and chest physiotherapy (CPT) had significant improvement in FEV₁ and other spirometry indices compared with patients who received CPT and placebo. The number of patients who received CPT during this study was small and the change in FEV₁ varied for these patients such that we could not determine the nature of the relationship. The impact of concurrent CPT use with TSI on lung function warrants further exploration in a larger long-term trial.

Patients with chronic infections are at increased risk of being colonized with resistant bacteria because they receive multiple courses of antibiotic therapy. Although no breakpoint has been established for administration of aerosolized tobramycin, four of the patients treated with TSI developed *P. aeruginosa* that would be reported as "resistant" based on the current breakpoint for parenteral tobramycin ($\geq 16 \mu\text{g/ml}$) (22). Previous studies of patients with CF showed that when the tobramycin MIC increased above the breakpoint for *P. aeruginosa*, it often decreased once the antibiotic pressure was removed (13, 26).

Pulmonary exacerbations are expected events in the course of bronchiectasis and often patients require hospitalization or antibiotics for treatment (18). A greater number of TSI-treated patients require hospitalization, but a greater number of placebo patients withdrew from the study to be treated with antibiotics. Even though more TSI patients than placebo patients reported respiratory adverse experiences, those symptoms did not limit therapy. In general, these patients did not withdraw from the study.

Increased pulmonary symptoms were seen in the adverse events in the TSI group despite the investigators' assessment of improved medical condition. The investigator assessment was subjective and requires further study to understand measures of quality of life as they relate to clinical benefit in bronchiectasis. It is also possible that inhaled tobramycin may cause adverse respiratory effects such as bronchospasm, and more studies are needed to evaluate this possibility.

The results of this study, which was designed and powered to determine the microbiological efficacy of tobramycin solution for inhalation, show that TSI markedly reduced sputum *P. aeruginosa* density. Further investigation is necessary to define and demonstrate clinical efficacy and safety in non-CF patients with bronchiectasis.

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References

- Barker, A. F., and E. J. Bardana. 1988. Bronchiectasis update of an orphan disease. *Am. Rev. Respir. Dis.* 137:969-978.
- Nicotra, M. B. 1994. Bronchiectasis. *Semin. Respir. Infect.* 9:31-40.
- Cole, P. 1995. Bronchiectasis. In R. A. L. Brewis, B. Corin, D. M. Geddes, and G. J. Gibson, editors. *Respiratory Medicine*, Vol. 2, 2nd ed. W. B. Saunders, London. 1286-1316.

4. Nicotra, M. B., M. Rivera, A. M. Dale, R. Shepherd, and R. Carter. 1995. Clinical, pathophysiologic, and microbiologic characterization of bronchiectasis in an aging cohort. *Chest* 108:955-961.
5. Chan, T. H., S. S. Ho, C. K. W. Lai, S. W. Cheung, R. C. Y. Chan, A. F. B. Cheng, and C. H. S. Chan. 1996. Comparison of oral ciprofloxacin and amoxicillin in treating infective exacerbations of bronchiectasis in Hong Kong. *Chemotherapy* 42:150-156.
6. Wilson, C. B., P. W. Jones, C. J. O'Leary, D. M. Hansell, P. J. Cole, and R. Wilson. 1997. Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. *Eur. Respir. J.* 10:1754-1760.
7. Evans, S. A., S. M. Turner, B. J. Bosch, C. C. Hardy, and M. A. Woodhead. 1996. Lung function in bronchiectasis: the influence of *Pseudomonas aeruginosa*. *Eur. Respir. J.* 9:1601-1604.
8. Miszkiel, K. A., A. U. Wells, M. B. Rubens, P. J. Cole, and D. M. Hansell. 1997. Effects of airway infection by *Pseudomonas aeruginosa*: a computed tomographic study. *Thorax* 52:260-264.
9. Hill, S. L., H. M. Morrison, D. Burnett, and R. A. Stockley. 1986. Short term response of patients with bronchiectasis to treatment with amoxicillin given in standard or high doses orally or by inhalation. *Thorax* 41:559-565.
10. Rayner, C. F. J., G. Tillotson, P. J. Cole, and R. Wilson. 1994. Efficacy and safety of long-term ciprofloxacin in the management of severe bronchiectasis. *J. Antimicrob. Chemother.* 34:149-156.
11. Ilowite, J. S., M. S. Niederman, and A. M. Fein. 1991. Delivery of topical antibiotics: pharmacokinetics and clinical problems. *Semin. Respir. Infect.* 6:158-167.
12. Lin, H.-C., H.-F. Cheng, C.-H. Wang, C.-Y. Liu, C.-T. Yu, and H.-P. Kuo. 1997. Inhaled gentamicin reduces airway neutrophil activity and mucus secretion in bronchiectasis. *Am. J. Respir. Crit. Care Med.* 155:2024-2029.
13. Smith, A. L., B. W. Ramsey, D. L. Hedges, B. Hack, J. Williams-Warren, A. Weber, E. J. Gore, and G. J. Redding. 1989. Safety of aerosol tobramycin administration for 3 months to patients with cystic fibrosis. *Pediatr. Pulmonol.* 7:265-271.
14. Ramsey, B. W., H. L. Dorkin, J. D. Eisenberg, R. L. Gibson, I. R. Harwood, R. M. Kravitz, D. V. Schidlow, R. W. Wilmott, S. J. Astley, M. A. McBurnie, *et al.* 1993. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *N. Engl. J. Med.* 328:1740-1746.
15. MacLusky, I. B., R. Gold, M. Corey, and H. Levison. 1989. Long-term effects of inhaled tobramycin in patients with cystic fibrosis colonized with *Pseudomonas aeruginosa*. *Pediatr. Pulmonol.* 7:42-48.
16. Steinkamp, G., B. Tümmler, M. Gappa, A. Albus, J. Potel, G. Döring, and H. von der Hardt. 1989. Long-term tobramycin aerosol therapy in cystic fibrosis. *Pediatr. Pulmonol.* 6:91-98.
17. Ramsey, B. W., M. S. Pepe, J. M. Quan, K. L. Otto, A. B. Montgomery, J. Williams-Warren, M. Vasiljev-K, D. Borowitz, C. M. Bowman, B. C. Marshall, *et al.* 1999. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *N. Engl. J. Med.* 340:23-30.
18. O'Donnell, A. E., A. F. Barker, J. S. Ilowite, and R. B. Fick. 1998. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase 1. *Chest* 113:1329-1334.
19. American Thoracic Society. 1995. Standardization of spirometry. *Am. J. Respir. Crit. Care Med.* 152:1107-1136.
20. Burns, J. L., J. Emerson, J. R. Stapp, D. L. Yim, J. Krzewinski, L. Loudon, B. W. Ramsey, and C. R. Clausen. 1998. Microbiology of sputum from patients at cystic fibrosis centers in the United States. *Clin. Infect. Dis.* 27:158-163.
21. Knudson, R. J., M. D. Lebowitz, C. J. Holberg, and B. Burrows. 1983. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am. Rev. Respir. Dis.* 127:725-734.
22. National Committee for Clinical Laboratory Standards. 1998. Performance Standards for Antimicrobial Susceptibility Testing: Eighth Informational Supplement. NCCLS, Wayne, PA. 18:1-83.
23. Currie, D. C. 1997. Nebulizers for bronchiectasis. *Thorax* 52(Suppl. 2): S72-S74.
24. Orriols, R., J. Roig, J. Ferrer, G. Sampol, A. Rosell, A. Ferrer, and A. Vallano. 1999. Inhaled antibiotic therapy in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa*. *Respir. Med.* 93:476-480.
25. Tsang, K. W. T., P.-I. Ho, K.-N. Chan, M. S. M. Ip, W.-K. Lam, C.-S. Ho, K. Y. Yuen, G. C. Ooi, R. Amitani, and E. Tanaka. 1999. A pilot study of low-dose erythromycin in bronchiectasis. *Eur. Respir. J.* 13:361-364.
26. Gilligan, P. H. 1991. Microbiology of airway disease in patients with cystic fibrosis. *Clin. Microbiol. Rev.* 4:35-51.

APPENDIX

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