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So Many Drugs, So Little Time

The Future Challenge of Cystic Fibrosis Care

After the identification of the cystic fibrosis (CF) gene in 1989[1] and the emergence of gene therapy in the early 1990s, great hope existed that a cure for CF could be developed rapidly. The last decade has led to the realization that while a cure for CF is still the long-term goal, more immediate gains may be made by developing therapies that target the chronic cycle of infection and inflammation that drives the progressive lung disease seen in CF.[2] Therapies that improve or correct the abnormal ion transport that is characteristic of the respiratory epithelium in CF may also eventually be effective in slowing the progression of CF lung disease. Numerous new therapeutic agents targeting these areas are in development. Many are currently in clinical trials being conducted by the Cystic Fibrosis Foundation Therapeutics Development Network (CFF-TDN), a national multicenter network that has been designed specifically to accelerate the development of new therapeutic agents for the treatment of CF.

Many of these trials take advantage of CF being an endobronchial disease and deliver the new therapeutic agents by aerosolization. The CFF-TDN alone is currently conducting clinical trials of six different inhaled CF therapeutic agents. The hope for these new aerosolized agents is that they would add to the effect of the many currently utilized aerosolized CF therapies (*eg*, tobramycin, human recombinant DNase, colistin, hypertonic saline solution, and bronchodilators).

The good news is that the increase in the number of CF therapeutic options over the last few decades has resulted in an improvement in expected survival for CF patients. The median survival time is now >30 years, a significant improvement over the expected survival of only 15 years in 1970.[3] The quality of life for individuals with CF also has improved, with about 30% completing college, 40% of adults with CF marrying, and 50% working full-time or part-time.[3] A growing challenge, however, is that at the same time that the improvement in length and quality of life in individuals with CF is allowing them to participate in and experience the time demands of career and family, the complexity and length of time required to complete their CF therapies also is increasing. A current standard CF treatment regimen of airway clearance, inhaled mucolytic agents, inhaled antibiotic agents, pancreatic enzymes, nutritional supplements, and exercise often requires ≥ 2 h each day.

The article by Geller and colleagues in this issue of *CHEST* (see page 28) demonstrating a method of more rapidly and efficiently delivering aerosolized tobramycin represents what is likely to be a research area of increasing importance in CF in the upcoming years: improving the delivery of inhaled medications. Aerosolized medications already are a cornerstone of CF therapy and will play an increasingly important role in the treatment of CF in the future. The use of a tobramycin solution for inhalation (TSI) [TOBI; Chiron; Emeryville, CA] already represents a significant

portion of the CF patient's time commitment for therapy, requiring 20 to 25 h per month when used.

Geller and colleagues compared the delivery of TSI by the standard PARI LC PLUS jet nebulizer (PARI Respiratory Equipment; Monterey, CA) and Pulmo-Aide compressor (DeVilbiss Corp; Somerset, PA) to delivery with a new aerosol device, the AeroDose 5.5 RP inhaler (Aerogen; Mountain View, CA). The AeroDose is slightly larger than a metered-dose inhaler and generates an aerosol by the rapid oscillation of a porous dome over the TSI, rather than by a jet of compressed air. An airflow sensor limits aerosol generation to inhalation only. With the use of AeroDose technology, Geller and colleagues demonstrated that TSI could be delivered in less than half the time normally required (8.0 vs 17.7 min, respectively). With the decrease in wasted TSI (*ie*, the amount of a drug remaining in the nebulizer cup after treatment or aerosolized during exhalation), a dose of 90 mg aerosolized TSI resulted in sputum concentrations comparable to 300 mg TSI delivered by the standard methods. There was no difference in the incidence of cough or bronchospasm between the two delivery methods.

For the individual with CF being treated with inhaled tobramycin, the utilization of AeroDose technology could result in time saved of $\geq$ 10 h per month. Over the course of a year, individuals on alternating months of TSI therapy could gain more than a full work week of free time. A decrease in the time required to deliver TSI also would likely result in increased adherence to the TSI regimen, as adherence to therapy in CF patients has been shown to correspond to the simplicity of the treatment.[4] AeroDose technology could have an even more significant impact on the time required for therapy as the number of aerosolized CF therapies increases in the future.

But now for the caveat. While providing a promise of improved aerosol technology, the article by Geller and colleagues also demonstrates the challenges that will be faced in improving the delivery of aerosolized therapies to individuals with CF. First, further advances in aerosol technology are still required. The AeroDose inhaler is not currently available, nor is it ready for widespread use by individuals with CF. Ten of the 53 participants in the study experienced a malfunction of the AeroDose inhaler. These malfunctions required that the study design be altered to allow a new AeroDose inhaler to be used for each tobramycin dose. Future studies of the AeroDose inhaler will need to demonstrate reliability along with improved efficacy of drug delivery. Second, aerosol delivery devices may require custom design for specific CF medications. An AeroDose inhaler can hold only one third of the 90-mg TSI dose, which would require stopping twice to refill the inhaler. A reconfiguration of the AeroDose inhaler from its current design would be needed to take full advantage of the potential time savings of using AeroDose technology to deliver tobramycin. Last, creative combinations of research funding from the National Institutes of Health, private foundations, and industry will be required to fully develop customized inhaled drug delivery systems for patients with CF. As opposed to COPD or asthma patients, the 30,000 individuals with CF in the United States are unlikely to provide sufficient potential financial gain for most pharmaceutical companies to justify committing the resources to develop, test, and gain Food and Drug Administration approval for CF-specific, inhaled drug-delivery systems. Despite the potential of the AeroDose inhaler to improve the quality of life of individuals with CF, Chiron Corporation is likely to think long and hard before committing itself to the development of a delivery system that might not significantly increase sales and may actually encourage patients to split up their current single-dose, 300-mg TSI vials into three 90-mg doses.

In the big picture, there are a number of new technologies for the delivery of inhaled medications that currently are in development. These include the AeroDose inhaler, systems based on dry-powder delivery, liquid multidose inhalers, and breath-actuated nebulizers.[5–7] Each one has different potential advantages and disadvantages, and it is not clear now which of these will be best-suited for the delivery of CF medications. What is clear is that the article by Geller and colleagues represents what will be an increasingly important topic of CF research: improving the delivery of inhaled therapies.

It is not unrealistic to believe that one day an individual with CF may protect their lung function by the daily inhalation of a mucolytic agent, an antibiotic agent (or agents), an anti-inflammatory agent (or agents), and a chloride transport agonist agent. With this in mind, a commitment to continued improvement in the efficacy and speed of delivery of inhaled medications is essential for the CF research community. This will ensure that future improvements in CF treatment will be limited only by our ability to identify new therapies, and not by the time that individuals with CF have to perform them.

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Altitude Pulmonary Edema Below 8,000 Feet

What Are We Missing?

Many of the "dogmas of the quiet past"[1] have given way to more well-founded concepts of disease in recent decades, as clinical science developed more precise investigative tools and effective therapies. Some dogmas have remained intact. One of these holds that high-altitude pulmonary edema (HAPE) is unknown[2] or rare[3] below 8,000 to 9,000 feet (2,440 to 2,745 m). Cases of HAPE at lesser altitudes are attributed to preexisting diseases such as skeletal or pulmonary vascular abnormalities.[3,4] In the current issue of *CHEST* (see page 49), however, Gabry et al describe 52 lowlanders who acquired HAPE after skiing at 1,400 to 2,400 m between 1992 and 2000. This remarkable account of previously healthy persons is all the more noteworthy because the skiers slept at a mean altitude of 1,300 m. (As Hultgren[3] points out, HAPE is usually attributed to altitude of repose, rather than that of daily activity.) Whereas the altitude exposure of these skiers was much more mild than that of previous reports, their illnesses were not. The symptoms, cardiorespiratory signs, and radiographic abnormalities—83% of the patients had bilateral shadows extending over at least half of each lung—were severe. Gas exchange was equally deranged: the mean alveolar-arterial oxygen difference was 45 mm Hg. It is thus no surprise that these persons sought emergency medical care at the nearest hospital in Moutiers. This is a town of approximately 5,000, nestled 500 m (approximately 1,640 feet) above sea level, in the valley where the Isere River wends its alpine way through the Tarentaise region of southeastern France. Some of the tallest peaks in Europe are nearby. For example, Mont Blanc (15,760 feet/4,807 m) is within 45 km (< 30 miles). But these lofty heights are not readily accessible from Moutiers since the mountain passes are impassible in winter. Although the patients documented by Gabry et al skied only at lower altitudes, they became very ill nonetheless.

Because their findings are surprising, one wonders if Gabry et al were exhaustive in excluding other conditions that can masquerade as HAPE? Not completely. Infection is the most obvious candidate. Viral pneumonia might mimic HAPE both in its presentation and its rapid resolution in healthy young patients such as Gabry et al describe. For decades preceding the identification of HAPE as a distinct clinical entity,[5] many patients who probably had this condition were thought to have pneumonia. Was it the other way around in the patients of Gabry et al? If so, what type of pneumonia did they have? As the authors point out, influenza pneumonia usually affects the ill, immunosuppressed, or aged, rather than healthy 37-years-olds. This pneumonia has a prodrome of 1 to 4 days that could be hard to distinguish from acute mountain sickness, but it often lasts 2 to 3 weeks, especially if complicated by secondary bacterial infections.[6] This was clearly not the case in the present patients, all of whom were hospitalized for less than a week. Given the retrospective nature of their analysis, it was beyond the reach of the authors to exclude infection by bacterial cultures or viral isolation from upper or lower airway secretions, or immunofluorescence, polymerase chain reaction, or enzyme-linked immunosorbent assay testing or other means. Future prospective investigations can incorporate such steps, however, thus establishing or excluding infectious etiology from the differential diagnosis in patients who appear to have HAPE at such modest altitudes.

To exclude drug-induced pulmonary edema such as that due to heroin (smoked, snorted, or injected),[7] the authors relied on the history of family and friends, and lack of pinpoint pupils, depressed respirations, and altered consciousness. The latter symptom was present in only 2 of their 52 patients, none of whom were treated with naloxone. Suspicious readers might insist on negative results of specific tests of urine or other body fluids to exclude this and other drugs,[8] including cocaine,[9,10] as causes of pulmonary edema in altitude visitors. Again, this is beyond the reach of a retrospective study. Assuming accuracy in the diagnosis of HAPE in 52 patients among the 11,420 admitted to the Moutiers emergency department over 9 years, one remains curious as to how many patients had pulmonary edema from other causes over the same time period. For exam-