ently shown\(^{14}\) to influence persistent respiratory symptoms in a pediatric population. If this is indeed the case, promotility agents or medications directed at increasing the lower esophageal sphincter tone may need to be added to the antacid therapy that we give to our asthmatic patients.

In conclusion, the study by Leggett et al is useful in that it points out the limitations of current medical therapy for GERD in improving asthma symptoms. The possible reasons for this failure to improve are several, as pointed out above. It remains to be seen whether a greater understanding of the potential mechanisms by which GERD causes/worsens asthma symptoms will allow us to change the outcomes in patients with asthma, and perhaps in patients with other respiratory illnesses.

Subin Jain, MBBS, FCCP
Louisville, KY

Dr. Jain is Assistant Professor of Medicine and Director, Adult Cystic Fibrosis Program, University of Louisville Health Sciences Center.

Dr. Jain has worked for the Speakers Bureau at Pfizer and Glaxo Smith Kline Beecham, and has received clinical trial funding from Pfizer.

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Correspondence to: Subin Jain, MBBS, FCCP, Section of Pulmonary Medicine, Veterans Affairs Medical Center, 800 Zorn Ave, Mail Code 111-i, Louisville, KY 40206; e-mail: subin.jain@louisville.edu

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Inhaled Tobramycin

Not Just for Cystic Fibrosis Anymore?

The use of inhaled medications for the treatment of pulmonary diseases is an attractive concept. In theory, this mode allows for the delivery of a high concentration of a drug at the site of disease with reduced systemic absorption and risk of systemic adverse effects. For asthma, this concept has become reality such that inhaled medications are now the mainstay of therapy.\(^{1}\) It is not surprising therefore that there has been great interest in the possibility of using inhaled antibiotics for the treatment of chronic and recurrent respiratory infections.

The most successful application of the use of inhaled antibiotics has been for the treatment of *Pseudomonas aeruginosa* infections in patients with cystic fibrosis. Chronic endobronchial *P aeruginosa* infection with recurrent exacerbations is a common complication of cystic fibrosis that is associated with increased morbidity (including worsening pulmonary function) and mortality.\(^{2}\) The traditional treatment for *P aeruginosa* exacerbations has been 1 to 3 weeks of IV antibiotic therapy, although therapy with oral antibiotics (eg, ciprofloxacin) may be prescribed for patients with less severe exacerbations.\(^{3,4}\) However, even with the frequent use of IV antibiotics, most patients continued to have a decline in lung function and eventually died from pulmonary complications.\(^{3}\) Therefore, it was recognized that longer term antibiotic treatment of *P aeruginosa* using an alternative delivery method might be beneficial.
In the early 1980s, a number of investigators demonstrated\textsuperscript{5–9} that antibiotics could be delivered safely via inhalation. These studies, all of which included small numbers of subjects and some of which were not controlled or randomized, also showed potential benefits for inhaled antibiotic therapy. Two large, placebo-controlled, randomized trials\textsuperscript{3} using a specially formulated solution of tobramycin delivered via jet nebulization followed. Over 500 patients were randomized to receive either 300 mg tobramycin bid or placebo. Inhaled drug therapy was administered for 4 weeks followed by 4 weeks without treatment. This was continued for three cycles for a total of 24 weeks. Compared to patients receiving placebo, those receiving inhaled tobramycin had improved pulmonary function and decreased density of \textit{P aeruginosa} in their sputum. Patients treated with inhaled tobramycin were also less likely to be hospitalized. Approximately one fourth of adolescent patients included in the original randomized trials were enrolled in a long-term (ie, 96 weeks), open-label, follow-on trial.\textsuperscript{10} Subjects in the follow-on trial continued to experience improvement in pulmonary function, which correlated with a reduction in \textit{P aeruginosa} burden.

In general, systemic absorption of inhaled tobramycin is low, and the consequent systemic adverse effects are rare. One pharmacokinetic study\textsuperscript{11} found that 95\% of patients achieved a sputum concentration of drug at least 25 times the minimal inhibitory concentration, with a ratio of median serum concentration to median sputum concentration of 0.01. In the large controlled trials conducted by Ramsey et al.,\textsuperscript{3} the only nonrespiratory adverse events that were significantly greater in the treated group than in the placebo group were tinnitus and voice alteration. No patients experienced hearing loss or renal insufficiency. Other clinical trials\textsuperscript{12} have had similar findings, although some patients have reported hearing loss in postmarketing studies. Determining whether this effect can be attributed to inhaled tobramycin is difficult because some of these patients had previously received or were concurrently receiving therapy with parenteral aminoglycosides.\textsuperscript{12} Subsequently, there have been case reports\textsuperscript{13,14} of acute renal failure and vestibular toxicity (the latter occurring in a patient with preexisting renal insufficiency) associated with inhaled tobramycin.

As might have been anticipated, transient bronchospasm immediately following the inhalation of tobramycin is not unusual.\textsuperscript{9,12} There is some controversy over whether this effect varies with the preparation of tobramycin that is being used. The preparation approved by the US Food and Drug Administration for inhalation does not contain preservatives. There is some evidence that the preservative-free preparation causes less bronchospasm, especially among patients without a history suggestive of asthma, although this is not entirely clear.\textsuperscript{15,16} Pretreatment with bronchodilators appears to mitigate this problem, and at least in the case of cystic fibrosis patients, bronchospasm does not seem to be a major impediment to the use of this therapy.

Although sputum concentrations of tobramycin that are obtained with inhalation of the drug reach many times the minimal inhibitory concentration, the eradication of \textit{P aeruginosa} usually does not occur. Thus, there is concern that long-term treatment with a single antibiotic might result in the emergence of drug-resistant organisms. Clinical trial data\textsuperscript{17,18} have shown that \textit{in vitro} resistance to tobramycin increases after inhaled tobramycin therapy. However, there has been no correlation between preexisting colonization with or emergence of tobramycin-resistant organisms and clinical outcome.\textsuperscript{17,18}

With the success of inhaled tobramycin for treating \textit{P aeruginosa} infection in patients with cystic fibrosis, interest developed in expanding the application of this therapy, particularly to patients with other types of bronchiectasis. In this issue of CHEST (see page 1420), Scheinberg and Shore report on the potential utility and pitfalls associated with the use of inhaled tobramycin for \textit{P aeruginosa} infections in patients with severe bronchiectasis that is unrelated to cystic fibrosis. These investigators enrolled 41 adults in an open-label clinical trial at nine sites in the United States. Subjects received 300 mg inhaled tobramycin bid for three cycles (14 days on, 14 days off), with an additional 40 day follow-up period. Outcomes of interest were symptomatic improvement, reduction in \textit{P aeruginosa} density, and occurrence of adverse events.

During the 12-week treatment period, patients experienced an improvement in symptoms and quality of life. About one fourth of the patients were considered to have had their \textit{P aeruginosa} infection eradicated. Of note, there was no correlation between symptom improvement and \textit{P aeruginosa} eradication, leading the authors to hypothesize that eradication may not be necessary to achieve clinical benefit. Adverse effects, especially cough, wheezing, and dyspnea, immediately following treatment were common, and 10 subjects withdrew from the study due to adverse effects. These effects occurred despite routine pretreatment with bronchodilators. The investigators did not report any renal insufficiency or ototoxicity resulting from inhaled tobramycin.

Three prior studies have examined the use of inhaled aminoglycosides in the treatment of \textit{P aeruginosa} infection in non-cystic fibrosis patients with bronchiectasis. A preliminary, placebo-con-
controlled trial assigned patients (28 total) to randomly receive aerosolized gentamicin or placebo (saline solution) for 3 days. Compared to the placebo group, patients receiving inhaled gentamicin experienced improvement in symptoms (ie, less dyspnea and less sputum production) and improved peak expiratory flow. A larger (74 patients) controlled, randomized study investigated the use of inhaled tobramycin for 4 weeks with 2 weeks of follow-up while not receiving medication. P aeruginosa was eradicated in 35% of patients in the treated group, and 62% of patients had subjective improvement in the treated group compared with 38% in the control group (the study was double blinded). There was no difference between the treatment and control groups, however, in change in pulmonary function, as evaluated by FEV1 values. Adverse effects of dyspnea, chest pain, and wheezing were associated with inhaled tobramycin. Finally, in a small nonblinded trial (17 patients total), patients were randomized to receive 12 months of twice-daily therapy with inhaled ceftazidime and tobramycin or no inhaled antibiotics. The treatment group had fewer hospitalizations than the control group, but there was no difference between the two groups in change in pulmonary function, as measured by spirometry findings and arterial blood gas analysis.

Should inhaled tobramycin be recommended for the treatment of P aeruginosa infection in patients with bronchiectasis, but without cystic fibrosis? Based on the evidence, the routine use of inhaled tobramycin cannot be recommended at this time. The studies performed to date have been relatively small or have involved the short-term use of the drug. In addition, they have tended to look at different outcome measures (eg, symptomatic improvement, bacterial density, pulmonary function, and hospitalization) and have produced somewhat mixed results. This differs from the studies in cystic fibrosis patients that have almost uniformly shown a benefit from the treatment. In part, this may be a reflection of less homogeneity among non-cystic fibrosis patients with bronchiectasis. Of concern is the greater frequency of bronchospasm, often leading to a discontinuation of therapy, in the non-cystic fibrosis patients. As Scheinberg and Shore indicate, however, existing clinical trials, including their own, have primarily enrolled patients with advanced bronchiectasis, and patients with milder disease may tolerate inhaled antibiotics better.

The evidence suggests that some patients with non-cystic fibrosis bronchiectasis may benefit from therapy with inhaled tobramycin. Further trials are needed to define those subpopulations of patients who receive the most benefit and are the least likely to experience adverse effects. The optimal treatment schedule also needs to be determined. Finally, other antipseudomonal antibiotics, including ciprofloxacin, ceftazidime, and aztreonam can be administered via inhalation. It is possible that using tobramycin in combination with these antibiotics, concurrently or in sequential rotation, may reduce the occurrence of in vitro drug resistance.

Scheinberg and Shore are to be commended for undertaking their investigation of an innovative solution for a difficult management problem. I hope that they and others will address the remaining uncertainties, and thus allow inhaled antibiotics to be applied more widely in the treatment of respiratory infections.

Philip A. LoBue, MD, FCCP
Atlanta, GA

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Dr. LoBue is Chief, Medical Consultation Team, Division of Tuberculosis Elimination, Centers for Disease Control and Prevention.

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Correspondence to: Philip A. LoBue, MD, FCCP, Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Mail Stop E-10, 1600 Clifton Rd, Atlanta, GA 30333; e-mail: pg5@cdc.gov
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