

Aerosolized Antibiotics for Non-Cystic Fibrosis Bronchiectasis

BRUCE K. RUBIN, M.Eng., M.D., M.B.A., F.R.C.P.C.

ABSTRACT

There are strong data supporting using the use of aerosolized antibiotics for the treatment of Gram-negative infections in patients with cystic fibrosis (CF). The regular use of aerosol tobramycin or colistin can decrease exacerbations of lung disease, decrease bacteria counts, and improve pulmonary function in persons with CF and *Pseudomonas aeruginosa* airway infection. Bronchiectasis is caused by reoccurring or continuous presence of bacteria in association with airway obstruction. Although CF is the most common cause of childhood bronchiectasis, there are many other causes. Because secretions in the bronchiectasis airway are similar to the pus found in the CF airway, and because pulmonary complications and progression of disease in non-CF bronchiectasis is similar to CF bronchiectasis, many centers treat patients with bronchiectasis using aerosolized tobramycin solution for inhalation (TSI). There have been only a few small studies of aerosolized antibiotics to treat pseudomonas infection in subjects with non-CF bronchiectasis. Unlike the CF experience, there does not seem to be an improvement of pulmonary function after treatment with aerosol tobramycin in this population despite a decreased sputum bacterial density and a trend toward a decrease in risk of hospitalization. Furthermore, the risk of adverse events such as bronchospasm may be more common in adults with non-CF bronchiectasis than reported in the CF population.

Key words: tobramycin, colistin, bronchiectasis, cystic fibrosis, *Pseudomonas aeruginosa*, aerosol therapy

INTRODUCTION

BRONCHIECTASIS IS A CHRONIC AIRWAY DISEASE characterized by infection, inflammation, sputum expectoration, and dilatation of the airway walls with epithelial and cartilage destruction. It is thought that chronic infection and inflammation with failure to clear secretions, or a serious airway infection leading to permanent destruction of airway support cartilage can cause bronchiectasis.⁽¹⁾

In the Western world the most common cause of bronchiectasis in children is cystic fibrosis (CF), and in most respects, the features of CF and the properties of CF airway secretions are similar to those of non-CF bronchiectasis.^(2,3) In the developing world, non-CF bronchiectasis is usually due to a severe or prolonged pulmonary infection in childhood. This is often localized to a few lobes, and the course may be less severe than generalized bronchiectasis due to an underlying disease.

Department of Pediatrics, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

Common causes of non-CF bronchiectasis in industrialized countries include both congenital and acquired immunodeficiency diseases, retained foreign body, intrinsic airway wall abnormalities such as bronchomalacia, and rarely aspiration pneumonia, which can cause bronchiectasis in patients with an ineffective cough. Primary abnormalities of mucociliary clearance such as primary ciliary dyskinesia have also been associated with bronchiectasis, as has been specific infections such as tuberculosis or pertussis.⁽⁴⁾

Although patients with bronchiectasis have chronic low-grade infection and inflammation, the airway disease is characterized by periods of exacerbation with increasing airway inflammation often triggered by concomitant viral infection, exposure to aero-irritants, or gastric contents. Management of non-CF bronchiectasis is similar to that of CF, with the frequent use of antibiotics particularly for exacerbation of disease, immunization against bacterial pathogens, attention to airway clearance, good nutrition, and exercise, and treatment of underlying problems such as immunodeficiency.⁽⁴⁾

Aerosol antibiotics: pro and con

The use of aerosol antibiotics is well accepted for the chronic treatment of CF airway disease and aerosol tobramycin solution for inhalation (TSI or TOBI, Novartis Pharmaceuticals, East Hanover, NJ), colistin, and other antibiotics have been demonstrated to reduce the frequency of exacerbations, reduce airway bacterial density in CF, improve pulmonary function, and decrease the frequency of exacerbations.⁽⁵⁾

The advantages of inhaled antibiotics are that they can produce high local concentrations in the airway giving good local efficacy with minimal systemic absorption and thus less systemic toxicity.⁽⁶⁾ Many children find the inhalation of antibiotics more acceptable than the use of intravenous medications because of the discomfort of accessing an intravenous port and a fear of needles.

There are disadvantages to inhaled antibiotics. Some patients find the taste of antibiotics unpalatable, and the time involved for inhalation administration to be excessive. Aerosol antibiotics are expensive—often more expensive than systemic antibiotic therapy. They can cause cough, irritation, and bronchospasm in some pa-

tients. In the CF TSI trials, laryngeal hoarseness and hemoptysis have been reported.⁽⁵⁾

Uncommon but severe risks include severe and even life-threatening bronchospasm⁽⁷⁾ and acute nonoliguric renal failure even with inhaled aminoglycosides.⁽⁸⁾ There is a low risk of infection from contamination of nebulizer solution.⁽⁹⁾ There is also a low incidence of tinnitus that has been reported in patients taking TSI for the treatment of CF.⁽⁶⁾

Both colistin and tobramycin have been reported to cause bronchospasm in susceptible persons with CF. This could be drug related (suggested for colistin), drug and preservative related (for tobramycin), and potentially related to the delivered dose, particularly when very high efficiency nebulizers are used. Inhaled colistin was compared with placebo in persons with CF having high and low risk for airway adverse effects based on personal or family history of asthma and previous response to bronchodilators. Subjects in the high-risk group had a greater fall in FEV₁ compared with placebo ($p < 0.002$).⁽¹⁰⁾ In a similar study, an aerosol treatment of preservative-free TSI (300 mg) was compared with an aerosol of the intravenous preparation of tobramycin containing the preservatives phenol and bisulfites (80 mg in a 2-mL vial diluted with 2 mL of saline) in 19 children with CF and mild to moderate pulmonary disease. Ten of these were at high risk for bronchospasm based on the previously defined criteria and nine were at low risk. Following a 12-h period off bronchodilators, subjects inhaled one or the other preparation in random order on two occasions, 2 weeks apart. Both preparations caused significant bronchoconstriction in the high-risk group, and the preservative-containing i.v. preparation caused more bronchospasm in the low-risk group than the preservative-free solution.⁽¹¹⁾ In both studies bronchospasm was successfully treated with bronchodilators, and the authors concluded that the risk of bronchospasm should not preclude a patient from receiving nebulized antibiotics if deemed necessary.

The most important drawback to aerosol antibiotics is that they do not penetrate to the deep lung. This means that there is an antibiotic concentration gradient from the very high levels achievable in the proximal airway to extremely low levels in distal airway. This gradient of antimicrobial concentration is ideal for fostering development of antimicrobial resistance. In general,

patients are treated with inhaled antibiotics only when they have chronic infection with bacteria that form biofilms, can be difficult to eradicate, and often have developed some degree of antimicrobial resistance. However, these very characteristics can also promote the development of antibiotic resistance.⁽¹²⁾ As well, although scintigraphic studies shown that particle deposition in the airways of healthy subjects follows ventilation, data suggest that in CF, there is significant coarse particle deposition in the airways of poorly ventilated lung regions.⁽¹³⁾ This has the potential to decrease aerosol deposition in the most severely affected portions of the bronchiectasis lung. The deposition of an aerosol of intravenous gentamicin solution was assessed by scintigraphy in subjects with CF and averaged 7.7% of the original amount placed in the nebulizer. When peak sputum levels were normalized for the amount deposited, there was a close correlation with central to peripheral (C/P) deposition ratio, there was an inverse relationship between the C/P ratio and the FEV1% predicted, and there was a bell-shaped relationship between deposited dose and minute ventilation suggesting that optimal dose and particle size may depend on severity of lung disease.⁽¹⁴⁾

Antimicrobial resistance with aerosol antibiotics has been shown to be time dependent. Although resistance often decreases over time after discontinuing antibiotics even with a regimen of 28 days on followed by 28 days off TSI, in the initial CF trials, there was a much higher resistance to the aminoglycosides in patients treated with the TSI than in those treated with placebo.⁽⁵⁾ A randomized clinical trial compared TSI using on- and off-drug cycles of 4 weeks each to placebo plus standard CF care to determine (1) the percentage of patients with at least one *Pseudomonas aeruginosa* strain having a minimal inhibitory concentration (MIC) >16 $\mu\text{g}/\text{mL}$, (2) changes in the lowest antibiotic concentration required to inhibit the growth of 50% of strains tested (MIC₅₀) and 90% of strains tested (MIC₉₀), (3) the percentage of patients with a change in the MIC of the most resistant and most prevalent pseudomonas strains, and (4) the percentage of patients in whom the pseudomonas strain with the highest MIC also was the most prevalent. During the first 6 months, the percentage of TSI-treated patients having at least one pseudomonas isolate with an MIC >16 $\mu\text{g}/\text{mL}$ was 13% at baseline, 26% at 20 weeks, and 23% at 24 weeks versus 10, 17, and 8%, respectively, for

placebo-treated patients. Although there was no significant change in MIC₅₀ or MIC₉₀ overall, after 6 months, 33% of the tobramycin group showed an increase in the MIC of the strain having the highest MIC. This decreased to 26% at 1 month off drug therapy. This return to susceptibility following an off-drug cycle did not persist at 24 months. At all time points, pulmonary function improved even in patients with the most resistant pseudomonas (MIC >128 $\mu\text{g}/\text{mL}$).⁽¹⁵⁾

Although it is possible to potentially decrease this risk by rotating the use of different antibiotics on alternate months—this is been termed “crop rotation” when used in ICU settings as a means of decreasing antibiotic resistance⁽¹⁶⁾—the safety and effectiveness of this strategy has not been established for aerosol antibiotics.

When inhaling an antibiotic even in the presence of a filter, some of the antibiotic will escape into the environment either from the nebulizer or from the patient exhaling. These environmental concentrations are probably too low to kill bacteria but are sufficient to induce the development of resistance in environmental strains, which then can be transported to other patients.⁽¹⁷⁾

Drug selection

In general, antibiotics studied for aerosolized administration have highly active, concentration-dependent (or minimum inhibitory concentration/area under the curve: MIC/AUC) activity that are most effective at high concentrations with minimal toxicity when a trough concentration falls to very low levels. Inhaled antimicrobials need to be well tolerated at the epithelial surface with no extremes of pH or osmolarity; they should penetrate infected sputum, and not be inactivated in the airway or by other medications taken by the patients. Often medications are chosen that are potentially toxic when given at systemic doses.⁽¹⁸⁾

Aerosolized antibiotics that have been evaluated include tobramycin, gentamicin, neomycin, amikacin, and other aminoglycosides, aztreonam, colistin, carbenicillin, amphotericin, ticarcillin, and ceftazidime. Airway appropriate forms of ciprofloxacin and other quinolones are currently being studied.

Effectiveness in CF and non-CF bronchiectasis

Theoretically, the ideal patients for receiving antibiotic aerosol therapy are those who need an-

TABLE 1. PUBLISHED CLINICAL TRIALS USING AEROSOL ANTIBIOTICS TO TREAT NON-CF BRONCHIECTASIS IN ADULT SUBJECTS WHO WERE CHRONICALLY INFECTED WITH *PSEUDOMONAS AERUGINOSA*

Study	Design	Number of subjects	Therapy given	Outcomes
Orriols et al., 1999	RCT PG	15 completed, 7 on active treatment	Aerosol ceftaz and tobra for 12 months	Significantly fewer admissions in the active group. Decrease in FEV ₁ while on active therapy compared with placebo (<i>p</i> = NS)
Barker et al., 2000; ⁽¹⁹⁾ Couch, 2001 ⁽²⁰⁾ NB: same study was reported twice	RCT	74: 37 TSI 37 placebo	TSI or placebo 4 weeks	Decrease in P.a. density on TSI but 11% developed P.a. resistance. Improved "general health" Decrease in FEV ₁ while on TSI compared with placebo (<i>p</i> = NS) and 32% developed dyspnea on TSI.
Drobnic, et al., 2005 ⁽²³⁾	RCT COT	30: 20 finished 5 died	6 months of TSI or placebo then cross after 1 month washout	Decrease in FEV ₁ while on TSI compared with placebo (<i>p</i> = NS) Ni change in antibiotic use or QOL 10% of subjects had bronchospasm while on TSI.
Scheinberg and Shore, 2005 ⁽³²⁾	OLT	41	3 × 14 days On and off cycles	Eradication of Pa in 22% and resistance developed in 7%. Nine withdrawals due to cough and wheezing.
Bilton et al., 2006 ⁽²¹⁾	RCT PG	53 enrolled 43 finished	TSI added to ciprofloxacin vs. cipro alone for 14 days	Significant decrease of P.a. in sputum. Decrease in FEV ₁ while on TSI compared with placebo (<i>p</i> = NS). 50% on TSI developed wheeze vs. 15% on placebo.

All studies used tobramycin solution for inhalation (TSI) 300 mg b.i.d. as active drug except Orriols⁽²⁴⁾ used aerosol ceftazidime 1 g every 12 h and tobramycin injection solution 100 mg every 12 h. *Abbreviations:* PG, parallel group trial; RCT, randomized controlled trial; OLT, open label trial; COT, crossover trial, NS, not significant; P.a., *Pseudomonas aeruginosa*; SGRQ, St George Respiratory Questionnaire; ceftz, ceftazidime; tobra, tobramycin; TSI, tobramycin solution for inhalation.

tibiotics frequently and have a high airway burden of bacteria with difficult to treat micro-organisms. This patient profile is consistent with longstanding non-CF bronchiectasis with chronic *Pseudomonas* infection.

A statistically significant two to three log fall in pseudomonas density has been reported as early as 7 days after starting therapy with inhaled tobramycin in subjects with non-CF bronchiectasis.⁽¹⁹⁻²¹⁾ However, there is no reported relationship between microbiologic efficacy and decrease in bacterial density and clinical efficacy as measured by pulmonary function or quality of life changes.⁽²¹⁻²³⁾ Aerosolized tobramycin has also been shown to significantly increase the time to exacerbation in persons with CF,⁽⁶⁾ but this has not been well investigated in non-CF bronchiectasis.

In CF there is a significant improvement in pulmonary function while on the medication and

soon after starting inhaled tobramycin there is a 7-12% improvement in FEV₁ with a mean of a 12% improvement relative to placebo.⁽⁵⁾ In contradistinction, it has been reported that patients with non-CF bronchiectasis who receive inhaled bronchodilators have a slight (nonsignificant) decrease in FEV₁ probably due to airway irritation.^(19-21,23,24) Coughing, hemoptysis, and pulmonary function decrease has been a significantly limiting factor in the adoption of aerosolized antibiotics for the treatment of non-CF bronchiectasis.

SUMMARY

The use of aerosolized tobramycin remains controversial in patients with non-CF bronchiectasis. Reported studies have been underpowered for long-term outcomes of interest such as

time to exacerbation, hospitalization, or frequency of exacerbation (Table 1). Although there is a consistent reduction in sputum bacterial density while patients are receiving aerosol tobramycin if *Pseudomonas* is the primary pathogen, this has not been associated with improved quality of life, decreased need for additional antibiotics, or improvement in pulmonary function. Dyspnea and wheezing appear to occur much more commonly in adult patients with non-CF bronchiectasis than in CF patients who receive aerosol tobramycin, and there is a consistent and concerning deterioration in airflow (FEV₁) among patients with non-CF bronchiectasis who receive aerosol tobramycin, when compared to those who receive placebo aerosol. It is unknown if other inhaled antibiotics such as colistin or aztreonam will be tolerated or have better long-term outcome for the treatment of non-CF bronchiectasis.

It is important when conducting studies not only to ensure that they have sufficient power to detect clinically significant outcomes, but that the study population is fairly homogeneous. For example, aerosolized antibiotics may not be the most effective or efficient way to deliver antibiotics to a patient with isolated lobar bronchiectasis resulting from a severe respiratory infection or retained foreign body. As well patients with weakness, poor cough, underlying immunodeficiency, or other systemic causes of bronchiectasis are at high risk of disease recurrence unless the underlying cause of the bronchiectasis is treated along with treating the infection itself. Further studies should be powered with clinically significant outcomes in populations with well defined and more uniform underlying diagnoses. Other goals should be to develop strategies to enhance the lower respiratory deposition of medications and the translocation of the antibiotic into the sputum and biofilm layer. Strategies to decrease the development of resistance should also be evaluated; perhaps by cycling antibiotics or by using aerosol antibiotics in combination with systemic antibiotics. Finally, for the therapy of non-CF bronchiectasis it seems especially important to develop new strategies or new formulations that are less likely to cause chest tightness and wheezing. Although the use of aerosol antibiotics for patients with non-CF bronchiectasis is theoretically attractive, this therapy cannot be recommended unless safety is improved and efficacy is assured.

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REFERENCES

1. Rubin BK: Overview of cystic fibrosis and non-CF bronchiectasis. *Semin Resp Crit Care Med.* 2003;24:619–627.
2. Daviskas, E Anderson SD, Gomes K, Briffa P, Cochrane B, Chan H-Kim, Young IH, and Rubin BK: Inhaled mannitol for the treatment of mucociliary dysfunction in patients with bronchiectasis—Effect on lung function, health status and sputum. *Respirology* 2005;10:46–56.
3. Bush A, Payne D, Pike S, Jenkins G, Henke MO, and Rubin BK: Mucus properties in children with primary ciliary dyskinesia: comparison with cystic fibrosis. *Chest.* 2006;129:118–123.
4. Barker AF: Bronchiectasis. *N Engl J Med.* 2002;346:1383–1393.
5. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, Vasitjev KM, Borowitz D, Bowman CM, Marshall BC, Marshall S, and Smith AL: Intermittent administration of inhaled tobramycin in patients with cystic fibrosis: Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med.* 1999;340:23–30.
6. Hagerman JK, Hancock KE, and Klepser ME: Aerosolised antibiotics: a critical appraisal of their use. *Expert Opin Drug Deliv.* 2006;3:71–86.
7. Melani AS, and DiGreggrio A: Acute respiratory failure due to gentamicin aerosolization. *Monaldi Arch Chest Dis.* 1998;53:274–276.
8. Hoffmann IM, Rubin BK, Iskandar SS, Schechter MS, Nagaraj SK, and Bitzan MM: Acute, non-oliguric renal failure in an adult with cystic fibrosis treated with inhaled tobramycin. *Pediatr Pulmonol.* 2002;34:375–377.
9. Lichtenberg DA, Goularte TA, Make BJ, and McCabe WR: Contaminated medication nebulizers in mechanically ventilated circuits: source of bacterial aerosols. *Am J Med.* 1984;77:834–838.
10. Althman GA, Ho B, Alsaadi MM, Ho SL, O'Drowsley L, Louca E, and Coates AL: Bronchial constriction and inhaled colistin in cystic fibrosis. *Chest.* 2005;127:522–529.
11. Althman GA, Alsaadi MM, Ho BL, Ho SL, Dupuis A, Corey M, and Coates AL: Evaluation of bronchial constriction in children with cystic fibrosis after inhaling two different preparations of tobramycin. *Chest.* 2002;122:930–934.

12. Delissalde F, and Amabile-Cuevas CF: Comparison of antibiotic susceptibility and plasmid content, between biofilm producing and non-producing clinical isolates of *Pseudomonas aeruginosa*. *Int J Antimicrob Agents*. 2004;4:405–408.
13. Brown JS, Zeman KL, and Bennett WD: Regional deposition of coarse particles and ventilation distribution in healthy subjects and patients with cystic fibrosis. *J Aerosol Med*. 2001;14:443–454.
14. Ilowite JS, Gorvovoy JD, and Smaldone GC: Quantitative deposition of aerosolized gentamicin in cystic fibrosis. *Am Rev Respir Dis*. 1987;136:1445–1449.
15. LiPuma JJ: Microbiological and immunologic considerations with aerosolized drug delivery. *Chest*. 2001;120:118S–123S.
16. Kollef MH, Vlasnik J, Sharpless L, Pasque C, Murphy D, and Fraser V: Scheduled change of antibiotic classes: a strategy to decrease the incidence of ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 1997;156:1040–1048.
17. Prober CG, Walson PD, and Jones J: Technical report: precautions regarding the use of aerosolized antibiotics. *Committee on Infectious Diseases and Committee on Drugs. Pediatrics*. 2000;106:E89.
18. Smith AL: Inhaled antibiotic therapy: What drug? what dose? What regimen? What formulation? *J Cyst Fibros*. 2002;1(Suppl. 2):189–193.
19. Barker AF, Couch L, Fiel SB, Gotfried MH, Ilowite J, Meyer KC, O'Donnell A, Sahn SA, Smith LJ, Stewart JO, Abuan T, Tally H, Van Dalfsen J, Wells CD, and Quan J: Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. *Am J Respir Crit Care Med*. 2000;162:481–485.
20. Couch LA: Treatment with tobramycin solution for inhalation in bronchiectasis patients with *Pseudomonas aeruginosa*. *Chest*. 2001;120:114S–117S.
21. Bilton D, Henig N, Morrissey B, and Gotfried M: Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of *Pseudomonas aeruginosa* infection in adult bronchiectasis. *Chest*. 2006;130:1503–1510.
22. Scheinberg P, and Shore E: A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. *Chest*. 2005;127:1420–1426.
23. Drobic ME, Sune P, Montoro JB, Ferrer A, and Orriols R: Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with *Pseudomonas aeruginosa*. *Ann Pharmacother*. 2005;39:39–44.
24. Orriols R, Roig J, Ferrer J, Sampol G, Rosell A, Ferrer A, and Vallano A: Inhaled antibiotic therapy in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa*. *Respir Med*. 1999;93:476–480.

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Paula Anderson, M.D.

Address reprint requests to:
Bruce K. Rubin, M.Eng., M.D., M.B.A., F.R.C.P.C.
Department of Pediatrics
Wake Forest University School of Medicine
Winston-Salem, NC 27157-1081

E-mail: brubin@wfubmc.edu